Harper Hospital
Detroit Medical Center/Wayne State University

4ICU/5ICU
Neuro ICU/Medical ICU

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Clinical Pearls for 4ICU and 5ICU
Harper University Hospital
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4ICU – Neurosurgery/Medicine:

4ICU is comprised primarily of neurosurgical and medical ICU patients.
The neurosurgical patients are followed by both neurosurgery and medical ICU teams.
General neurosurgical PA pager is **#5859**

Care of the Neurosurgical Patients:

- There are pre-printed neurosurgical orders forms for most procedures.
- The neurosurgery team is responsible for all of the issues relating to the surgical care of the patient. They round daily at 06:00am.
- MICU team rounds daily on all of the patients and takes care of the daily medication orders. MICU rounds begin daily at 0900.
- The white board on the units will tell you which resident and which RN are caring for the patient on a daily basis.
- Antibiotic and anti-epileptic issues should be communicated with *both* teams.
- We follow ALL pharmacokinetics.

Issues Common to 4ICU Patients:

1. **Neurosurgical Infections** – See Attached CNS Shunt Infections (Appendix A)
   - For empiric treatment of **nosocomial** meningitis, use Vancomycin and Cefepime. (Ceftazadime may be used as an alternative to Cefepime since more data is available on CSF penetration).
   - I would suggest calculating parameters for vancomycin and verifying with nomogram, if serious CNS infection. Do not solely rely on the nomogram, as your trough level may be too low to provide an adequate CSF concentration.
   - Desired trough 10-20 mg/L for meningitis.

2. **Antiepiletics**
   - Phenytoin is routinely used for prophylaxis and/or treatment of seizures
   - Neurosurgery team usually adjusts phenytoin during their rounds at 06:00am.
   - See dosing tools for phenytoin found under PharmWeb Clinical Services – neurology
   - Status Epilepticus (see attached review article Appendix B)
     - Lorazepam at a dose of 0.1 mg/kg is the preferred first-line agent
     - For refractory status epilepticus, various agents can be used including midazolam infusions, phenobarbital, pentobarbital, phenytoin and/or propofol. This is one indication for propofol infusions that is not listed in our sedation algorithm.
     - If phenobarbital is used for **Status Epilepticus** – 10-20 mg/kg is the Loading dose. Maintenance dose should target levels = 15-40 mcg/ml.

- If a ***barbituate coma*** is required-
- Patient must be on mechanical ventilation
- Pentobarbital is our barbiturate of choice for this indication. An initial loading dose of 5-7mg/kg over 30-60 minutes, followed by a maintenance infusion of 2-3mg/kg/hr is recommended. Use actual body weight unless the patient obese (use adjusted BW).
- I would suggest a bag with 2.5gm in 250ml or 5gm in 500ml (D5W or 0.9% NaCl). Choose your bag size dependant upon the patient's weight.
- Expect levels 10-100mcg/ml. No need to monitor routine levels, as the continuous EEG will guide treatment, and not your levels.
- Barbiturates will cause respiratory and cardiovascular depression. Monitor MAP very closely during the first hour of the infusion. Anticipate a drop in MAP by 10-40 mmHg.

3. Anticoagulation

- Many of the subarachnoid hemorrhage patients will go for coiling of their aneurysms. The postoperative orders will differ based on which physician does the procedure.
  - Dr. Fernandez, who is a neuroendovascular physician will put her patients on IV heparin and targets a goal aPTT range of 40-50 or 50-60 seconds. We are consulted to follow all of these patients. Dr. Fernandez is pretty aggressive and she wants us to make sure that we account for the boluses given in the OR before we hold the heparin based on a high PTT.
  - Dr. Fessler does not practice this way. He will often prescribe a low dose of heparin (500 Units/hour) and he does not monitor PTT. He will infuse the heparin for approximately 18 hours.
- Follow the **Stroke Nomogram** for neurosurgical indications.

4. Hypertonic Solutions

It is common for the neuro patients to be on 3% saline. See attached sheet for calculating solutions(appendix C).

5. Drotrecogin Alfa, activated (Xigris→) – See 5ICU

6. Nutrition – See 5ICU

5ICU- Medical Intensive Care Unit:

5ICU is comprised primarily of medical ICU patients.

Care of the MICU Patients:

- MICU team rounds daily at 09:00.
- White board on the unit will tell you which resident and which RN are caring for the patient on a daily basis.
- The On-Call list is posted under the tube station and should be utilized for orders written after 4:00 pm. This will tell you the attending, fellow and resident on call. Please do not call the attending after hours, unless there is an emergency.
- MICU team takes care of all orders. When writing orders for these patients, do not write v/o for the attending. Orders from consulting services must be approved by the MICU team.
- The M-I-C-U pager (#6428) is always carried by the fellow 24hr/day.
- 5ICU is the ONLY ICU that can have CRRT patients on it.
- We follow ALL pharmacokinetics and anticoagulation for the MICU patients.

Issues Common to 5ICU Patients:

1. **Pharmacokinetics**

   - Critically ill patients have altered pharmacokinetics, including the following:
     - Increased Vd.
     - Altered protein binding
     - Renal dysfunction and/or liver dysfunction
     - Decreased hepatic blood flow
     - Decreased cardiac output

   - Often their Vd is very large. Consider using 0.4L/kg for initial doses for septic patients. All first dose antibiotics must be treated as STAT orders for critically ill, septic patients. This is ESSENTIAL to a positive outcome!
   - Renal function and Vd change very rapidly. Assess levels early and frequently for life-threatening infections.
   - If uncertain about renal function, check levels after 1st dose.
   - If levels are ordered, the RN can draw any time. AM labs are at 03:00am.
   - No need to write, "Check BUN/Cr 2-3 times/week" in an ICU patient. These patients have at least daily lytes checked anyway.

2. **Anticoagulation**
   - Pharmacy follows all patients unless otherwise stated.
   - Obtain an official consult if not written in the orders.
   - Automatic consult for CRRT anticoagulation. (On pre-printed orders)
   - AM Labs are daily at 03:00am. No need to write for CBC's, since they are checked daily.

3. **CRRT**
   - CRRT stands for continuous renal replacement therapy. Also known as CVVHD, CHHD, CVVHDF and SCUF.
   - CRRT is a form of dialysis that is a continuous process (24 hours a day) used in hemodynamically unstable patients.

- ***Pharmacokinetics for CVVHD***:
  - CVVHD will remove both vancomycin and aminoglycosides.
  - Dosing usually ends up at q24-q48
  - CVVHD machine is often interrupted due to clotting, or clogging of the filter. This will affect dosing. Need to check on machine DAILY.
  - Doses for the aminoglycosides and vancomycin should be based on levels initially.
  - For aminoglycosides, order a loading dose to achieve a peak consistent conventional dosing. Use an increased Vd (0.4-0.5 L/kg) and then check a peak level and a random level 8-12 hours later to verify parameters. Re-dose the aminoglycosides based on your levels. Levels obtained without interruption of the circuit are preferred.
  - For dosing of other agents, see the dosing table provided (Appendix D). This is NOT a DMC-approved dosing table, but it will provide guidance based on available literature.
  - When dosing recommendations are not provided, please use an estimated clearance of 30-40 ml/min for dosing purposes.

- ***Anticoagulation* for CVVHD**:
  - Pharmacy is automatically consulted for anticoagulation on the CRRT order forms.
  - Anticoagulation is indicated in all patients unless PLT < 50,000, baseline aPTT > 60sec; baseline INR > 2, or patient has active bleeding, or is deemed too high risk
  - Dosing: 50 Units/kg, then 10 Units/kg/hr
  - Indication on profile should state "Regional anticoagulation for CRRT."
  - Be cautious. These are usually the most critical, unstable patients! They are at high risk for bleeding.
  - Do not send the standard heparin bag. Heparin will be sent in a 20 ml syringe at a concentration of 20,000Units/20 ml (1000 Units/ml)

4. Drotrecogin Alfa, activated (Xigris→)

- See Xigris binders located in any ICU unit, and in central pharmacy.
- All information is included in the binder, including the order forms.
- Patients must meet inclusion and exclusion criteria.
- Attending physician must approve. Any MICU attending can approve. Limited surgeons are approved; however, any surgeon holding Board Certification in Critical Care Medicine will be approved. *(See list provided in binder)*
- Anyone can write the order; however, the authorizing attending's name must be on the order form.
- When a patient is on Xigris→, pharmacy needs to write a small note in the chart stating that patient is on Xigris→ for "Severe Sepsis". This is important for reimbursement.

- **<u>Pharmacist's Role in Following Xigris→ Patients:</u>**
  - Evaluate patient to ensure criteria are met.
  - Evaluate dosing, weight, and order form for completeness.
  - Verify attending approval.

- Write clearly visible note in chart stating "Xigris→ for Severe Sepsis".
- Monitor daily for bleeding
- ***Save ALL profiles for Krista***
- ***Drotrecogin alfa MUE must be completed (Appendix E)***

- **Commonly asked Questions:**
  - ***What should you do if INR or aPTT is elevated?***
    - *Nothing unless patient is bleeding!*
  - ***What if an unauthorized attending wants to use it?***
    - *Need to contact an authorized physician for approval*
  - ***Does the attending need to sign the order?***
    - *No, but his name is required as the authorizing physician*
  - ***Can they use it if a patient has an exclusion criteria?***
    - *Yes, but they need to check the box stating that they want to give the drug anyway.*
  - ***What if a patient bleeds?***
    - *Discontinue the drip. Document on MUE form.*
    - *Enter Dr. Quality*
  - ***What is the patient is on CVVHD?***
    - *Guidelines are not developed, however, Xigris→ may clog the filter, and cause disruption of CVVHD. Can still use it, just be aware.*
    - *Do not use heparin for anticoagulating filter, if patient is on Xigris→.*

5. Total Parenteral Nutrition

- The TPN team does not follow patients in the ICU. It is the ultimate responsibility of the MICU team to write the orders.
- **Steps for Writing TPN:**
  - Collect baseline data: Ht, Wt, IBW, AdjBW, LFT's, Albumin and Prealbumin and triglycerides. If not ordered, please order with the AM labs.
  - Determine Goals: Start out slowly, as hyperglycemia and refeeding syndrome are serious concerns.
    - Calories: Start with 20-25kcal/kg/day. Disregard stress factors for now.
      - Divide calories into 60%/40% or 70%/30% carbs/fats.
      - See handout for conditions that may alter substrate needs (Appendix F).
      - The maximum concentration of dextrose for a Peripheral IV is 10%.
  - Proteins: Start with 0.8-2gm/kg/day.
    - Use lower end for liver failure or acute renal failure
    - Be more aggressive for severe sepsis, hemodialysis, HIV, CF, non-healing wounds, and cancer patients
    - Only use Hepatamine if severe hepatic encephalopathy not responding to treatment
  - Fluids: Easy Method – Fluid requirement should equal total calories (25ml-35ml/kg/day).
  - Monitor electrolytes daily.
  - Monitor LFT's, TG and prealbumin weekly.
  - ***Trouble Shooting with TPN's***
    - Write orders early and tube to pharmacy

- Never add insulin to the TPN until their insulin requirements are well established.
- For renal failure – Do not add K+ or PO4 initially, especially if they are not receiving HD. Reduce MVI to 5ml for ESRD.
- Optimize acetate if acidotic with low bicarb. (Acetate converts to HCO_3)
- Acceptable Triglyceride Level while on TPN < 400. If > 400, remove lipids from TPN until level < 400, then supplement IVPB 2-3 times/week.
- If patient has pancreatitis, check TG level before adding lipids
- If fluid restricted need to calculate minimum volume:
  - Use the most concentrated products available. For example, 70% dextrose, 15% amino acids and 20% lipids.

- See attached handout for more detailed information (Appendix F).

6. Flolan/Remodulin Patients:

- All new initiation patients will be admitted to 5ICU or 9ICU.
- With the exception of a life-threatening emergency, all patients must be pre-approved through one of the designated drug companies listed below. The company name and contact information must be made readily accessible on the patient's bedside clipboard.
- Accredo: 1-866-FIGHT-PH
- Priority Healthcare: 1-866-474-8326
- Caremark/Theracom: 1-877-356-5264
- Pharmacy needs to ensure that we have the drug available.
- The supplies and CADD pumps are not to be started until the patient is ready for discharge from the hospital.
- All patients admitted to the ICU who are already on a stable dose of Flolan or Remodulin will be required to convert to our hospital approved pumps -Baxter Colleague pump. This will eliminate the need to purchase tubing, batteries and supplies for the patient.
- Dosing and preparation of the drug should be made in order to provide a continuous infusion rate of at least 5- 10 ml/hr.
- All questions about the individual patient should be addressed first with Dr. Mubarak (Pager #11555) and secondly with their respective drug company.

7. Sedation/Analgesia: (Appendix H)

8. Insulin Nomogram: (Appendix I)

- All patients that are hyperglycemia and meet the inclusion criteria will be started on the insulin nomogram. It is a nursing nomogram, and pharmacy does not have to actively follow these patients**.**

9. Neuromuscular Blockers Order Form: (Appendix J)

CNS Shunt Infections – Intraventricular Antibiotics
Harper University Hospital 2005
Prepared by Krista Wahby, Pharm.D.

Ventriculitis (Reservoir and Shunt-Related Infection)

- CSF shunting devices are placed to control hydrocephalus and increased intracranial pressure. Reservoirs are often placed to allow administration of pharmaceuticals directly into the CSF (chemotherapy, etc).

Common pathologies requiring CNS shunt or reservoirs include:

- Spina bifida
- Infantile hydrocephalus
- Subarachnoid hemorrhage
- Intracranial neoplasms

Common Pathogens:

- Gram positive organisms (most commonly coagulase negative staphylococci)

Issues to Consider:

- Patients with ventriculitis usually mount only a mild inflammatory process. Therefore, it is difficult to achieve and maintain adequate drug levels in the CSF.
- Estimation of CSF volume – roughly 150ml of ventricular and subarachnoid CSF in adults. Usually 25ml is within the ventricular system. (Adolecents 100ml, children 80ml and infants 50ml).
- CSF turnover occurs 3-4 times per day and influences drug clearance from the CSF. If there is an external, functional drain in place, drug removal in accelerated. The opposite is true for malfunctioning drains.

Treatment Options:

- Removal of the shunt will reduce morbidity & mortality.
- Intravenous Vancomycin should be the initial treatment for **methicillin-resistant** organisms. If IV vancomycin fails to clear the CSF within 48-72 hours, then consider intraventricular or intrathecal vancomycin.
- For synergy, Rifampin IV or PO, or intraventricular or intrathecal gentamicin could be considered.

Adult Dosing:

A. Vancomycin:

- 10mg – 20 mg Intraventricularly or Intrathecally Q24 h.
- For lumbar intrathecal dosing may want to start with the higher dose = 20mg IT Q24.
- Continue IVT dosing until CSF cultures are negative for 3-4 days.

How to Prescribe:

- Order should clearly read "Vancomycin 10mg Intraventricularly (or intrathecally) Q24. (Volume = 3ml)
- Order should state to, "Use preservative free products."
- First order is always a **STAT**. Subsequent orders should be scheduled at **06:00 daily.**
- The neurosurgery resident or PA-C must administer the drug. Nurses are not allowed to administer IVT or IT doses.

Preparation:

- Use Vancomycin hydrochloride for injection (contains no preservatives).
- Make in a **10 ml** syringe, so that the drug can be mixed with CSF prior to instillation into the ventriculostomy.
- Dilute with 0.9% NaCl to a concentration of 2.5 to 25 mg/mL (Osmolality = 280-308 mOsm/kg that is consistent with physiologic Osmolality in CSF).
- Volume of drug = 3ml.
- Dextrose can be used, but is not routinely recommended.

Procedure for Administration:

- Only the physician or physician assistant can administer the drug.
- Daily administration will be performed at 06:00, so drug should always be scheduled for 06:00.
- Intraventricular Instillation - Aspirate 2-3 ml of the patients own CSF into the antibiotic-filled syringe. Invert the syringe 3 times to mix the CSF and the vancomycin.
- Flush drain with 1 ml of 0.9% NaCl, then clamp for 30-60 minutes

Monitoring:

- Check CSF concentration on day #2 or 3.
- NOTE** The half life of drugs in the CSF are usually 2-3 times longer than the blood half life.
- Apply similar rules to CSF peak & trough as we do with the IV dosing. Peak 30-40, Trough 5-20 mg/L.
- There is likely no additional benefit from concentration exceeding 30 mg/L in the CSF.
- If CSF level is 20-30 mg/L, decrease dose by 50%.
- If CSF level is > 30 mg/L, hold one dose, then decrease dose by 50-75%
- If CSF level is <5 mg/L, increase dose by 50%.
- For any dose changes, consider repeating CSF level in 3 days.
- Continue to monitor blood levels, as indicated.

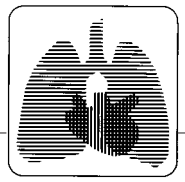
Toxicity:

- Severe headaches.
- CSF eosinophilia.
- Excessively high CSF concentration may cause local tissue necrosis
- No reported cases of IVT induced ototoxicity.

Gram Negative CNS Infections
Requiring Intraventricular or Intrathecal Aminoglycosides

Gentamicin:

- Intraventricular/Intrathecal Dosing – 4-10mg Intraventricularly Q24 h.
- Intrathecal gentamicin is no longer made, however, we have preservative free gentamicin
- Discontinue when CSF cultures are negative for 3-4 days
- Trough concentrations should be no greater than 5mg/ml
- Neurotoxicity and aseptic meningitis have been reported.
- Amikacin and Tobramycin are suitable alternatives if resistance to gentamicin is an issue
- Procedure for administration, timing, are preparation are the same as for vancomycin



critical care review

The Management of Status Epilepticus*

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Status epilepticus is a major medical emergency associated with significant morbidity and mortality. Status epilepticus is best defined as a continuous, generalized, convulsive seizure lasting > 5 min, or two or more seizures during which the patient does not return to baseline consciousness. Lorazepam in a dose of 0.1 mg/kg is the drug of first choice for terminating status epilepticus. Patients who continue to have clinical or EEG evidence of seizure activity after treatment with lorazepam should be considered to have refractory status epileptics and should be treated with a continuous infusion of propofol or midazolam. This article reviews current information regarding the management of status epilepticus in adults.

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Key words: anticonvulsants; barbiturates; lorazepam; midazolam; phenytoin; propofol; refractory status epilepticus; status epilepticus

Abbreviations: CI = confidence interval; GABA = γ-aminobutyric acid; NMDA = N-methyl-D aspartate; VA = Veterans Affairs

Status epilepticus is a major medical emergency associated with significant morbidity and a mortality rate of up to 76% in elderly patients with refractory status epilepticus.[1] This clinical entity requires prompt management. The complications of status epilepticus include cardiac dysrrhythmias, derangements of metabolic and autonomic function, neurogenic pulmonary edema, hyperthermia, rhabdomyolysis, and pulmonary aspiration. Permanent neurologic damage occurs with prolonged uncontrolled convulsive activity. This article reviews the current information regarding the management of status epilepticus in adults.

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Definition of Status Epilepticus

Status epilepticus is usually defined as continuous seizure activity lasting 30 min or as two or more discrete seizures between which consciousness is not fully regained.[2–4] Lowenstein et al[5] have proposed that status epilepticus be defined as a continuous, generalized, convulsive seizure lasting > 5 min, or two or more seizures during which the patient does not return to baseline consciousness. The rationale for this revised definition is based on the fact that a typical, generalized tonic-clonic seizure rarely lasts > 5 min, that spontaneous termination becomes less likely in seizures of > 5 min, and that the longer the seizure continues, the more difficult the seizure becomes to control with antiepileptic drugs, and the greater the degree of neuronal damage.[5–9] This definition is consistent with common clinical practice in which it would be unreasonable to wait 30 min before initiating antiepileptic drug therapy.

Refractory status epilepticus is usually defined as seizures lasting > 2 h, or seizures recurring at a rate of two or more episodes per hour without recovery to baseline between seizures, despite treatment with conventional antiepileptic drugs.[10] However, from a clinical perspective, it is preferable to consider refractory status epilepticus in any patient who has not responded to first-line therapy.[3,11]

Classification

Many types of epileptic seizures have been described, and, therefore, it follows that there are many types of status epilepticus. This has led to complex classifications of status epilepticus.[12] However, using electroclinical features, status epilepticus may be classified simply by the presence of motor convulsions (*convulsive status epilepticus*) or their absence (*nonconvulsive status epilepticus*). They may be further divided into status epilepticus that affects the whole brain (*generalized status epilepticus*) or only part of the brain (*partial status epilepticus*). This review will focus predominantly on generalized convulsive status epilepticus, which is the form most commonly observed in clinical practice.

Epidemiology

It has been estimated that up to150,000 cases of status epilepticus and 55,000 deaths from it occur annually in the United States.[13] Geography, sex, age, and race influence the epidemiology of status epilepticus. An incidence of between 6.2 and 18.3 per 100,000 population has been reported in the United States.[13–15] Regardless of geographic influences, status epilepticus appears to be more frequent among men, blacks, and the aged.[14,16–18] The incidence of status epilepticus in the elderly population is at least twice that of the general population.[19,20] Status epilepticus in the elderly is of great concern because of the existence of concurrent medical conditions that are more likely to complicate therapy and worsen the prognosis.[20,21]

Etiology

In many patients with a preexistent seizure disorder, no obvious precipitating factor can be determined. A fall in serum levels of antiepileptic drugs due to poor compliance with medications or to due to increased clearance associated with concurrent illness has been implicated in some patients.[22,23] Adult patients with a new diagnosis of epilepsy may first present while in status epilepticus.[20] Genetic factors likely play a role as twin studies[24] have demonstrated a greater concordance in monozygotic as apposed to dizygotic twins. Table 1 depicts the most common causes of status epilepticus seen in "first-world" populations.[8,9,16,18,25–32]

Table 1—*Common Causes of Status Epilepticus*

Antiepileptic drug noncompliance
Alcohol related
Cerebrovascular accidents
Drug toxicity (*ie*, cephalosporins, penicillins, ciprofloxacin, tacrolimus, cyclosporin, theophylline, and cocaine)
CNS infections (*eg*, meningitis and encephalitis)
CNS tumors (primary or secondary)
Metabolic disturbances (*eg*, electrolyte abnormalities, sepsis, and uremia)
Head trauma
Cerebral anoxia/hypoxia
Hypoglycemia or hyperglycemia

Pathophysiology

It is likely that the ineffective recruitment of inhibitory neurons together with excessive neuronal excitation play a role in the initiation and propagation of the electrical disturbance occurring in status epilepticus. γ-Aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the CNS. It is released from GABAergic neurons and binds to several types of GABA receptors (*ie*, GABA-A, GABA-B, and GABA-C receptors). GABA receptors are macromolecular proteins that form a chloride ion channel complex and contain specific binding sites for GABA and a number of allosteric regulators, including barbiturates, benzodiazepines, and a number of anesthetic agents. GABA receptor-mediated inhibition may be responsible for the normal termination of a seizure. In addition, the activation of the N-methyl-D aspartate (NMDA) receptor by the excitatory neurotransmitter glutamate may be required for the propagation of seizure activity.[33,34] The activation of NMDA receptors results in increased levels of intracellular calcium, which may responsible for the nerve cell injury seen in patients in status epilepticus.[33–35] A growing body of basic science and clinical observation supports the concept that status epilepticus becomes more difficult to control as its duration increases.[7–9] It is been postulated that this may occur due to a mechanistic shift from inadequate GABAergic inhibitory receptor-mediated transmission to excessive NMDA excitatory receptor-mediated transmission.[36–41]

In humans and experimental animals, sustained seizures cause selective neuronal loss in vulnerable regions such as the hippocampus, cortex, and thalamus.[42,43] The degree of neuronal injury is closely related to the duration of seizures, underscoring the importance of the rapid control of status epilepticus.[43,44] Meldrum and Brierley,[45] and Nevander et al[46] have demonstrated that even without attendant hypoxia, acidosis, hyperthermia, or hypoglycemia, ongoing seizures in primates and rats can cause neuronal death. Wasterlain et al[47] reported neuronal loss in the hippocampus and other brain regions in patients with nonconvulsive status epilepticus who

did not have preexisting seizures or systemic abnormalities. Neuron-specific enolase, a marker for acute neurologic injury, has been demonstrated to be increased in patients with nonconvulsive status epilepticus who did not have preceding or coexistent cerebral injury.[48–51] Thom and coworkers[52] demonstrated evidence of acute neurol injury using heat shock protein-70 and c-Jun immunochemistry in patients who had sudden and unexpected death from epilepsy. Neuronal death is probably caused by the release of excitatory neurotransmitters. In an experimental model, Mikati and coauthors[53] have demonstrated that increased NMDA activation results in increased ceramide levels followed by programmed cell death.

Diagnosis

Status epilepticus may be divided into two stages.[54] The first stage is characterized by generalized convulsive tonic-clonic seizures that are associated with an increase in autonomic activity that results in hypertension, hyperglycemia, sweating, salivation, and hyperpyrexia. During this phase, cerebral blood flow is increased due to increased cerebral metabolic demands. After approximately 30 min of seizure activity, patients enter the second phase, which is characterized by the failure of cerebral autoregulation, decreased cerebral blood flow, an increase in intracranial pressure, and systemic hypotension. During this phase, electromechanical dissociation may occur in which, although electrical cerebral seizure activity continues, the clinical manifestations may be restricted to minor twitching.

The diagnosis of status epilepticus is straightforward in patients with witnessed generalized convulsive tonic-clonic seizures. However, status epilepticus may not be considered in patients who have progressed to the nonconvulsive phase of status epilepticus and present in coma. All comatose patients should therefore be carefully examined for evidence of minor twitching, which may involve the face, hands, or feet, or may present as nystagmoid jerking of the eyes. Towne and colleagues[28] evaluated 236 patients with coma and no overt seizure activity. Eight percent of patients in this study were found to have nonconvulsive status epilepticus, as determined by EEG monitoring. Therefore, it is essential that an urgent EEG be performed in patients with unexplained coma.

Treatment

Status epilepticus is a medical emergency that requires rapid and aggressive treatment to prevent neurologic damage and systemic complications. The longer status epilepticus remains untreated, the greater the neurologic damage. In addition, the longer an episode of status continues, the more refractory to treatment it becomes and the greater is the likelihood of chronic epilepsy. The management of status epilepticus involves the rapid termination of seizure activity, airway protection, the taking of measures to prevent aspiration, the management of potential precipitating causes, the treatment of complications, the prevention of recurrent seizures, and the treatment of any underlying conditions.

General Measures

As with any critically ill patient, the first step in the management of a patient with status epilepticus should be to ensure an adequate airway and to provide respiratory support. The patient should be positioned so that they cannot harm themselves during the seizure activity. Two large-gauge IV catheters should be inserted to allow fluid resuscitation and pharmacotherapy. Should peripheral venous access be difficult, the placement of a central venous catheter is recommended. Despite the periods of apnea and cyanosis that occur during the tonic or clonic phases of their seizure, most patients in status epilepticus breathe sufficiently well as long as the airway remains clear. An oral airway may be required once the seizure has terminated to prevent airway obstruction. Once the seizures are controlled, and if the patient is oxygenating and ventilating adequately, endotracheal intubation may not be required for airway protection, even if the patient remains comatose.[55] However, in this situation precautions should be taken to avoid aspiration, and a nasogastric tube should be placed to ensure that the stomach is empty. Endotracheal intubation will be required in patients who continue to experience seizures despite receiving first-line therapy. There are no available data as to the pharmacologic agents that are preferred for achieving endotracheal intubation. As these patients will be comatose and would already have received therapy with lorazepam, a hypnotic agent is usually not required. However, an anesthetic induction dose of propofol, midazolam, or etomidate may terminate the seizure activity and facilitate intubation.[56,57] Neuromuscular blockade will be required to facilitate intubation in patients who continue to have tonic-clonic seizure activity despite these pharmacologic interventions. Rocuronium (1 mg/kg), a short-acting, non-depolarizing muscle relaxant that is devoid of significant hemodynamic effects and does not increase intracranial pressure, is the preferred agent.[58,59] Succinylcholine should be avoided, if possible, as the patient may be

hyperkalemic as a consequence of experiencing rhabdomyolysis. Prolonged neuromuscular blockade should be avoided.

Hypoglycemia must be excluded rapidly, and corrective measures must be instituted if serum levels of glucose are low. If the prompt measurement of blood glucose levels is not possible, the patient should receive100 mg IV thiamine followed by a 50-mL bolus of 50% dextrose. BP, ECG, and temperature should be monitored. If the patient develops significant hyperthermia (*ie*, temperature $> 40°C$), then passive cooling is required.[11] Blood specimens should be obtained for the determination of serum chemistry levels. Continuous motor seizures may lead to muscle breakdown, with the release of myoglobin into the circulation. The maintenance of adequate hydration is necessary to prevent myoglobin-induced renal failure. Forced saline solution diuresis and urinary alkalinization should be considered in the presence of myoglobinuria or significantly elevated serum creatine kinase levels (*ie*, > 5,000 to 10,000 U/L).[4,11] Brain imaging with a CT scan and/or MRI as well as a lumbar puncture will be required in patients presenting with a previously undiagnosed seizure disorder once the seizure activity has been controlled. It is important to emphasize that the first priority is to control the seizures. Imaging studies should be performed only once the seizure activity has been controlled. Endotracheal intubation and neuromuscular paralysis for the sole purpose of imaging the patient may increase morbidity and is strongly discouraged.

Pharmacotherapy

Because only a small fraction of seizures go on to become status epilepticus, the probability that a given seizure will proceed to status is small at the start of the seizure and increases as the seizure duration increases. If a seizure lasts > 5 min, clinical experience suggests that the likelihood of spontaneous termination decreases. The goal of pharmacologic therapy is to achieve the rapid and safe termination of the seizure, and to prevent its recurrence without adverse effects on the cardiovascular and respiratory systems or altering the level of consciousness.[4] Diazepam, lorazepam, midazolam, phenytoin, fosphenytoin, and phenobarbital have all been used as first-line therapy for the termination of status epilepticus. These drugs have different pharmacodynamic and pharmacokinetic properties, which determine their rapidity of clinical effect, their efficacy in terminating status epilepticus, and their duration of action. The benzodiazepines bind to the benzodiazepine binding site on the GABA receptor complex, increasing GABAergic transmission, while the barbiturates act directly on the GABA receptor. The antiseizure activity of phenytoin is complex, however, its major action appears to block the voltage-sensitive, use-dependent sodium channels.

The publication of the Veterans Affairs (VA) cooperative trial in 1998[9] and the San Francisco Emergency Medical Services study in 2001[25] allows for an evidence-based approach to the choice of the first-line agent to use in terminating status epilepticus. The VA cooperative study[9] randomized 384 patients with overt generalized status epilepticus into four treatment arms, as follows: lorazepam, 0.1 mg/kg; diazepam, 0.15 mg/kg, followed by 18 mg/kg phenytoin; phenytoin, 18 mg/kg; and phenobarbital, 15 mg/kg. Successful treatment required both clinical and EEG termination of seizures within 20 min of the start of therapy, and no seizure recurrence within 60 min from the start of therapy. Patients who did not respond to the first treatment received a second choice of treatment drug and, if necessary, a third choice. The latter choices were not randomized, because this would have resulted in some patients receiving two loading doses of phenytoin, but the treating physician remained blinded to the treatments being given. Status epilepticus was terminated in 64.9% of patients randomized to lorazepam, 58.2% of those randomized to phenobarbital, 55.8% of those randomized to diazepam and phenytoin, and 43.6% of those randomized to phenytoin ($p = 0.002$ for lorazepam vs phenytoin). There was no difference between the arms in recurrence rates.

The San Francisco Emergency Medical Services study[25] was a randomized, double-blind trial to evaluate IV benzodiazepine administration by paramedics for the treatment of out-of-hospital patients with status epilepticus.[25] In this study, 205 patients were randomized to IV diazepam (5 mg), lorazepam (2 mg), or placebo. An identical second injection was administered if needed. Status epilepticus had terminated at arrival in the emergency department in 59.1% of the patients treated with lorazepam, in 42.6% of the patients treated with diazepam, and in 21.1% of patients treated with placebo (lorazepam vs diazepam: odds ratio, 1.9; 95% confidence interval [CI], 0.9 to 4.3). The duration of the status epilepticus was shorter in the lorazepam group compared to the diazepam group (adjusted relative hazard, 0.65; 95% CI, 0.36 to 1.17). These data are supported by a double-blind study reported by Leppik et al[60] in 1983 in which 78 patients with status epilepticus were randomized to receive one or two doses of either lorazepam (4 mg) or diazepam (10 mg). Seizures were controlled in 89% of the episodes treated with lorazepam and in 76% of those treated with diazepam. Although the

dosages of lorazepam and diazepam differed in these three studies and phenytoin was added to diazepam in the VA study,[25] the summed data indicate that lorazepam is significantly more effective in terminating seizures than is diazepam (odds ratio, 1.74; 95% CI, 1.14 to 2.64; $p = 0.01$). Furthermore, the pharmacokinetic properties of lorazepam favor its use over that of diazepam. The anticonvulsant effect of a single dose of diazepam is very brief (20 min), whereas that of lorazepam is much longer (> 6 h), and the risk of respiratory depression may be greater with diazepam.[61] Although diazepam has a much longer elimination half-life, due to its high lipid solubility it is rapidly redistributed from the brain to the peripheral fat stores, accounting for its shorter antiseizure activity.

Based on these data, lorazepam in a dose of 0.1 mg/kg is recommended as first-line therapy for the control of status epilepticus. Although refrigeration is recommended for lorazepam, but not for diazepam, Gottwald and coworkers[62] have demonstrated that lorazepam retains 90% of its original concentration when stored without refrigeration in ambulances (in San Francisco) for 5 months. Based on this information, lorazepam should replace diazepam in hospital code carts and "orange bags," it should be stored in light-proof containers, and should be restocked every 4 to 6 months.[25,62] Many authorities recommend phenytoin, 20 mg/kg (or fosphenytoin), following the administration of lorazepam. While there are no data that demonstrate that phenytoin increases the response rate following the use of lorazepam, this agent may prevent recurrent seizures and is recommended in patients without a rapidly reversible process (*eg*, the effect of subtherapeutic antiepileptic drug concentrations).[3]

Continuous EEG monitoring is required in patients who do not recover consciousness once the convulsive seizure has aborted. In a study by DeLorenzo and colleagues,[63] after the cessation of convulsions, 48% of patients continued to have seizure activity and 14% of patients had persistent nonconvulsive status epilepticus.

Management of Refractory Status Epilepticus

In the VA cooperative study,[9] 55% of patients with generalized convulsive status epilepticus did not respond to first-line therapy. The aggregate response rate to a second first-line agent (*eg*, lorazepam, diazepam, phenytoin, or phenobarbital) was 7%, and to a third first-line agent it was 2.3%. Only 5% of patients with status epilepticus who did not respond to lorazepam and phenytoin therapy, responded to phenobarbital administration. These data suggest that refractory status epilepticus is much more common than is generally appreciated and that phenobarbital should not be used as a second (or third-line) agent in patients who have failed to respond to lorazepam. Furthermore, the limited data available suggest that the administration of further doses of lorazepam will not be useful.[60]

A variety of agents has been recommended for the treatment of refractory status epilepticus, including midazolam, propofol, high-dose thiopentone or pentobarbital, IV valproate, topiramate, tiagabine, ketamine, isoflurane, and IV lidocaine. Treatment guidelines are difficult to formulate as refractory status epilepticus has not been studied in a prospective clinical trial. Currently, however, a continuous IV infusion of midazolam or propofol together with continuous EEG monitoring is the preferred mode of treatment.[8,64] Both agents have been reported[10,65–77] to be successful in the control of patients with refractory status epilepticus. It should, however, be pointed out that this recommendation is based on limited clinical data, with just > 100 cases of treatment with these agents having been reported.[64,67]

Claassen and colleagues[64] reported a "systematic review" that compared the outcome of patients with refractory status epilepticus who had been treated with pentobarbital, propofol, or midazolam. In this report, there were fewer treatment failures and breakthrough seizures with the use of pentobarbital than with the use of propofol or midazolam. As this study was a summation of 28 individual case series that did not control for the underlying medical condition, the cause of seizure, type of seizure, length of time prior to treatment, prior therapy, and end points of therapy, it is difficult to make any definitive conclusions regarding drug efficacy from this report.

The goal regarding the activity on the EEG remains a matter of debate. There is no prospectively collected evidence that a burst-suppression EEG pattern is required for, or is efficacious for, the termination of status epilepticus. Many patients can achieve complete seizure control with a background of continuous slow activity and do not incur the greater risks associated with higher doses of medication required to achieve a burst-suppression pattern.

Midazolam is a fast-acting, water-soluble benzodiazepine with a half-life of 4 to 6 h. The drug undergoes hepatic transformation into an active metabolite that is renally cleared. One of the major disadvantages of midazolam is tachyphylaxis. After 24 to 48 h, the dose of the drug often must be increased severalfold to maintain seizure control. Furthermore, the drug accumulates with prolonged infusion, which may result in a prolonged time to

awakening.[69,78] Midazolam is given as a loading dose of 0.2 mg/kg, followed by an infusion of 0.1 to 2.0 mg/kg/h titrated to produce seizure suppression by continuous EEG monitoring.

Propofol is an IV alkylphenol (2,6-diisopropylphenol), which has been used extensively for the induction and maintenance of anesthesia and for sedation in the ICU.[79] Propofol is a global CNS depressant. It directly activates the GABA receptor.[79,80] In addition, propofol inhibits the NMDA receptor, modulates calcium influx through slow calcium ion channels, and has antioxidant activity.[81–87] Experimental data have shown propofol to have strong anticonvulsant properties,[88–92] which have proved to be very effective in controlling refractory status epilepticus.[10,71–77,93] Propofol is highly lipophilic with a large volume of distribution. This property results in rapid uptake and elimination from the CNS, resulting in rapid onset of action and rapid recovery when discontinued. Recovery is rapid even with prolonged use. Propofol is metabolized by glucuronide and sulfate conjugation, and does not accumulate with long-term infusion. Dose reduction is not required in patients with hepatic or renal disease. Furthermore, the drug is easily titratable. A loading dose of 3 to 5 mg/kg is recommended followed by an infusion of 30 to 100 μg/kg/min titrated to EEG seizure suppression. After 12 h of seizure suppression, the dose is gradually titrated by 50% over the next 12 h and then titrated to 0% over the subsequent 12 h. If seizure activity should recur during the weaning period, a further loading dose of 1 to 3 mg/kg should be administered followed by infusion with the rate increased to obtain another 12-h seizure-free period.[71]

Propofol has been administered to >40 million patients with a remarkable safety record. The most severe complication associated with propofol is the "propofol infusion syndrome," a very rare complication reported predominantly in pediatric patients and associated with high-dose propofol infusion.[94–96] The propofol infusion syndrome is characterized by severe metabolic acidosis, rhabdomyolysis, and cardiovascular collapse frequently leading to death.[94–96] Circumstantial data suggest that this disorder is due to interference with mitochondrial respiration.[97–100] It is possible that the full-blown propofol infusion syndrome occurs only in those individuals with a genetic susceptibility. However, the risk appears to be higher in children, in whom the drug is contraindicated. It is currently recommended that the dosage not exceed 100 μg/kg/min in adults.[94,101,102] Hyperlipidemia may result from the failure of free fatty acid metabolism and hence may be a useful early marker of the development of the syndrome. Consequently, triglyceride and creatine kinase levels (a marker of rhabdomyolysis) should be monitored in patients receiving prolonged high-dose infusions of propofol.

High-dose barbiturate therapy is associated with hemodynamic instability and immune paresis. Due to their side effects, therapy with barbiturates is reserved for those patients who do not respond to midazolam or propofol. Pentobarbital therapy, in a dose of 10 to 15 mg/kg/h followed by a dose of 0.5 to 1.0 mg/kg/h, is recommended. The pharmacologic approach to a patient in status epilepticus is outlined in Figure 1.

The Management of Nonconvulsive Status Epilepticus

Nonconvulsive status epilepticus constitutes approximately 20 to 25% of status epilepticus cases,[103,104] occurring in about 8% of all comatose patients without clinical signs of seizure activity,[28] and persisting in 14% of patients after generalized convulsive status epilepticus.[63] Some have suggested[104–107] that nonconvulsive status epilepticus is a benign condition that does not require aggressive therapy. However, the prognosis of nonconvulsive status epilepticus depends on the etiology and the level of consciousness. These are associated with significant morbidity in those patients with a depressed level of consciousness.[108–110] Furthermore, experimental and clinical data suggest that nonconvulsive status epilepticus may cause ongoing neuronal injury.[42,43,48–51] Shneker and Fountain[111] reviewed their experience with 100 cases of nonconvulsive status epilepticus. In this report, nonconvulsive status epilepticus was associated with a high mortality rate (18%) and a significant morbidity rate (39%), with the mortality rate correlating with the underlying etiology of nonconvulsive status epilepticus, the degree of impairment in mental status, and the development of acute complications. The mortality rate was 18% in those patients with cryptogenic nonconvulsive status epilepticus, attesting to the serious sequelae of ongoing seizures. Based on this information, we suggest that comatose patients with nonconvulsive status epilepticus and nonconvulsive status epilepticus following generalized convulsive status epilepticus be treated aggressively as outlined above for refractory convulsive status epilepticus.

Prevention of Seizure Recurrence Once Status Epilepticus Is Terminated

Once status epilepticus is controlled, attention turns to preventing its recurrence. The best regimen

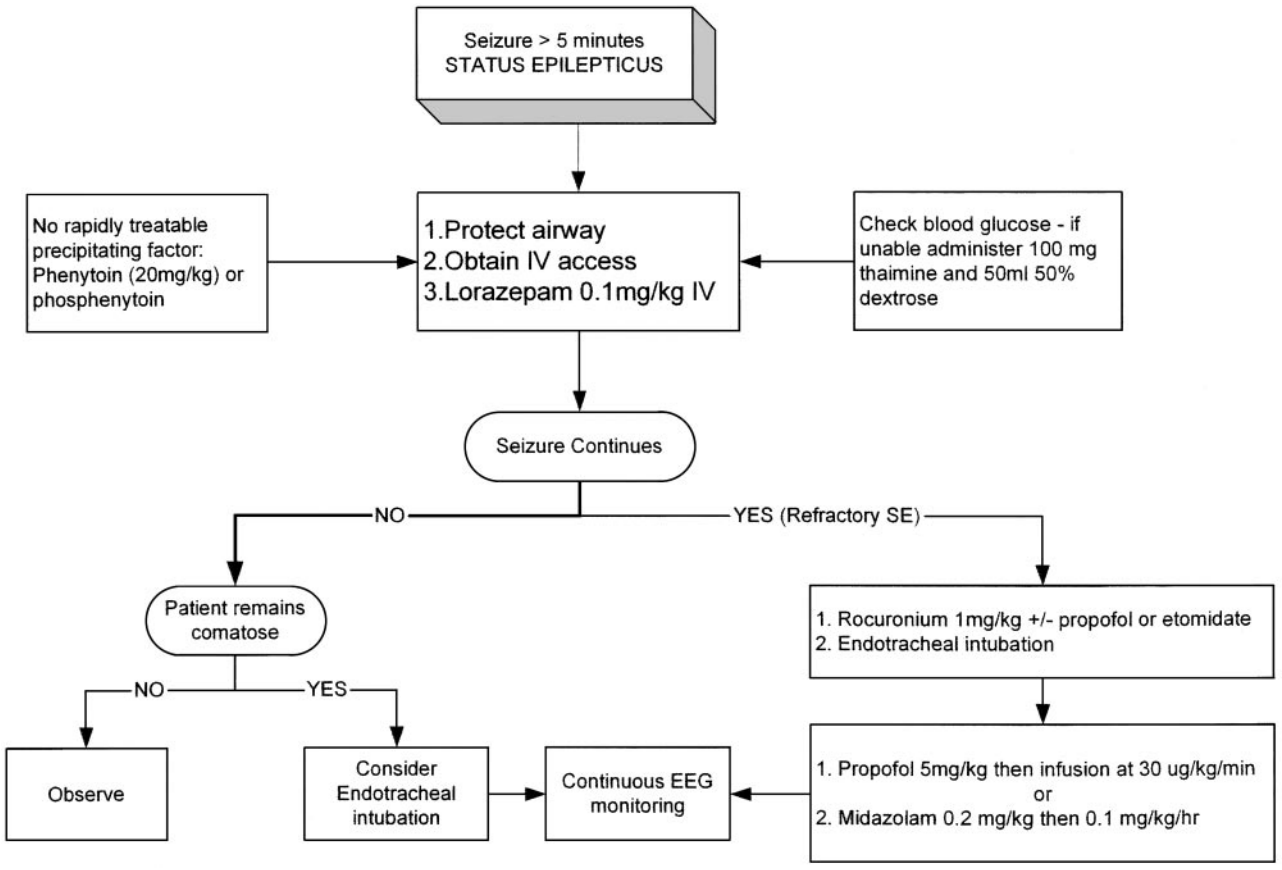


FIGURE 1. The pharmacologic approach to a patient in status epilepticus.

for an individual patient will depend on the cause of the seizure and any history of antiepileptic drug therapy. A patient who develops status epilepticus in the course of ethanol withdrawal may not need antiepileptic drug therapy once the withdrawal has run its course. In contrast, patients with new, ongoing epileptogenic stimuli (*eg*, encephalitis) may require high dosages of antiepileptic drugs to control their seizures.

PROGNOSIS

The prognosis of status epilepticus depends on several factors including the clinical presentation, the duration of seizures, the age of the patient, and, most importantly, the underlying disorder causing the seizures.[1] Refractory status epilepticus has a mortality rate of up to 76% in elderly patients.[1] In a population-based, long-term mortality study,[1] the 10-year cumulative mortality rate among 30-day survivors was 43%, with a standardized mortality ratio of 2.8. However, the mortality rate of those patients with idiopathic status epilepticus was not increased (standardized mortality ratio, 1.1).

CONCLUSIONS

Patients who have generalized seizures that continue for more than 5 min should be considered to have status epilepticus and should be treated with a single IV dose of lorazepam (0.1 mg/kg). Patients who continue to have clinical or EEG evidence of seizure activity after receiving treatment with lorazepam should be considered to have refractory status epilepticus and should treated with a continuous infusion of propofol or midazolam.

REFERENCES

1 Logroscino G, Hesdorffer DC, Cascino GD, et al. Long-term mortality after a first episode of status epilepticus. Neurology 2002; 58:537–541
2 Epilepsy Foundation of America. Treatment of convulsive status epilepticus: recommendations of the Epilepsy Foundation of America's Working Group on Status Epilepticus. JAMA 1993; 270:854–859
3 Lowenstein DH, Alldredge BK. Status epilepticus. N Engl J Med 1998; 338:970–976
4 Chapman MG, Smith M, Hirsch NP. Status epilepticus. Anaesthesia 2001; 56:648–659
5 Lowenstein DH, Bleck T, Macdonald RL. It's time to revise the definition of status epilepticus. Epilepsia 1999; 40:120–122

6 DeLorenzo RJ, Garnett LK, Towne AR, et al. Comparison of status epilepticus with prolonged seizure episodes lasting from 10 to 29 minutes. Epilepsia 1999; 40:164–169
7 Walton NY, Treiman DM. Response of status epilepticus induced by lithium and pilocarpine to treatment with diazepam. Exp Neurol 1988; 101:267–275
8 Mayer SA, Claassen J, Lokin J, et al. Refractory status epilepticus: frequency, risk factors, and impact on outcome. Arch Neurol 2002; 59:205–210
9 Treiman DM, Meyers PD, Walton NY. A comparison of four treatments for generalized convulsive status epilepticus: Veterans Affairs Status Epilepticus Cooperative Study Group. N Engl J Med 1998; 339:792–798
10 Prasad A, Worrall BB, Bertram EH, et al. Propofol and midazolam in the treatment of refractory status epilepticus. Epilepsia 2001; 42:380–386
11 Bleck TP. Management approaches to prolonged seizures and status epilepticus. Epilepsia 1999; 40(suppl):S59–S63
12 Browne TR, Holmes GL. Epilepsy. N Engl J Med 2001; 344:1145–1151
13 DeLorenzo RJ, Pellock JM, Towne AR, et al. Epidemiology of status epilepticus. J Clin Neurophysiol 1995; 12:316–325
14 Wu YW, Shek DW, Garcia PA, et al. Incidence and mortality of generalized convulsive status epilepticus in California. Neurology 2002; 58:1070–1076
15 Hesdorffer DC, Logroscino G, Cascino G, et al. Incidence of status epilepticus in Rochester, Minnesota, 1965–1984. Neurology 1998; 50:735–741
16 Knake S, Rosenow F, Vescovi M, et al. Incidence of status epilepticus in adults in Germany: a prospective, population-based study. Epilepsia 2001; 42:714–718
17 DeGiorgio CM, Altman K, Hamilton-Byrd E, et al. Lidocaine in refractory status epilepticus: confirmation of efficacy with continuous EEG monitoring. Epilepsia 1992; 33:913–916
18 Coeytaux A, Jallon P, Galobardes B, et al. Incidence of status epilepticus in French-speaking Switzerland: (EPISTAR). Neurology 2000; 55:693–697
19 Parviainen I, Uusaro A, Kalviainen R, et al. High-dose thiopental in the treatment of refractory status epilepticus in intensive care unit. Neurology 2002; 59:1249–1251
20 Hauser WA. Status epilepticus: epidemiologic considerations. Neurology 1990; 40:9–13
21 Ramsay RE, Pryor F. Epilepsy in the elderly. Neurology 2000; 55:S9–S14
22 Lowenstein DH, Alldredge BK, Allen F, et al. The prehospital treatment of status epilepticus (PHTSE) study: design and methodology. Control Clin Trials 2001; 22:290–309
23 Alldredge BK, Lowenstein DH. Status epilepticus: new concepts. Curr Opin Neurol 1999; 12:183–190
24 Corey LA, Pellock JM, Boggs JG, et al. Evidence for a genetic predisposition for status epilepticus. Neurology 1998; 50:558–560
25 Alldredge BK, Gelb AM, Isaacs SM, et al. A comparison of lorazepam, diazepam, and placebo for the treatment of out-of-hospital status epilepticus. N Engl J Med 2001; 345:631–637
26 Dennis LJ, Claassen J, Hirsch LJ, et al. Nonconvulsive status epilepticus after subarachnoid hemorrhage. Neurosurgery 2002; 51:1136–1143
27 Krieger AC, Takeyasu M. Nonconvulsive status epilepticus in theophylline toxicity. J Toxicol Clin Toxicol 1999; 37:99–101
28 Towne AR, Waterhouse EJ, Boggs JG, et al. Prevalence of nonconvulsive status epilepticus in comatose patients. Neurology 2000; 54:340–345
29 Rumbach L, Sablot D, Berger E, et al. Status epilepticus in stroke: report on a hospital-based stroke cohort. Neurology 2000; 54:350–354
30 Dixit S, Kurle P, Buyan-Dent L, et al. Status epilepticus associated with cefepime. Neurology 2000; 54:2153–2155
31 Martinez-Rodriguez JE, Barriga FJ, Santamaria J, et al. Nonconvulsive status epilepticus associated with cephalosporins in patients with renal failure. Am J Med 2001; 111:115–119
32 Labovitz DL, Hauser WA, Sacco RL. Prevalence and predictors of early seizure and status epilepticus after first stroke. Neurology 2001; 57:200–206
33 Boggs JG, Painter JA, DeLorenzo RJ. Analysis of electrocardiographic changes in status epilepticus. Epilepsy Res 1993; 14:87–94
34 Rice AC, DeLorenzo RJ. NMDA receptor activation during status epilepticus is required for the development of epilepsy. Brain Res 1998; 782:240–247
35 Pal S, Sombati S, Limbrick DD Jr, et al. *In vitro* status epilepticus causes sustained elevation of intracellular calcium levels in hippocampal neurons. Brain Res 1999; 851: 20–31
36 Bleck TP. Refractory status epilepticus in 2001. Arch Neurol 2002; 59:188–189
37 Kapur J, Stringer JL, Lothman EW. Evidence that repetitive seizures in the hippocampus cause a lasting reduction of GABAergic inhibition. J Neurophysiol 1989; 61:417–426
38 Kapur J, Lothman EW. Loss of inhibition precedes delayed spontaneous seizures in the hippocampus after tetanic electrical stimulation. J Neurophysiol 1989; 61:427–434
39 Kapur J, Macdonald RL. Rapid seizure-induced reduction of benzodiazepine and Zn2+ sensitivity of hippocampal dentate granule cell GABAA receptors. J Neurosci 1997; 17: 7532–7540
40 Walton NY, Treiman DM. Motor and electroencephalographic response of refractory experimental status epilepticus in rats to treatment with MK-801, diazepam, or MK-801 plus diazepam. Brain Res 1991; 553:97–104
41 Borris DJ, Bertram EH, Kapur J. Ketamine controls prolonged status epilepticus. Epilepsy Res 2000; 42:117–122
42 During MJ, Spencer DD. Extracellular hippocampal glutamate and spontaneous seizure in the conscious human brain. Lancet 1993; 341:1607–1610
43 Lowenstein DH, Simon RP, Sharp FR. The pattern of 72-kDa heat shock protein-like immunoreactivity in the rat brain following flurothyl-induced status epilepticus. Brain Res 1990; 531:173–182
44 Tanaka K, Graham SH, Simon RP. The role of excitatory neurotransmitters in seizure-induced neuronal injury in rats. Brain Res 1996; 737:59–63
45 Meldrum BS, Brierley JB. Prolonged epileptic seizures in primates: ischemic cell change and its relation to ictal physiological events. Arch Neurol 1973; 28:10–17
46 Nevander G, Ingvar M, Auer R, et al. Status epilepticus in well-oxygenated rats causes neuronal necrosis. Ann Neurol 1985; 18:281–290
47 Wasterlain CG, Fujikawa DG, Penix L, et al. Pathophysiological mechanisms of brain damage from status epilepticus. Epilepsia 1993; 34(suppl):S37–S53
48 DeGiorgio CM, Gott PS, Rabinowicz AL, et al. Neuron-specific enolase, a marker of acute neuronal injury, is increased in complex partial status epilepticus. Epilepsia 1996; 37:606–609
49 Rabinowicz AL, Correale JD, Bracht KA, et al. Neuron-specific enolase is increased after nonconvulsive status epilepticus. Epilepsia 1995; 36:475–479
50 Rabinowicz AL, Correale JD, Couldwell WT, et al. CSF neuron-specific enolase after methohexital activation during

electrocorticography. Neurology 1994; 44:1167–1169
51 DeGeorgio CM, Correale JD, Ginsburg DL. Serum neuron specific enolase in status epilepticus [abstract]. Neurology 1994; 44(suppl):205
52 Thom M, Seetah S, Sisodiya S, et al. Sudden and unexpected death in epilepsy (SUDEP): evidence of acute neuronal injury using HSP-70 and c-Jun immunohistochemistry. Neuropathol Appl Neurobiol 2003; 29:132–143
53 Mikati MA, Abi-Habib RJ, El Sabban ME, et al. Hippocampal programmed cell death after status epilepticus: evidence for NMDA-receptor and ceramide-mediated mechanisms. Epilepsia 2003; 44:282–291
54 Lothman E. THe biochemical basis and pathophysiology of status epilepticus. Neurology 2003; 40(suppl):13–23
55 Coplin WM, Pierson DJ, Cooley KD, et al. Implications of extubation delay in brain-injured patients meeting standard weaning criteria. Am J Respir Crit Care Med 2000; 161: 1530–1536
56 Yeoman P, Hutchinson A, Byrne A, et al. Etomidate infusions for the control of refractory status epilepticus. Intensive Care Med 1989; 15:255–259
57 Wauquier A. Profile of etomidate: a hypnotic, anticonvulsant and brain protective compound. Anaesthesia 1983; 38(suppl):26–33
58 Marshall RJ, Muir AW, Sleigh T, et al. An overview of the pharmacology of rocuronium bromide in experimental animals. Eur J Anaesthesiol Suppl 1994; 9:9–15
59 Hudson ME, Rothfield KP, Tullock WC, et al. Haemodynamic effects of rocuronium bromide in adult cardiac surgical patients. Can J Anaesth 1998; 45:139–143
60 Leppik IE, Derivan AT, Homan RW, et al. Double-blind study of lorazepam and diazepam in status epilepticus. JAMA 1983; 249:1452–1454
61 Mitchell WG. Status epilepticus and acute repetitive seizures in children, adolescents, and young adults: etiology, outcome, and treatment. Epilepsia 1996; 37(suppl):S74–S80
62 Gottwald MD, Akers LC, Liu PK, et al. Prehospital stability of diazepam and lorazepam. Am J Emerg Med 1999; 17:333–337
63 DeLorenzo RJ, Waterhouse EJ, Towne AR, et al. Persistent nonconvulsive status epilepticus after the control of convulsive status epilepticus. Epilepsia 1998; 39:833–840
64 Claassen J, Hirsch LJ, Emerson RG, et al. Treatment of refractory status epilepticus with pentobarbital, propofol, or midazolam: a systematic review. Epilepsia 2002; 43:146–153
65 Koul RL, Raj AG, Chacko A, et al. Continuous midazolam infusion as treatment of status epilepticus. Arch Dis Child 1997; 76:445–448
66 Igartua J, Silver P, Maytal J, et al. Midazolam coma for refractory status epilepticus in children. Crit Care Med 1999; 27:1982–1985
67 Ulvi H, Yoldas T, Mungen B, et al. Continuous infusion of midazolam in the treatment of refractory generalized convulsive status epilepticus. Neurol Sci 2002; 23:177–182
68 Singhi S, Murthy A, Singhi P, et al. Continuous midazolam versus diazepam infusion for refractory convulsive status epilepticus. J Child Neurol 2002; 17:106–110
69 Naritoku DK, Sinha S. Prolongation of midazolam half-life after sustained infusion for status epilepticus. Neurology 2000; 54:1366–1368
70 Claassen J, Hirsch LJ, Emerson RG, et al. Continuous EEG monitoring and midazolam infusion for refractory nonconvulsive status epilepticus. Neurology 2001; 57:1036–1042
71 Stecker MM, Kramer TH, Raps EC, et al. Treatment of refractory status epilepticus with propofol: clinical and pharmacokinetic findings. Epilepsia 1998; 39:18–26
72 Harrison AM, Lugo RA, Schunk JE. Treatment of convulsive status epilepticus with propofol: case report. Pediatr Emerg Care 1997; 13:420–422
73 Merigian KS, Browning RG, Leeper KV. Successful treatment of amoxapine-induced refractory status epilepticus with propofol. Acad Emerg Med 1995; 2:128–133
74 Tobias JD. The use of propofol to treat status epilepticus in a nine-month-old female patient. Pediatr Emerg Care 1998; 14:248–249
75 Pitt-Miller PL, Elcock BJ, Maharaj M. The management of status epilepticus with a continuous propofol infusion. Anesth Analg 1994; 78:1193–1194
76 Campostrini R, Bati MB, Giorgi C, et al. Propofol in the treatment of convulsive status epilepticus: a report of four cases. Riv Neurol 1991; 61:176–179
77 Mackenzie SJ, Kapadia F, Grant IS. Propofol infusion for control of status epilepticus. Anaesthesia 1990; 45:1043–1045
78 Hall RI, Sandham D, Cardinal P, et al. Propofol vs midazolam for ICU sedation: a Canadian multicenter randomized trial. Chest 2001; 119:1151–1159
79 Smith I, White PF, Nathanson M, et al. Propofol: an update on its clinical use. Anesthesiology 1994; 81:1005–1043
80 Hara M, Kai Y, Ikemoto Y. Propofol activates GABAA receptor-chloride ionophore complex in dissociated hippocampal pyramidal neurons of the rat. Anesthesiology 1993; 79:781–788
81 Orser BA, Bertlik M, Wang LY, et al. Inhibition by propofol (2,6 di-isopropylphenol) of the N-methyl-D-aspartate subtype of glutamate receptor in cultured hippocampal neurones. Br J Pharmacol 1995; 116:1761–1768
82 Hans P, Bonhomme V, Collette J, et al. Propofol protects cultured rat hippocampal neurons against N-methyl-D-aspartate receptor-mediated glutamate toxicity. J Neurosurg Anesthesiol 1994; 6:249–253
83 Zhou W, Fontenot J, Liu S, et al. Modulation of cardiac calcium channels by propofol. Anesthesiology 1997; 86:670–675
84 Olcese R, Usai C, Maestrone E, et al. The general anesthetic propofol inhibits transmembrane calcium current in chick sensory neurons. Anesth Analg 1994; 78:955–960
85 Green TR, Bennett SR, Nelson VM. Specificity and properties of propofol as an antioxidant free radical scavenger. Toxicol Appl Pharmacol 1994; 129:163–169
86 Tsuchiya M, Asada A, Maeda K, et al. Propofol versus midazolam regarding their antioxidant activities. Am J Respir Crit Care Med 2001; 163:26–31
87 Grasshoff C, Gillessen T. The effect of propofol on increased superoxide concentration in cultured rat cerebrocortical neurons after stimulation of N-methyl-d-aspartate receptors. Anesth Analg 2002; 95:920–922
88 Holtkamp M, Tong X, Walker MC. Propofol in subanesthetic doses terminates status epilepticus in a rodent model. Ann Neurol 2001; 49:260–263
89 Lee VC, Moscicki JC, DiFazio CA. Propofol sedation produces dose-dependent suppression of lidocaine-induced seizures in rats. Anesth Analg 1998; 86:652–657
90 Momota Y, Artru AA, Powers KM, et al. Posttreatment with propofol terminates lidocaine-induced epileptiform electroencephalogram activity in rabbits: effects on cerebrospinal fluid dynamics. Anesth Analg 1998; 87:900–906
91 Hasan Z, Hasan M, al Hader A, et al. A comparison of the anticonvulsant effects of propofol and thiopentone against pentylenetetrazol-induced convulsions in the rat. Clin Exp Pharmacol Physiol 1991; 18:691–695
92 Lowson S, Gent JP, Goodchild CS. Anticonvulsant properties of propofol and thiopentone: comparison using two tests in laboratory mice. Br J Anaesth 1990; 64:59–63

93 Hantson P, Van Brandt N, Verbeeck R, et al. Propofol for refractory status epilepticus. Intensive Care Med 1994; 20:611–612
94 Vasile B, Rasulo F, Candiani A, et al. The pathophysiology of propofol infusion syndrome: a simple name for a complex syndrome. Intensive Care Med 2003; 29:1417–1425
95 Parke TJ, Stevens JE, Rice AS, et al. Metabolic acidosis and fatal myocardial failure after propofol infusion in children: five case reports. BMJ 1992; 305:613–616
96 Kang TM. Propofol infusion syndrome in critically ill patients. Ann Pharmacother 2002; 36:1453–1456
97 Branca D, Roberti MS, Lorenzin P, et al. Influence of the anesthetic 2,6-diisopropylphenol on the oxidative phosphorylation of isolated rat liver mitochondria. Biochem Pharmacol 1991; 42:87–90
98 Branca D, Vincenti E, Scutari G. Influence of the anesthetic 2,6-diisopropylphenol (propofol) on isolated rat heart mitochondria. Comp Biochem Physiol C Pharmacol Toxicol Endocrinol 1995; 110:41–45
99 Rigoulet M, Devin A, Averet N, et al. Mechanisms of inhibition and uncoupling of respiration in isolated rat liver mitochondria by the general anesthetic 2,6-diisopropylphenol. Eur J Biochem 1996; 241:280–285
100 Schenkman KA, Yan S. Propofol impairment of mitochondrial respiration in isolated perfused guinea pig hearts determined by reflectance spectroscopy. Crit Care Med 2000; 28:172–177
101 McKeage K, Perry CM. Propofol: a review of its use in intensive care sedation of adults. CNS Drugs 2003; 17:235–272
102 Short TG, Young Y. Toxicity of intravenous anaesthetics. Best Pract Res Clin Anaesthesiol 2003; 17:77–89
103 Celesia G. Modern concepts of status epilepticus. JAMA 1976; 235:1571–1574
104 Dunne JW, Summers QA, Stewart-Wynne EG. Non-convulsive status epilepticus: a prospective study in an adult general hospital. Q J Med 1987; 62:117–126
105 Tomson T, Lindbom U, Nilsson BY. Nonconvulsive status epilepticus in adults: thirty-two consecutive patients from a general hospital population. Epilepsia 1992; 33:829–835
106 Cockerell OC, Walker MC, Sander JW, et al. Complex partial status epilepticus: a recurrent problem. J Neurol Neurosurg Psychiatry 1994; 57:835–837
107 Aminoff MJ. Do nonconvulsive seizures damage the brain? No. Arch Neurol 1998; 55:119–120
108 Kaplan PW. No, some types of nonconvulsive status epilepticus cause little permanent neurologic sequelae (or: "the cure may be worse than the disease"). Neurophysiol Clin 2000; 30:377–382
109 Kaplan PW. Assessing the outcomes in patients with nonconvulsive status epilepticus: nonconvulsive status epilepticus is underdiagnosed, potentially overtreated, and confounded by comorbidity. J Clin Neurophysiol 1999; 16:341–352
110 Kaplan PW. Prognosis in nonconvulsive status epilepticus. Epileptic Disord 2000; 2:185–193
111 Shneker BF, Fountain NB. Assessment of acute morbidity and mortality in nonconvulsive status epilepticus. Neurology 2003; 61:1066–1073

Detroit Medical Center
Wayne State University

HYPTERTONIC SOLUTION USE IN BRAIN-INJURED PATIENTS

Calculation and Preparation of Hypertonic Solutions

Sodium Acetate for injection (20 ml)
Concentration: 2meq/ml **(164mg/ml)**
Molecular weight: Sodium acetate: 82

Sodium Chloride for injection (20 ml)
Concentration (14.6%): 2.5meq/ml **(146mg/ml)**
Molecular weight: Sodium chloride: 58.5

Meq (milliequivalents)= mg(milligrams substance) * valence
mw (molecular weight)

Weight-in-Volume Calculation:
% of substance= number of grams
100 ml
eg., 1 liter of 3% NaCl = 3 grams OR 30 grams per liter
100 ml

I. Preparation of 3% NaCl (1 liter)

Note: 3% NaCl is available in pre-mixed bags (500 ml)
If Pre-mix not available:

1. 3% Na solution= 3 grams/100 ml = 30 grams/ liter needed
   30 grams= 30,000 mg
2. 30,000 mg * 1ml = *205 ml of 14.6% NaCl needed*
   146 mg

Ans: **Use pre-mixed bags. If not available, withdraw 205 ml from a 1 liter bag of Sterile Water for injection; then add 205 ml of 14.6% NaCl.**

II. **Preparation of 3% Na acetate (1 liter)**

1. 3% Na solution= 3 grams/100 ml = 30 grams/ liter needed
   30 grams= 30,000 mg
2. 30,000 mg * 1 ml / 164 mg = *183 ml of Na acetate needed*

Ans: **Withdraw 183 ml from a 1 liter bag of Sterile Water for injection; then add 183 ml of 2meq/ml Na acetate.**

III. **Preparation of 3% hypertonic NaCl/Na acetate (50:50) solution**

1. 3% Na solution= 3 grams/100 ml = 30 grams/ liter needed
   30 grams= 30,000 mg; give half as NaCl and half as Na acetate
   15 grams NaCl + 15 grams Na acetate= 30 grams total
2. 15,000 mg * $\frac{1 \text{ ml}}{146 \text{ mg}}$ = 102.5 or *103 ml 14.6% NaCl needed*

   15,000 mg * $\frac{1 \text{ ml}}{164 \text{ mg}}$ = 91.5 or *92 ml Na acetate needed*

Ans: **Withdraw 195 ml from a 1 liter bag of Sterile Water for injection; then add 103 ml 14.6% NaCl and 92 ml of Na acetate.**

IV. **Preparation of 2% hypertonic NaCl/Na acetate (50:50) solution**

1. 2% Na solution= 2 grams/100 ml = 20 grams/ liter needed
   20grams =20,000 mg; give half as NaCl and half as Na acetate
   10 grams NaCl + 10 grams Na acetate =20 grams total
2. 10,000 mg * $\frac{1 \text{ ml}}{146 \text{ mg}}$ = 68.3 or *68 ml of 14.6% NaCl needed*

   10,000 mg * $\frac{1 \text{ ml}}{164 \text{ mg}}$ = 61 ml *Na acetate needed*

Ans: **Withdraw 130 ml from a 1 liter bag of Sterile Water for injection; then add 68 ml 14.6% NaCl and 61 ml of Na acetate.**

Aurora Health Care®

IV ANTI-INFECTIVE MEDICATION DOSING IN CRRT

(Continuous Renal Replacement Therapy)

IV Anti-infective Medications	Recommended dose for CrCl <50 ml/min	CVVH Dose (Continuous Venovenous Hemofiltration)	CVVHD Dose (Continuous Venovenous Hemodialysis)	CVVHDF Dose (Continuous Venovenous Hemodiafiltration)
Acyclovir (Zovirax®)	5 - 10 mg/kg q8h	5 mg/kg q12h		
Amikacin	5 – 7.5 mg/kg q8h	7.5 mg/kg q24h		
Amphotericin B	0.25 – 1 mg/kg q24h (max daily dose 1.5mg/kg)	NO CHANGE		
Amphotericin B Lipid Complex (ABLC, Abelcet®)	3 – 5 mg/kg q24h	NO CHANGE		
Aztreonam (Azactam®)	1 - 2 gm q8-12h	2 gm load, then 1 gm q12h **(CVVHDF: consider 2gm q12h for severe infxn)**		
Ampicillin/Sulbactam (Unasyn®)	1.5 – 3 gm q6h	1.5 – 3 gm q8-12h	1.5 – 3 gm q8-12h	1.5 – 3 gm q6-8h
Azithromycin (Zithromax®)	500 mg load, then 250-500 mg q24h	NO CHANGE		
Cefazolin (Ancef®)	1 – 2 gm q8h	1 gm q8-12h	1 gm q8h	1 gm q8h or 2gm q12h
Cefepime (Maxipime®)	1 - 2 gm q12h	2 gm load, then 1 gm q12h		2 gm q12h
Cefotaxime (Claforan®)	1 – 2 gm q6-12h	1 gm q8-12h		1 gm q6-8h
Ceftazadime (Fortaz®)#	1 gm q8-12h	2 gm load, then 1 gm q12h **(CVVHDF:consider 2gm q12 for severe infxn/high UFR orDFR)**		
Ceftriaxone (Rocephin®)	1 – 2 gm q24h	1 – 2 gm q24h		
Cefuroxime (Zinacef®)	1.5 gm q8h	1.5 gm q8-12h	1.5 gm q8h	
Ciprofloxacin	400 mg q8-12h	400 mg q24h	400 mg q12h	
Clindamycin	600 mg q6h/900mg q8h	NO CHANGE		
Doxycycline	100 – 200 mg q12h	NO CHANGE		
Fluconazole (Diflucan®)	200 – 800 mg q24h	200 – 400 mg q24h (consider 400 mg load)		400 – 800 mg q24h
Ganciclovir (Cytovene®)	5 mg/kg q12h	2 mg/kg q24h	2 – 3 mg/kg q24h	2.5 mg/kg q12h
Gatifloxacin (Tequin®)	400 mg q24h	400 mg q24h		
Gentamicin	1.5 – 2.5 mg/kg q8h	2mg/kg load, 1.5-2 mg/kg q24 ***(individualize dosing)*		
Imipenem/cilastatin (Primaxin®)	500 mg q6h	500 mg q8h	500 mg q6-8h	

Medications	CrCl >50 ml/min	CVVH	CVVHD	CVVHDF
Itraconazole (Sporanox®)	200 mg q12h	NO CHANGE Caution: in severe renal impairment (CrCl < 30ml/min), the clearance of hydroxypropyl-β-cyclodextrin (an excipient in the iv formulation) is reduced.		
Levofloxacin (Levaquin®)#	500 mg q24h	500 mg q24h		
Linezolid (Zyvox®)	600 mg q12h	NO CHANGE		
Meropenem (Merrem®)	1 – 2 gm q8h	1 gm q12h	1gm q12h or 500mg q8h	1 gm q8 – 12h
Metronidazole (Flagyl®)	500 mg q6-8h	500 mg q8h		
Nafcillin	1 – 2 gm q4-6h	NO CHANGE		
Penicillin	4 million units q4h	4 million units q8h	4 million units q6-8h	4 million units q4-6h
Pipercillin	3 - 4 gm q4-6h	3 - 4 gm q8-12h	3 – 4 gm q8h	3 – 4 gm q6h
Pipercillin/tazobactam (Zosyn®)	3.375 gm q6h	2.25 - 3.375gm q8h (consider alt w/pip as tazo is less removed)		3.375 gm q6-8h (consider alt w/pip)
Quinupristin/dalfopristin (Synercid®)	7.5 mg/kg q8-12h	NO CHANGE		
Rifampin	300 – 600 mg q12h	NO CHANGE		
Ticarcillin	2 – 4 gm q4h	2 gm q6-8h	2 gm q6h	2 gm q4-6h
Ticarcillin/clavulanic acid (Timentin®)#	3.1 gm q4-6h	2 gm q8-12h	2 gm q6-8h	2 – 3.1 gm q6-8h
Tobramycin	1.5 – 2.5 mg/kg q8h	2mg/kg load, 1.5-2 mg/kg q24 ***(individualize dosing)*		
TMP/SMX (Bactrim®)	5 mg/kg TMP q6-8h	2.5 mg/kg TMP q8h (consider higher doses with CVVHDF)		
Vancomycin		15-20 mg/kg load then 10 mg/kg q24h ***(individualize dosing)*		15-20 mg/kg load; 7.5mg/kg q12h or 15mg/kg q24h ***(individualize dosing)*

*****The dosing recommendations presented here are based on published literature, personal experience, and clinical judgement. These recommendations should be used as "initial" guidelines and individualized dosing is advocated when possible.*****

These dosing recommendations are made on the assumption that the patient is in anuric/oliguric acute renal failure, has normal hepatic function and has a UFR and DFR of at least 1 Liter/hr each. Higher UFR and/or DFR may increase the potential for drug removal.

References are available in the Aurora Drug Information Center at St. Luke's Medical Center. The reference list and articles are filed under CRRT/Anti-infective Dosing Card. Any questions or comments, please, contact DI at (414) 649-5100 or Melissa Hentges, Pharm.D. at pager (414) 222-9600.

Abbreviations/Key:
# = nonformulary medication within Aurora Health Care
UFR = ultrafiltration rate
DFR = dialysate flow rate

10/01 mjh

Allaouchiche, B., et al. Pharmacokinetics of Cefepime during Continuous Hemodiafiltration. *Antimicrob Agents Chemother* 41(11): 2424-2427, Nov. 1997

Armendariz, E., Chelluri, L., Ptachinski, R. Pharmacokinetics of Amikacin during Continuous Veno-venous Hemofiltration. *Crit Care Med* 18(6): 675-676, 1990

Armstrong, D., Hidalgo, H., Eldadah, M. Vancomycin and Tobramycin Clearance in an Infant during Continuous Hemofiltration. *Ann Pharmacother* 27: 224-227, 1993

Bellomo, R., Ernest, D., Parkin, G., Boyce, N. Clearance of Vancomycin During Continuous Arteriovenous Hemodiafiltration. *Crit Care Med* 18(2): 181-183, Feb. 1990

Bellomo, R., Ronco, C., Mehta, R. Nomenclature for Continuous Renal Replacement Therapies. *Am J Kidney Dis* 28(5), Suppl 3: S 2-S 7, Nov. 1996

Bleyzac, N., et al. Assessment of Acyclovir Intraindividual Pharmacokinetic Variability during Continuous Hemofiltration, Continuous Hemodiafiltration, and Continuous Hemodialysis. *Ther Drug Monit* 21: 520-525, 1999

Boereboom, F., et al, Vancomycin Clearance During Continuous Hemofiltration in Critically Ill Patients. *Intensive Care Med* 25: 1100-1104, 1999

Bohler, J., Donauer, J., Keller, F. Pharmacokinetic Principles during Continuous Renal Replacement Therapy: Drugs and Dosage. *Kidney Int* 56(Suppl 72): S 24- S28, 1999

Boulieu, R., Bastien, O., Bleyzac, N. Pharmacokinetics of Ganciclovir in Heart Transplant Patients Undergoing Continuous Venovenous Hemodialysis. *Ther Drug Monit* 15(2): 105-107, 1993

Boulieu, R., Bastein, O., Gaillard, S., Flamens, C. Pharmacokinetics of Acyclovir in Patients Undergoing Continuous Venovenous Hemodialysis. *Ther Drug Monit* 19: 701-704, 1997

Bressolle, F., et al. Clinical Pharmacokinetics during Continuous Hemofiltration. *Clin Pharmacokinet* 26(6): 457-471, 1994

Brophy, P., McBryde, K., Mottes, T., Bunchman, T. Gentamicin and Vancomycin Dosing in a Pediatric Intensive Care Unit Population Receiving Renal Replacement Therapy (abstract). *Blood Purif* 18:61-90, 2000

Brunet, S., et al. Diffusive and Convective Solute Clearances during Continuous Renal Replacement Therapy at Various Dialysate and Ultrafiltration Flow Rates. *Am J Kidney Dis* 34(3): 486-492. Sept. 1999

Capellier G., et al. Removal of Piperacillin in Critically Ill Patients Undergoing Continuous Venovenous Hemofiltration. *Crit Care Med* 26(1):88-91, 1998

Coronel, B., et al. Itraconazole Concentrations during Continuous Hemodiafiltration. *J Antimicrob Chemother* 34:448-449, 1994

Cotterill, S. Antimicrobial Prescribing in Patients on Hemofiltration. *J Antimicro Chemother* 36: 773-780, 1995

Davies, S., Azadian B., Kox W., Brown, E. Pharmacokinetics of Ciprofloxacin and Vancomycin in Patients with Acute Renal Failure Treated by Continuous Hemodialysis. *Nephro Dial Transplant* 7: 848-854, 1992

De Bock, V., Berbeelen, D., Maes, V., Sennesael, J. Pharmacokinetics of Vancomycin in Patients Undergoing Hemodialysis and Hemofiltration. *Nephrol Dial Transplant* 4: 635-639, 1989

Dehne M., Kroh, U. Imipenem/Cilastin Dosage During Acute Renal Failure and Hemofiltration. *Intensive Care Med* 21: 863-864, 1995

Ernest, D., Cutler, D. Gentamicin Clearance During Continuous Arteriovenous Hemodiafiltration. *Crit Care Med* 20(5): 586-589, May 1992

Flanagan, P., Barnes, R. Hazards of Inadequate Fluconazole Dosage to Treat Deep-seated or Systemic *Candida albicans* Infection. *J Infect* 35:295-297, 1997

Gando, S., et al. Pharmacokinetics and Clearance of Ganciclovir During Continuous Hemodiafiltration. *Crit Care Med* 26(1):184-187, 1998

Giles, L., et al. Pharmacokinetics of Meropenem in Intesive Care Unit Patients Receiving Continuous Venovenous Hemofiltration or Hemodiafiltration. *Crit Care Med* 28(3): 632-637, March 2000

Hashimoto, S., et al. Pharmacokinetics of Imipenem and Cilastatin during Continuous Venovenous Hemofiltration in Patients Who are Critically Ill. *ASAIO Journal* 43: 84-88, 1997

Heinemann, V., et al . Pharmacokinetics of Liposomal Amphotericin B (Ambisome®) in Critically Ill Patients. *Antimicrob Agents Chemother* 41(6): 1275-1280, June 1997

Joos, B., Schmidli, M., Keusch, G. Pharmacokinetics of Antimicrobial Agents in Anuric Patients during Continuous Venovenous Hemofiltration. *Nephrol Dial Transplant* 11: 1582-1585, 1996

Joy, M., Matzke, G., Frye, R., Palevsky, P. Determinants of Vancomycin Clearance by Continuous Venovenous Hemofiltration and Continuous Venovenous Hemodialysis. *Am J Kidney Dis* 31(6):1019-1027, June 1998

Kishino, S., et al. Effective Fluconazole Therapy of Liver Transplant Recipients during Continuous Hemodiafiltration. *Ther Drug Monit* 23(1):4-8, 2001

Kroh, U., Lennartz, H., Edwards, D., Stoeckel, K. Pharmacokinetics of Ceftriaxone in Patients Undergoing Continuous Veno-venous Hemofiltration. *J Clin Pharmacol* 36:1114-1119, 1996

Krueger, W., et al. Pharmacokinetics of Meropenem in Critically Ill Patients with Acute Renal Failure Treated by Continuous Hemodiafiltration. *Antimicrob Agents Chemother* 42(9): 2421-2424, Sept. 1998

Lindsay, C., Bawdon, R., Quigley, R. Clearance of Ticarcillin-Clavulanic Acid by Continuous Venovenous Hemofiltration in Three Critically Ill Children, Two With and One Without Concomitant Extracorporeal Membrane Oxygenation. *Pharmcother* 16(3): 458-462, 1996

Malone, R., Fish, D., Abraham, E., Teitlbaum, I. Pharmacokinetics of Levofloxacin and Ciprofloxacin during Continuous Renal Replacement Therapy in Critically Ill Patients. *Antimicrob Agents Chemother* 45(10): 2949-2954, October 2001

Matzke, G., Frye, R., Joy, M., Palevsky, P. Determinants of Ceftazidime Clearance by Continuous Venovenous Hemofiltration and Continuous Venovenous Hemodialysis. *Antimicrob Agents Chemother* 44(6): 1639-1644, June 2000

Matzke, G., Frye, R., Joy, M., Palevsky, P. Determinants of Ceftriaxone Clearance by Continuous Venovenous Hemofiltration and Hemodialysis. *Pharmacother* 20(6):635-643, June 2000

Meyer, M., Munar, M., Kohlhepp, S., Bryant, R. Meropenem Pharmacokinetics in a Patient with Multiorgan Failure from Meningococcemia Undergoing Continous Venovenous Hemodiafiltration. *Am J Kidney Dis* 33(4): 790-795, Apr. 1995

Mueller, B., Scarim S., Macias, W. Comparison of Imipenem Pharmacokinetics in Patients with Acute or Chronic Renal Failure Treated with Continuous Hemofiltration. *Am J Kidney Dis* 21(2): 172-179, Feb. 1993

Mueller, B. CVVH Initial Dosing Guidelines. www.home.eznet.net/~webtent/cvvh-dosing.html May 2000

Munar M., Doyle, I., Meyer, M. Cyclosporine and Vancomycin Disposition During Continuous Venovenous Hemofiltration. *Ann Pharmcother* 29:374-377, April 1995

O'Rullian, J., et al. The Effects of Hemofiltration on Cefazolin Levels during Cardiopulmonary Bypass. *Perfusion* 13: 176-180, 1998

Reetze-Bonorden, P., Bohler, J., Keller, E. Drug Dosage in Patients during Continuous Renal Replacement Therapy: Pharmacokinetic and Therapeutic Considerations. *Clin Pharmacokinet* 24(5): 362-379, 1993

Robert, Rene, et al. Amikacin Pharmacokinetics during Continuous Veno-venous Hemofiltration (letter). *Crit Care Med* 19(4): 588-589, 1991

Rohde, B., et al. Pharmacokinetics of Mezlocillin and Sulbactam under Continuous Veno-venous Hemodialysis (CVVHD) in Intensive Care Patients with Acute Renal Failure. *Eur J Clin Pharmacol* 53: 111-115, 1997

Sante, Ch., et al. Pharmacokinetics of Vancomycin During Continuous Hemodiafiltration. *Int Care Med* 19: 347-350, 1993

Scholz, J., et al. Fluconazole is Removed by Continuous Venovenous Hemofiltration in a Liver Transplant Patient. *J Mol Med* 73:145-147, 1995

Singh, N., et al. Preemptive Prophylaxis with a Lipid Preparation of Amphotericin B for Invasive Fungal Infections in Liver Transplant Recipients Requiring Renal Replacement Therapy. *Transplantation* 71(7): 910-913, April 2001

Tegeder, I., et al. Pharmacokinetics of Imipenem-Cilstatin in Critically Ill Patients Undergoing Continuous Venovenous Hemofiltration. *Antimicrob Agents Chemother* 41(12): 2640-2645, Dec. 1997

Tegeder, I., et al. Pharmacokinetics of Meropenem in Critically Ill Patients with Acute Renal Failure Undergoing Continuous Venovenous Hemofiltration. *Clin Pharmacol Ther* 65(1): 50-57, 1999

Thalhammer, F., et al. Single-dose Pharmacokinetics of Meropenem During Continuous Venovenous Hemofiltration. *Antimicrob Agents Chemother* 42(9): 2417-2420, Sept. 1998

Thalhammer, F. Meropenem and Continuous Renal Replacement (letter). *Crit Care Med* 29(8): 1653-1654, Aug 2001

Valtonen, M., Tiula, E., Backman, J., Neuvonen, P. Elimination of Meropenem during Continuous Veno-venous Hemofiltration and Hemodiafiltration in Patients with Acute Renal Failure. *J Antimicrob Chemother* 45:701-704, 2000

van der Werf, T., et al. Pharmacokinetics of Piperacillin and Tazobactam in Critically ill Patients with Renal Failure, Treated with Continuous Venovenous Hemofiltration (CVVH). *Int Care Med* 23: 873-877, 1997

Ververs, T., et al, Pharmacokinetics and Dosing Regimen of Meropenem in Critically Ill Patients Receiving Continuous Venovenous Hemofiltration. *Crit Care Med* 28(10):3412-3416, 2000

Wolter K., Marggraf, G., Dermoumi, H., Fritschka, E. Elimination of Fluconazole during Continuous Veno-venous Hemodialysis (CVVHD) in A Single Patient. *Eur J Clin Pharmacol* 47:291-292, 1994

Detroit Medical Center
Wayne State University

Patient Identifier

Weight_____

Drotrecogin Alfa (Xigris®)

Medication Use Evaluation
Data Collection Form

******Photocopy order form and attach to data collection form******

1. Were DMC prescribing criteria were fully met? **θ YES** **θ NO**

a. Known or suspected infection ……θ YES θ NO
Type/location of infection_____
Organism isolated_____

b. SIRS (≥3)…… ……θ YES θ NO
θ Temp (≥38°C or ≤36°C)
θ WBC (≥ 12K or ≤ 4K or > 10% neutrophils)
θ HR (≥ 90 beats/min)
θ RR (≥ 20 or $PaCO_2$ ≤ 32 mmHg or mechanically ventilated)

c. Organ Dysfunction (at least one) ……θ YES θ NO
θ Hypotension θ Metabolic acidosis
θHypoxemia θThrombocytopenia
θ Oliguria

d. Contraindications……..….θ YES θ NO
If yes, what?
θAbsolute
Specify:_____
θRelative
Specify:_____

2. Did an approved DMC attending authorized use of the drug? θ YES θ NO

3. APACHE II score: (Please complete attached worksheet)
a. admission _____
b. 24 hrs prior to drotrecogin alfa_____

4. Did the patient experience adverse events associated with the drug? θ YES θ NO

If **yes**, what? θ Major bleeding

Site of bleed:_____

Magnitude of decrease in Hgb_____

Did patient receive a transfusion? θ YES θ NO
If yes, please quantify blood products given (on reverse)

Was drug infusion stopped? θ YES θ NO

Was infusion restarted? θ YES θ NO

θ Other

Explain:_____

θ Doctor Quality™ entry initiated θ YES θ NO

Other comments:_____
_____

5. Did patient survive hospitalization? θ YES θ NO

Length of ICU stay (days): _____

Total length of hospital stay (days): _____

If survived, patient was discharged to:

θ Rehabilitation θ Skilled-nursing facility

θ Home with care nurse θ Home

6. Were there any drug-related medication errors? θ YES θ NO

If **yes,** please explain:_____
_____

7. Was any drug wasted? θ YES θ NO

If **yes**, please explain: _____
_____

8. Was patient assessed for indigent reimbursement? θ YES θ NO

9. Was proper documentation of severe sepsis placed in chart? θ YES θ NO

Nutritional Support in the ICU
KristaWahby, Pharm D.
Harper University Hospital

Critically ill patients have increased metabolic rates and often have altered utilization of substrates. Malnutrition results in increased ventilatory dependence, infections and impaired wound healing. This often results in higher ICU and hospital length of stay as well.
Under stress the body exerts a rapid breakdown of protein and increases fat oxidation and energy expenditure.

Metabolic Issues in Critical Illness:

1. Glucose

–increased production
-decreased utilization
-impaired insulin secretion & activity
-Max. dextrose infusion is 5.75 gm/kg/day

2. Protein

-body protein breakdown
-increased urea production
-decreased tolerance, but increased requirements
-Max = 2 gm/kg/d

A. INDICATIONS FOR TPN:

- Unable to absorb nutrients via GI tract
  - small bowel resection/disease, radiation enteritis, intractable vomiting or diarrhea
- Patients receiving chemotherapy, radiation, BMT
- Moderate to severe pancreatitis
- Bowel obstruction, perforation or peritonitis
- Severe malnutrition with nonfunctional GIT
- Severe catabolism when GIT is not usable for > 5 days

B. ENTERAL NUTRITION*: If the Gut works….Use it!!*

a) Benefits of Using Enteral Route:
   - Maintains gut structure and function
   - More complete/physiologic formulations than TPN
   - Safety. Less hepatobiliary and metabolic complications
   - Decreased cost
   - No sterile technique required
   - Prevents/decreases *"bacterial translocation"*

b) Administration of Feedings:

<u>Continuous is preferred in the ICU</u>
   - Daily volume delivered over 24 hours
   - Risk of aspiration lower with continuous vs. intermittent
   - Tolerance may be better based of stool number, consistency
   - Start slow and increase gradually

<u>Cyclic:</u>
   - Daily volume delivered over several hours
   - Usually done at night so patient may eat during the day

Intermittent/Bolus:

- Daily volume in certain number of feedings/day
- 3-6 feedings over 30-60 minutes
- more convenient, especially with drug interactions
- less tolerated because of the large amount over small time frame

C. TYPES OF TPN:

1. Peripheral

Advantages: lower technical risk, and lower infection risk
No hypertonic dextrose
Preferred in pts who will require < 7 days of TPN

Disadvantages: need large veins (not for elderly, oncology, malnourished)
Inadequate calories
Phlebitis if Osm > 600 mOsm/L

(may be able to minimize risk of phlebitis by giving low-dose heparin 1000 U/L and/or hydrocortisone 5 mg/L, to decrease or prevent inflammation and clot formation)

2. Central

Advantages: Can give much more concentrated formulations
Good in fluid restricted patients
Home TPN patients

Disadvantages: Catheter insertion
Need dedicated line
Greater potential for infection

D. PATIENT ASSESSMENT:

Order baseline LFT, albumin, prealbumin, transferring and triglycerides if not done within 7 days

E. DETERMINING APPROPRIATE TPN FORMULA:

1. Determine dosing weight:

-Obtain actual body weight (ABW)
-Calculate ideal body weight (IBW)
Male: 50 kg + (2.3kg x inches > 5ft)
Female: 45 kg + (2.3kg x inches > 5ft)
Special considerations: AKA: reduce IBW by 15%
BKA: reduce IBW by 7%
Paraplegic ↓ IBW by 4.5kg
Quadriplegic ↓ IBW by 9 kg

2. Compare ABW to IBW:

…if ABW < 120%of the IBW, use ABW
…if ABW > 125% (obese) use corrected weight=IBW + 0.4(ABW-IBW)

3. Calculate Caloric Requirements:

BEE: males: 66 + (13.7 x kg) + (5x cm) - (6.8 x age)
females: 655 + (9.6 x kg) + (1.7 x cm) - (4.7 x age)

Activity Factors: Ambulatory 30%
Bedrest 20%
NMB 10%

Stress Factors: Surgery=1.2 - 1.2 Burns=1.5 - 1.9
Infection=1.2 - 1.6 Trauma=1.35 - 1.6
Pentobarb. Coma=25kcal/kg/day

SHORT CUT: equally effective for initial estimates:
Mild to Moderate Stress: Start with 25 kcal/kg/day (Total calories)
Trauma/Critical Illness: Start with 25 kcal/kg/day (NPC)
Fluid Requirements: approx. 1 mL/kcal

4. Calculate Protein Requirements: (4 kcal/gm protein)

Normal Renal Function	Mild stress	1.2 - 1.5 gm/kg/day
Trauma/Burns/Severe stress		1.5 - 2 "
Renal Insufficiency	No dialysis	0.8 - 1 "
	HD	1 - 1.2 "
	PD	1.2 - 1.5 "
Hepatic Insufficiency		
with encephalopathy		0.7 - 0.8 "
without encephalopathy		normal

*****Available Formulations*****
- Standard amino acids: 8.5%, 10%, 15%
- Hepatamine: 8%

Monitoring Parameters: **BUN**- increases with large protein load
-GI Bleed
-Renal failure
-Corticosteroids
Ammonia- clinical encephalopathy
Albumin, Prealbumin, Transferrin

5. Calculate Carbohydrate Requirements: (3.4 kcal/gm dextrose)

- Goal is 30-70% of total calories/day
- Approximately 2-5 g/kg/day
- Maximum 5mg/kg/min or 7.2 g/kg/d
- *Watch glucose closely-may need to add insulin*
- Keep Glc < 110 mg/dl

Available Solutions: 10-70%

Issues: -Fluid status

-Renal function
-Respiratory function

Monitor: -Glucose, LFT (fatty liver)

6. Calculate Fat Requirements; (9 kcal/gm fat)

- Minimum 4% NPC, maximum 60%
- Provides essential fatty acids, prevents fatty acid deficiency
- 9 kcal/gram fat
- Acceptable serum triglyceride level while on TPN </= 400

Contraindications:

- Hypertriglyceridemia
- Lipid-induced pancreatitis
- Egg allergy

Available Formulations: 10% lipids = 1.1 kcal/ml
20% lipids = 2 kcal/ml

Monitor: -TG
-LFT's
-platelets
-Adverse Effects: fevers/chills/ vomiting

E. TPN ORDERING:

Evaluate Patient:

Renal failure: require fluid restriction and electrolyte alterations (potassium, phosphate and calcium)
Liver Failure: May require modified proteins (if severe encephalopathy), less fat and less glucose.
Vent Dependent: may require more fat (max=60% total NPC)
CHF: May require fluid restriction.
IDDM: Utilize less glucose and more frequent CBG monitoring. Can add insulin into the TPN.

1. Divide total calories required into Carbohydrates (30-70%) and Lipids (4-60%):

Example: Pt weighs 70 kg

- **Total calories**= 25 = 1750 kCal/day
- Want to give 70 % calories from dextrose= 0.7 X 1750 =1225 kcal

- **Dextrose** has 3.4 kcal/gram = 1225 kcal/3.4 kcal/gm = 360 gm

- **Fats**: remaining calories from fat 30%= 0.3 X 1225 = 368 kcal **(use 10% 400ml)**
- **Proteins:** for renal function, we will use 1 – 1.5 gm/kg IBW = 70 – 105 gm

If Fluid Restricted:

CARBOHYDRATES:

- If patient is fluid restricted - highest concentration of dextrose is 70%
- Therefore, there are 70 grams in every 100ml
- $\frac{360 \text{ gm}}{0.70} =$ **514 ml**

LIPIDS:

- Use most concentrated solution (20%)= 200 ml = 400 kcal

PROTEINS:

- For least amount of fluid, use 15% = $\frac{70 \text{ gm}}{0.15} =$ **466ml**

- **TOTAL VOLUME:**

  -Dextrose= 514 ml + Fats= 200 ml + Proteins =466ml

  =1180 (allow 100-200ml for additives) = **1300 ml**

To determine % Dextrose = 360 gm dextrose ÷ 1300 ml = 28 %

Nutritional Monitoring Parameters:

- Albumin t1/2 = 20 days -- long term marker for nutritional status
- Prealbumin t1/2 = 1-2 days
- Transferrin t1/2 = 8-10 days
- LFT's - may see increased AST, Alk Phos, Bili
- Mental Status
- Electrolytes (Refeeding syndrome)
- Exhaled Gas Analysis-- RQ > 1 is significant for overfeeding
- RQ = 0.86 - 1, increased CO_2 production
- Goal RQ = 0.85
- 24 hour UUN Collection

Complications of TPN:

1. Overfeeding with Carbohydrate (> 5mg/kg/min)

   Lungs: CO2 production, minute ventilation, respiratory failure, prolonged ventilation

   Hyperglycemia: electrolytes (K+, Mg++, PO4); Impaired WBC phagocytosis, neutrophil chemotaxis

2. Overfeeding Calories (> 150% TEE): Fatty liver, increased AST, ALT, Alk Phos; hepatomegaly; cholestasis

3. Overfeeding Fats: (> 2gm/kg/d): Congestion of RES; Increased triglycerides; eicosanoids may cause hypoxia, increased PAP

4. Overfeeding Protein: increased ureagenesis

SPECIFIC CONSIDERATIONS

Condition	Problems	Solution
SIRS	Require increased total calories/requirements Hyperglycemia TG intolerance Protein catabolism	Inc. calories Insulin s/s Protein 1.5-2g/kg/d (not > 2.2g/kg/d)
Renal Failure	Increases in K, Mg, PO4 Hemodialysis (removes amino acid 3-5g/hr) Peritoneal dialysis-removes aa 40-60g/d, and provides Glc	Acute RF-no changes other than fluid restr. Chronic RF-dec. protein 0.5-0.8 g/kg/d
Hepatic Failure	Hypermetabolic Loss of K, Mg, Zinc Fluid restriction Encephalopathy	Fluid restriction Protein 1-1.3 g/kg Hepatamine-↑BCAAs and ↓ aromatics
Vent Dependent	Increased oxygen consumption demands Increased CO2 makes it difficult to wean	RQ analysis Limit CO2 production, more fat max 60% NPC
Malnutrition	Refeeding Syndrome Dysrhythmias	Salt and fluid restriction Monitor ECG
Obesity	Overfeeding	Use IBW if > 25%

Other Additives:

Zinc – 25 mg/d (diarrhea, severe burns, fistula)
Albumin – NOT RECOMMENDED to add to TPN
H2 Antagonists – compatible with TPN
Ascorbic Acid 300-500 mg/day (wound healing, burns)
Insulin (Regular)
Glutamine

Title:	Prostanoids (Epoprostenol (Flolan®) and Treprostinil (Remodulin®)	Page 1 of 5
Policy No:	3 HAR xxxx	Effective Date: DRAFT

OBJECTIVE
To provide Epoprostenol Sodium (Flolan®) and Treprostinil (Remodulin) administrative guidelines for caregivers.

SCOPE
Physicians, nurses, pharmacists and other healthcare providers.

LOCATION:
Infusion of these medications will be allowed on the following units:
See Attachment #1

DEFINITIONS
1. Epoprostenol Sodium (Flolan®) is used to treat Pulmonary Arterial Hypertension.

   Flolan® is a lyophilized powder, which must be reconstituted with Sterile Diluent prior to administration. Flolan® has a limited stability once reconstituted. It requires daily mixing by the patient or nursing caregiver using a special diluent.

2. Treprostinil Sodium (Remodulin®) is used to treat Pulmonary Arterial Hypertension.

   Remodulin® is a sterile salt formulated for subcutaneous or intravenous administration. Remodulin® is supplied as a solution and does not require reconstitution.

POLICY

Due to the nature of these medications, they may only be prescribed by a qualified physician.

1. Upon admission, all patients on Flolan® or Remodulin® must be admitted to one of the designated nursing care units.
2. New initiation of Flolan® or Remodulin® must be performed in one of the designated Intensive Care Units. ***See Attachment #1***
3. Continuation of therapy of Flolan® or Remodulin® requires verification of the patient's current dose and weight. The nurse must verify the infusion rate by looking at the patient's infusion pump, and contact pharmacy with the infusion rate. The dose is then verified by pharmacy by contacting the patient's drug company and Dr. Mubarak (Pager #11555) for instructions on preparation and dosing.
4. With the exception of a life-threatening emergency, all patients on Flolan® or Remodulin® must be pre-approved through one of the designated drug companies. **See Attachment #2.** Without approval, the patient cannot be discharged from the hospital on the medication.
5. The company name and contact information must be made readily available in the patient's medical record for every patient.
6. All patients have an emergency family member that is educated and familiar with the pump. This designated emergency family member's name and phone number is listed in the patient's medical record.
7. Upon admission, all patients on an intravenous CADD Pump are converted to the DMC standard infusion pump – the Baxter Colleague Pump.

Flolan® - Epoprostenol Sodium:

8. Flolan® is:
   - A. Only administered by a continuous IV infusion through a central venous catheter.
   - B. Infused in a designated central IV line used only for Flolan®.
     - i. A second intravenous access line must be available.
     - ii. A peripheral line can be used in the case of an emergency.
   - C. Reconstituted only with the given diluent and is not be mixed with any other parenteral solution or medication.

9. Abrupt withdrawal or rapid fluctuations in dose of drug is avoided. Any disruption in Flolan therapy could result in severe life threatening consequences. The physician must be alerted immediately if disruption occurs.
10. Upon admission, patients using the CADD pump are converted to the Baxter Colleague Infusion pump. The pharmacy ensures drug availability and prepares the drug at a concentration appropriate to provide a continuous infusion rate of at least 4-10 ml/hr using the Baxter Colleague Infusion Pumps.
11. Two identical bags of Flolan® are supplied initially to each patient. One bag is hung and the second bag is stored in the refrigerator in case of an emergency.
12. The bag in the refridgerator is replaced daily by pharmacy, and the bags are used in chronological order, to ensure that there is always a new bag available in case of an emergency.
13. Flolan® solution is changed every 24 hours.
14. Flolan® must always be kept cold to maintain its limited stability. Ice packs are hung with the solution and need to be changed every 8 hours.
15. Patients may use their own CADD-Legacy™ 1 pumps and tubing supplies for a maximum of 24 hours, or until pharmacy has prepared a new bag and the Baxter Colleague Infusion pump is available for use. A physician order is required designating their use.
16. RN staff estimate catheter dead space by attaching a syringe to the catheter and withdrawing fluid until blood appears in the syringe. This total represents amount of intravenous medicated solution that is programmed for bolus during initiation of therapy.

Treprostinil Sodium (Remodulin®)

17. Remodulin® is administered by a continuous IV infusion through a central venous catheter or by the subcutaneous route.
18. For intravenous use, Remodulin® is infused in a designated central IV line. A second intravenous access line must be available. A peripheral line can be used in the case of an emergency.
19. For intravenous use Remodulin® can be diluted with Preservative Free Normal Saline. The infusion is not be mixed with any other parenteral solution or medication.
20. Abrupt withdrawal or rapid fluctuations in dose of drug is avoided. Any disruption in Remodulin® therapy could result in severe life threatening consequences. The physician must be alerted immediately if disruption occurs.
21. Upon admission, patients using the intravenous CADD pump are converted to the Baxter Colleague Infusion pump. The pharmacy ensures drug availability and prepares the drug at a concentration appropriate to provide a continuous infusion rate of at least 4-10 ml/hr using the Baxter Colleague Infusion Pumps.
22. Remodulin® is prepared by the pharmacy at a concentration appropriate to provide a 48-hour infusion. Only one bag is prepared at a time. If something happens to this bag, pharmacy is contacted immediately to prepare an emergency replacement.
23. Remodulin®has a longer half-life than Flolan®. If something happens to disrupt therapy, there is a 4-hour window of safety with Remodulin®.
24. The intravenous Remodulin® bags are changed every 48 hours.
25. Patients may use their own CADD-Legacy™ 1 pumps and tubing supplies for a maximum of 48 hours or until pharmacy has prepared a new bag and the Baxter Colleague Infusion pump is available. A physician order is required designating their use.
26. Patients on subcutaneous Remodulin® remain on their current pumps only if they, or their family member or caregiver are able to manipulate and operate the pump, and be able to change their syringe, dressing and infusion site. If a patient or caregiver is unable to perform these tasks, they are converted to the intravenous route at an equal dose, using the Baxter Colleague Infusion pumps.
27. Patients using their own pumps must provide the extra pump within 24 hours of admission. The pump remains at the bedside in case of an emergency. If the extra pump cannot be provided, then the patient is converted to the IV route, at an equal dose, if problems are encountered with the subcutaneous pump.
28. Pharmacy is responsible for ensuring that tubing, batteries, syringes and all other supplies are available for the patient.

29. Subcutanous Remodulin® requires use of a Mini-Med infusion pump and requires a complete change of tubing, syringe and infusion site every 72 hours.
30. For the patients on subcutaneous Remodulin®, a contact number to handle pump-related troubleshooting issues is made available in the patient's medical record and clipboard. This is the number that the nurse should contact for any issues relating to the pump. **See Attachment #2.**

PROVISIONS
Monitoring for ICU:

1. Vital signs with continuous SpO_2 monitored.
2. Every 15 minutes for the first hour.
3. Every 30 minutes for the first 2 hours after each titration.
4. Then vital signs per ICU protocol.
2. Alert physician for hemodynamic instability or $SpO_2 < 90\%$.

Monitoring Acute Care for maintenance therapy:

1. Vital signs and SpO_2 monitoring every 8 hours.
2. Alert physician for hemodynamic instability or $SpO_2 < 90\%$.

DOCUMENTATION:
Document the following on the Critical Care Flow Sheet, Acute Care Flow Record (ACFR), Trending Record, or Progress Note:

1. Vital signs and SpO_2 monitoring. I
2. Infusion site.
3. Response to titration or maintenance dose.
4. Patient/family teaching by designated drug company representative.

ATTACHMENTS

1. Location of Units
2. Drug Distributors
3. CADD-Legacy™ 1 Pump Operations
4. Mini-Med Pump Operations
5. Admission checklist
6. Standing order set
7. Titration Guide for Flolan®
8. Titration Guide for Remodulin®

ADMINISTRATIVE RESPONSIBILITY
Defines which management function or individual(s) within the system who is charged with enforcement, interpretation of, or exception to the approved policy.

APPROVAL SIGNATURE(S)

_____ _____
Title Date

_____ _____
Title Date

REVIEW DATE
February 2007

SUPERSEDES
None

Sponsor:

Attachment #1:

Location of Units

Initiation of Therapy:
Harper University Hospital - Intensive care units: Medical ICU (5ICU) and Cardiothoracic ICU (9ICU).
Detroit Receiving Hospital – Medical ICU (5R)

Continuation of Therapy:
Harper University Hospital - Acute Care: Cardiology (8WS). Medicine: Infectious Disease Unit (5BS) and Pulmonary Care Unit (8PCU).
Detroit Receiving Hospital –

Attachment #2:

Drug Distributors:

1) Accredo: 1-866-FIGHT-PH
2) Priority Healthcare: 1-866-474-8326
3) Caremark/Theracom: 1-877-356-5264

Flolan/Remodulin
Pharmacy Instructions for New Initiations

Harper University Hospital
July 2005

The following steps need to be completed for all patients admitted for initiation of Epoprostenol Sodium (Flolan®) or Treprostinil Sodium (Remodulin®).

- Ensure pre-approval from the company. Dr. Mubarak (pager 11555) provides this information for all **new initiations**.
  (ICU emergency cases (using Flolan only) are permitted without prior approval but cannot be continued as an outpatient without company approval)

- Contact designated company to verify patient information including weight, initiation dose, plan for teaching, etc. Contact the patient's distributor at the number listed below:
  - Accredo: 1-866-FIGHT-PH
  - Priority/Integrity Healthcare: 1-866-474-8326
  - Caremark/Theracom: 1-877-356-5264

- Verify warfarin held until after the Hickman catheter is placed. The INR should be < 1.4 or Interventional Radiology will not place the Hickman catheter.

- Verify drug availability and expiration dates. The drug and supplies are stored in the Biotech fridge. If Flolan is prescribed, ensure adequate supply of diluent as well as drug.

- All patients admitted for initiation and subsequent titration are required to use our DMC Baxter Colleague Infusion pumps.

- Alert clinical specialist to follow patient.

- The initial Flolan bag(s) will be made as follows:
  0.1 mg of Flolan in 100ml of diluent. Two bags will be sent up initially, one will be used for the infusion and the second will be stored in the fridge for emergencies. For patients who remain in the hospital and are being titrated up, subsequent bags should be made to ensure a 24 hour duration. An extra bag of Flolan should always be available in the fridge on the unit, in case of an emergency.

- The initial Remodulin bag will be made as follows:
  0.5mg of Remodulin in 500ml of 0.9% NaCl. Bag must be made as Total Volume = 500ml. For patients who remain in the hospital and are being titrated up, subsequent bags should be made to ensure a 48 hour duration. The Formula for determining the new Remodulin bag concentration:
  # mg = Dose (nanograms/kg/min) x Weight (kg) x 60 min x 48 hr
  = _____ nanograms in 500 ml NaCl. Round to the nearest 0.5mg.
  # mg = # nanograms ÷ 1,000,000. 1 mg = 1,000,000 nanograms.

- Complete patient information sheet and add it to the Flolan®/Remodulin® binder.

Initiation of Flolan/Remodulin
Physician Checklist for Admission

This following checklist needs to be completed by the physician prior to an **elective hospital admission for the initiation** of Epoprostenol Sodium (Flolan®) or Treprostinil Sodium (Remodulin®).

- ❑ Ensure pre-approval from the company.
- ❑ If patient is on warfarin, instuct patient to hold doses for 72 hours prior to admission.
- ❑ Verify that INR is < 1.4 prior to admission for Hickman catheter.
- ❑ Contact central pharmacy at 313-745-8623 at least 48 hours prior to admission date. Pharmacy will need to know the patient's name, weight, company supplier and the admission date.
- ❑ Contact the nursing supervisor for admission bed on 5ICU (745-1809).
- ❑ Contact 5ICU unit manager.
- ❑ Contact MICU fellow (Pager #6428).

April 25, 2005
HUH/KAW

Flolan® - Epoprostenol Sodium
Drug Summary Sheet

Prepared by: Krista Wahby, Pharm.D.
July 6, 2005

Indication:
- Epoprostenol is indicated for the long-term treatment of pulmonary hypertension in patients with NYHA Class III-IV

Pharmacology:
- Epoprostenol is a direct acting vasodilator of the pulmonary and systemic arterial vasculature. Epoprostenol also inhibits platelet aggregation
- Epoprostenol will increase cardiac output and decrease mean pulmonary artery pressure and pulmonary vasculature resistance

Pharmacokinetics:
- Hydrolyzed in blood and undergoes enzymatic degradation
- Half life in humans is only about 6 minutes

Adverse Effects:
- Flushing, headache, jaw pain, hypotension, chest pain, nausea, vomiting, backache, restlessness, diarrhea, bradycardia
- Flu-like symptoms, thrombocytopenia

Monitoring:
- Hypotension, pulmonary artery pressures (if applicable)

Caution:
- Sudden withdrawal or interruption in the infusion of drug, or large dose reductions, could worsen PAH symptoms, and could be life-threatening
- Flolan must be reconstituted ONLY with the given Sterile Diluent

Dosing:
- FDA-approved for the intravenous route. Administer through a central venous catheter.
- Peripheral lines can be used temporarily
- Standard starting dose = 2 ng/kg/min. Doses are based on actual BW.
- Dose titration in the ICU = Initiate at 1-2 ng/kg/min and titrate dose, as tolerated in 2 ng/kg/min increments every 15 minutes, or longer, until a dose-limiting effect occurs.

Supplied as a freeze-dried powder with 0.5 mg or 1.5 mg.
The Sterile Diluent is supplied in 50ml vials.
Must be used with a Cold Pouch/Freezer pack!
Pharmacy will ensure that there is always a second bag available in the fridge for emergencies.
Do not allow bag to run dry, or pump to malfunction. The window of safety is only about **15 minutes** off of the drug!

NOTE: 1 mg = 1,000,000 ng

Flolan/Remodulin Patient Information Sheet
Date: July 6, 2005

PATIENT NAME: _____

ADMISSION DATE: _____

PATIENT IS ON: □ **REMODULIN SubQ** □ **REMODULIN IV** □ **FLOLAN**

CURRENT WEIGHT: _____

CURRENT DOSE: _____**nanograms/kg/min.**

PREPARATION INSTRUCTIONS:

_____
_____
_____
_____
_____

COMPANY NAME: _____

COMPANY CONTACT INFORMATION:

_____
_____

OTHER:

_____
_____
_____
_____
_____
_____

Detroit Medical Center
Wayne State University

Epoprostenol - Flolan(Rx) Order Form

☐ CHM
☐ DRH
■ Harper
☐ Hutzel
☐ HVS
☐ RIM
☐ Sinai-Grace

(Patient Identification)

ALLERGIES:	Estimated or Actual (circle one) Wt_____lb Ht_____in Wt_____kg Ht_____cm

USE BALL POINT PEN - PRESS FIRMLY

MEDICATION AND IV ORDERS ONLY

EPOPROSTENOL (FLOLAN) DOSING:

1. New Initiation - ICU Use Only

☐ **Epoprostenol 0.1 mg IVPB in 100 ml diluent.**
Begin infusion at 2 nanograms/kg/min.
☐ Titrate infusion by _____ nanograms/kg/min every _____,
as tolerated up to maximum dose = _____.
■ Hang with ice packs. Change ice packs q8 hr.

FLOLAN - Infusion Rates for Concentration= 1000 nanograms/ml

Weight (kg)	Dose or Rate in nanograms/kg/min	
	2	4
	Infusion Delivery Rate (ml/hr)	
40	4.8	9.6
50	6	12
60	7.2	14.4
70	8.4	16.8
80	9.6	19.2
90	10.8	21.6
100	12	24

The FLOLAN concentration should be changed when any of the following occur:
The bag requires changing more than every 8 hours
The patient weighs > 90 kg
The infusion rate is titrated above 4 nanograms/ kg / min.
Contact pharmacy to request a new concentration.
(See Infusion Rate Guide located in the FLOLAN binder).

2. Epoprostenol (Flolan) Continuation:

☐ **Epoprostenol _____ mg IVPB in 100 ml diluent.**
Infuse at _____ nanograms/kg/min using the Baxter Colleague Infusion pump. Do not titrate. Change epoprostenol bag q 24hr.
■ Hang with ice packs. Change ice packs q8 hr.

Note: 1 milligram = 1,000,000 nanograms

ALL OTHER ORDERS

ADMIT TO: _____
(See Policy for approved units)

ATTENDING_____
INTERN/RESIDENT_____

CONSULT
☑ Dr. Mubarak for Pulmonary Hypertension (#11555)
☑ Pharmacy for dose verification
☐ Case management specialist for discharge planning

LABS
☐ _____
☐ _____

MONITORING

1. FOR INITIATION:
☑ Blood pressure monitoring and saturation:
- Every 15 min for the first hour and after each titration
- Every 30 min for the first 2 hrs
- Every 1 hr thereafter

2. FOR CONTINUATION:
☑ Blood pressure monitoring q8 hrs
☑ Pulse oximetry monitoring q8 hrs. Alert physician if < 90%.

3. Nursing Implications/Monitoring:
Reduce dose to last previously tolerated dose if patient experiences hypotension (drop in SBP > 20 mmHg), desaturation to < 90%, or severe headache, flushing, nausea, vomiting or jaw pain.
Use dedicated central intravenous line.
☐ Insert heplock if no other intravenous access is available. Avoid abrupt withdrawal of drug.
■ Change battery pack every 14 days

4. Contact Information:
☐ Drug distributor name: _____
☐ Drug distributor phone #: _____
Emergency Contact Information:_____

STANDARD TURNAROUND TIMES
STAT 20 MIN NOW 1 HR ROUTINE 4 HRS

FLOLAN® - Epoprostenol Infusion Guide

The first bag sent to all patients for initiation of FLOLAN therapy should be the 0.1 mg in 100ml diluent. Once it is determined that the patient tolerated the therapy and/or the rate is titrated upward, then the concentration of the infusion bag should be determined by the pharmacy department and should last as close to 24 hours as possible. Always send the bag up with ice packs surrounding it. An extra bag will be kept in the refrigerator at all times.

A. This concentration is for Initiation Bag Only: 0.1 mg in 100 ml diluent. Concentration = 1000 ng/ml

Infusion Rates for FLOLAN® at a Concentration of 1000 ng/ml

Weight (kg)	Dose or Rate in nanograms/kg/min	
	2	4
	Infusion Delivery Rate (ml/hr)	
40	4.8	9.6
50	6	12
60	7.2	14.4
70	8.4	16.8
80	9.6	19.2
90	10.8	21.6
100	12	24

B. FLOLAN® 0.3 mg in 100 ml diluent. Concentration = 3000 ng/ml

Infusion Rates for FLOLAN at a Concentration of 3000 ng/ml

Wt (kg)	Dose or Rate in ng/kg/min							
	2	4	6	8	10	12	14	16
	Infusion Delivery Rate (ml/hr)							
40	1.6	3.2	4.8	6.4	8.0	9.6	11.2	12.8
50	2.0	4.0	6.0	8.0	10.0	12.0	14.0	16.0
60	2.4	4.8	7.2	9.6	12.0	14.4	16.8	19.2
70	2.8	5.6	8.4	11.2	14.0	16.8	19.6	22.4
80	3.2	6.4	9.6	12.8	16.0	19.2	22.4	25.6
90	3.6	7.2	10.8	14.4	18.0	21.6	25.2	28.8
100	4.0	8.0	12.0	16.0	20.0	24.0	28.0	32.0

C. FLOLAN® 0.5 mg in 100 ml diluent. Concentration = 5000 ng/ml

Infusion Rates for FLOLAN at a Concentration of 5000ng/ml

Wt (kg)	Dose or Rate in ng/kg/min							
	2	4	6	8	10	12	14	16
	Infusion Delivery Rate (ml/hr)							
40	1	1.9	2.9	3.8	4.8	5.8	6.7	7.7
50	1.2	2.4	3.6	4.8	6.0	7.2	8.4	9.6
60	1.4	2.9	4.3	5.8	7.2	8.6	10.1	11.5
70	1.7	3.4	5.0	6.7	8.4	10.1	11.8	13.4
80	1.9	3.8	5.8	7.7	9.6	11.5	13.4	15.4
90	2.2	4.3	6.5	8.6	10.8	13.0	15.1	17.3
10	2.4	4.8	7.2	9.6	12.0	14.4	16.8	19.2

D. FLOLAN® 1 mg in 100 ml diluent. Concentration = 10,000 ng/ml

Infusion Rates for FLOLAN at a Concentration of 10,000ng/ml

Wt (kg)	Dose or Rate in ng/kg/min							
	2	4	6	8	10	12	14	16
	Infusion Delivery Rate (ml/hr)							
40	-	1.0	1.4	1.9	2.4	2.9	3.4	3.8
50	-	1.2	1.8	2.4	3.0	3.6	4.2	4.8
60	-	1.4	2.2	2.9	3.6	4.3	5.0	5.8
70	-	1.7	2.5	3.4	4.2	5.0	5.9	6.7
80	-	1.9	2.9	3.8	4.8	5.8	6.7	7.7
90	-	2.2	3.2	4.3	5.4	6.5	7.6	8.6
10	-	2.4	3.6	4.8	6.0	7.2	8.4	9.6

Remodulin™ - Treprostinil sodium

Prepared by: Krista Wahby, Pharm.D.
July 6, 2004

Indication:

- Treprostinil is indicated for treatment of pulmonary hypertension in patients with NYHA Class II-IV

Pharmacology:

- Treprostinil is a direct acting vasodilator of the pulmonary and systemic arterial vasculature. Treprostinil also inhibits platelet aggregation
- Treprostinil will increase cardiac output and decrease mean pulmonary artery pressure and pulmonary vasculature resistance

Pharmacokinetics:

- Metabolized by the liver
- Eliminated in urine (parent drug and metabolites)
- Half life = 2-4 hours subcutaneously

Adverse Effects:

- Headache, jaw pain, chest pain, nausea, vomiting, backache, restlessness, diarrhea
- Infusion site pain and erythema (with the subcutaneous infusion)

Monitoring:

- Hypotension, pulmonary artery pressures (if applicable)

Caution:

- Sudden withdrawal of drug or large dose reductions could worsen PAH symptoms, and could be life-threatening

Dosing:

- FDA-approved for subcutaneous and intravenous routes.
- The SubQ route causes significant pain at injection site.
- Standard starting dose = 1.25 ng/kg/min subcutaneously. Doses are based on actual BW.
- Intravenous dosing = Initiate at 1 ng/kg/min and titrate dose, as tolerated in1- 2 ng/kg/min increments
- Intravenous dosing is now FDA-approved.
- The intravenous bag is stable for 48 hours and the subcutaneous syringes are stable for 72 hours.

Supplied as 20 ml vials – 1mg/ml; 2.5 mg/ml; 5 mg/ml; 10 mg/ml

NOTE: 1 mg = 1,000,000 ng

DO NOT DISCARD MULTI_DOSE VIAL!!!! Keep open vial in fridge. Date & time label. Opened vial is stable for 30 days.

Detroit Medical Center
Wayne State University

Treprostinil (Remodulin) Order Form

☐ CHM
■ DRH
■ Harper
☐ Hutzel
☐ HVS
☐ RIM
☐ Sinai-Grace

(Patient Identification)

ALLERGIES:

Estimated or Actual (circle one)
Wt_____lb Ht_____in
Wt_____kg Ht_____cm

USE BALL POINT PEN - PRESS FIRMLY

MEDICATION AND IV ORDERS ONLY

1. New Initiation - ICU Use Only

Intravenous Administration:

☐ **Treprostinil 0.5 mg in 500 ml of 0.9% NaCl.**
Total volume=500 ml. Infuse at 1 nanogram/kg/min IVPB.

☐ Titrate infusion by ____ nanograms/kg/min every _____
as tolerated up to maximum dose = _____.

Remodulin-Infusion Rates for Conc. = 1000 nanograms/ml

Weight (kg)	Dose or Rate in nanograms/kg/min		
	1	2	4
	Infusion Delivery Rate (ml/hr)		
40	2.4	4.8	9.6
50	3	6	12
60	3.6	7.2	14.4
70	4.2	8.4	16.8
80	4.8	9.6	19.2
90	5.4	10.8	21.6
100	6	12	24

2. Treprostinil (Remodulin) Continuation:

a) Subcutaneous Infusion:

☐ **Subcutaneous Treprostinil. Draw up _____ ml of the ____ mg/ml vial (undiluted) into the 3ml syringe reservoir.**
Attach tubing. Infuse at ___ nanograms/kg/min =_____ml/hr) SubQ using the Mini-Med infusion pump. Patient may use own pump. Change syringe, site and tubing every 72 hours.

b) Intravenous Infusion:

☐ **Intravenous Treprostinil.** Draw up _____ mg in 500 ml of 0.9% NaCl. Total volume = 500ml. Infuse at ___ nanograms/kg/min (= ____ ml/hour), using the Baxter Colleague Pump. Do not titrate.
Change treprostinil bag every 48 hours.

STANDARD TURNAROUND TIMES
STAT 20 MIN NOW 1 HR ROUTINE 4 HRS

ALL OTHER ORDERS

ADMIT TO: _____
(See Policy for approved units)
ATTENDING_____
INTERN/RESIDENT_____

CONSULT:
■ Dr. Mubarak for Pulmonary Hypertension (#11555)
■ Pharmacy for dose verification
☐ Case Management Specialist

LABS:
☐ _____
☐ _____

MONITORING:

1. FOR INITIATION:
☑ Blood pressure monitoring and saturation:
- Every 15 min for the first hour and after each titration
- Every 30 min for the first 2 hrs
- Every 1 hr thereafter

2. FOR CONTINUATION
☑ Blood pressure monitoring q8 hrs
☑ Pulse oximetry monitoring q8 hrs. Alert physician if saturation < 90%.

3. Nursing Implications/Monitoring:
Reduce dose to last previously tolerated dose if patient experiences hypotension (drop in SBP > 20 mmHg), desaturation to < 90%, or severe headache, flushing, nausea, vomiting or jaw pain.
For IV use, use dedicated central intravenous line
☐ Insert Saline lock if no other intravenous access is available.
Avoid abrupt withdrawal of drug.

4. Contact Information:
☐ Drug distributor name: _____
☐ Drug distributor phone #: _____
Emergency Contact Information:_____

REMODULIN® - Treprostinil Infusion Guide

The first bag sent to all patients for initiation of REMODULIN therapy should be the 0.5 mg in 500ml NaCl. *ALL REMODULIN BAGS SHOULD BE MADE AS TOTAL VOLUME.* Once it is determined that the patient tolerated the therapy and/or the rate is titrated upward, then the concentration of the infusion bag should be determined by the pharmacy department and should last as close to 48 hours as possible.

A. This concentration is for Initiation Bag Only: 0.5 mg in 500 ml NaCl. Concentration = 1000 nanograms/ml

Weight (kg)	Dose or Rate in nanograms/kg/min		
	1	2	4
	Infusion Delivery Rate (ml/hr)		
40	2.4	4.8	9.6
50	3.0	6.0	12
60	3.6	7.2	14.4
70	4.2	8.4	16.8
80	4.8	9.6	19.2
90	5.4	10.8	21.6
100	6.0	12.0	24

B. TREPROSTINIL 1 mg in 500 ml NaCl. Concentration = 2000 nanograms/ml

Wt (kg)	Dose or Rate in nanograms/kg/min							
	2	4	6	8	10	12	14	16
	Infusion Delivery Rate (ml/hr)							
40	2.4	4.8	7.2	9.6	12	14.4	16.8	19.2
50	3.0	6.0	9.0	12.0	15.0	18.0	21.0	24.0
60	3.6	7.2	10.8	14.4	18.0	21.6	25.2	28.8
70	4.2	8.4	12.6	16.8	21.0	25.2	29.4	33.6
80	4.8	9.6	14.4	19.2	24.0	28.8	33.6	38.4
90	5.4	10.8	16.2	21.6	27.0	32.4	37.8	43.2
100	6.0	12.0	18.0	24.0	30.0	36.0	42.0	48.0

C. TREPROSTINIL 2 mg in 500 ml NaCl. Concentration = 4000 nanograms/ml

Wt (kg)	Dose or Rate in nanograms/kg/min							
	2	4	6	8	10	12	14	16
	Infusion Delivery Rate (ml/hr)							
40	-	2.4	3.6	4.8	6.0	7.2	8.4	9.6
50	-	3.0	4.5	6.0	7.5	9.0	10.5	12.0
60	-	3.6	5.4	7.2	9.0	10.8	12.6	14.4
70	-	4.2	6.3	8.4	10.5	12.6	14.7	16.8
80	-	4.8	7.2	9.6	12.0	14.4	16.8	19.2
90	-	5.4	8.1	10.8	13.5	16.2	18.9	21.6
100	-	6.0	9.0	12.0	15.0	18.0	21.0	24.0

D. TREPROSTINIL 3 mg in 500 ml NaCl. Concentration = 6000 nanograms/ml

Wt (kg)	Dose or Rate in nanograms/kg/min							
	2	4	6	8	10	12	14	16
	Infusion Delivery Rate (ml/hr)							
50	-	-	3.0	4.0	5.0	6.0	7.0	8.0
60	-	-	3.6	4.8	6.0	7.2	8.4	9.6
70	-	-	4.2	5.6	7.0	8.4	9.8	11.2
80	-	-	4.8	6.4	8.0	9.6	11.2	12.8
90	-	-	5.4	7.2	9.0	10.8	12.6	14.4
100	-	-	6.0	8.0	10.0	12.0	14.0	16.0

E. TREPROSTINIL 4 mg in 500 ml NaCl. Concentration = 8000 nanograms/ml

Wt (kg)	Dose or Rate in nanograms/kg/min							
	2	4	6	8	10	12	14	16
	Infusion Delivery Rate (ml/hr)							
70	-	-	-	4.2	5.3	6.3	7.4	8.4
80	-	-	-	4.8	6.0	7.2	8.4	9.6
90	-	-	-	5.4	6.8	8.1	9.5	10.8
100	-	-	-	6.0	7.5	9.0	10.5	12.0

June 15, 2005
HUH/KAW

Harper University Hospital – Sedation/Analgesia Algorithm

The purpose of this nomogram is to provide guidelines for the pharmacologic management of sedation and analgesia in adult mechanically ventilated patients. This algorithm assumes that all non-pharmacologic treatments, including environmental issues are optimized.

Is the patient comfortable? Is the patient at their target goal for sedation?

NO

Correct underlying causes, if possible. Sleep deprivation, fear, electrolyte imbalances, medications, etc
Assess Causes

YES

Reassess goal at beginning of each shift (q12h).

Titrate as needed to maintain goal.

PAIN?

Check VAS/PBS scale. Set goal for analgesia.

Hemodynamically stable?
Morphine: 2-5mg IVP q 10 min

Hemodynamically Unstable?
Fentanyl: 25 mcg IVP q5-15min
Or
Hydromorphone: 0.25 –0.75 mg IVP q5-15min

Requiring IVP doses > q2hr?

YES

Hemodynamically stable?
Morphine gtt
@ 2 mg/hr
Titrate to goal.

Hemodynamically unstable?
Fentanyl gtt
@ 50 mcg/hr
Or
Hydromorphone gtt
@ 50 mcg/hr.
Titrate to goal.

ANXIETY?

Check MRSS. Set goal for sedation.

< 24 hrs?

Midazolam:
2-5 mg IVP q10-15 min
Convert to lorazepam if > 24 hrs.

> 24 hrs?

Lorazepam:
1-4 mg IVP q10-20 min.
If IVP doses required > q2 hr, start gtt @ 2 mg/hr

Consider converting to lorazepam.

Reassess plan

Neurosurgery Patients:
Propofol: start @ 5 mcg/kg/min, titrate q5 min by 5 mcg/kg/min. Max dose 50 mcg/kg/min.

≥ 3 days propofol?

DELERIUM?

Alcohol Withdrawal?

Yes

Initiate Alcohol Withdrawal Protocol

No

Haloperidol: 2-5mg q 20 min until desired effect, then 50% total dose scheduled q6 hr. Max.= 60 mg/dose.

Taper sedation/analgesia infusions if on for > 1 week, at high doses.

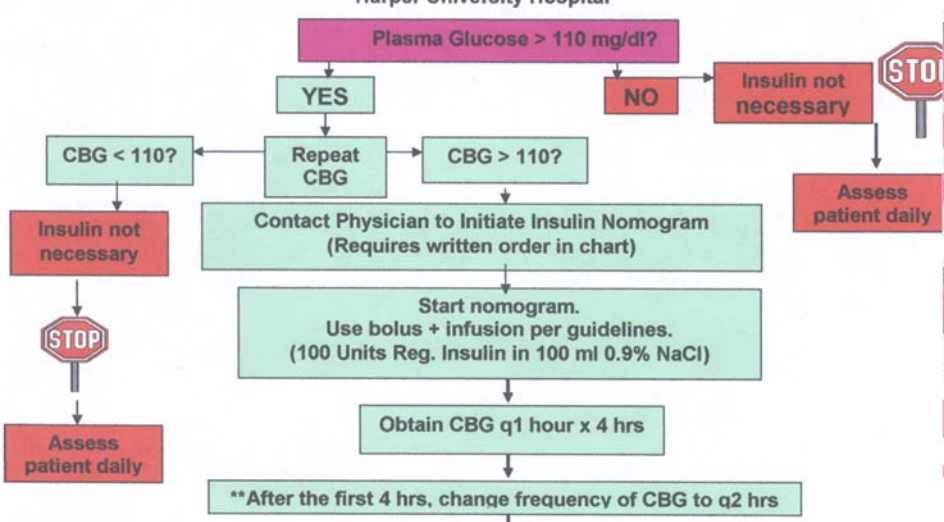
Taper gtt by 10-25%/day, if possible. Monitor for withdrawal

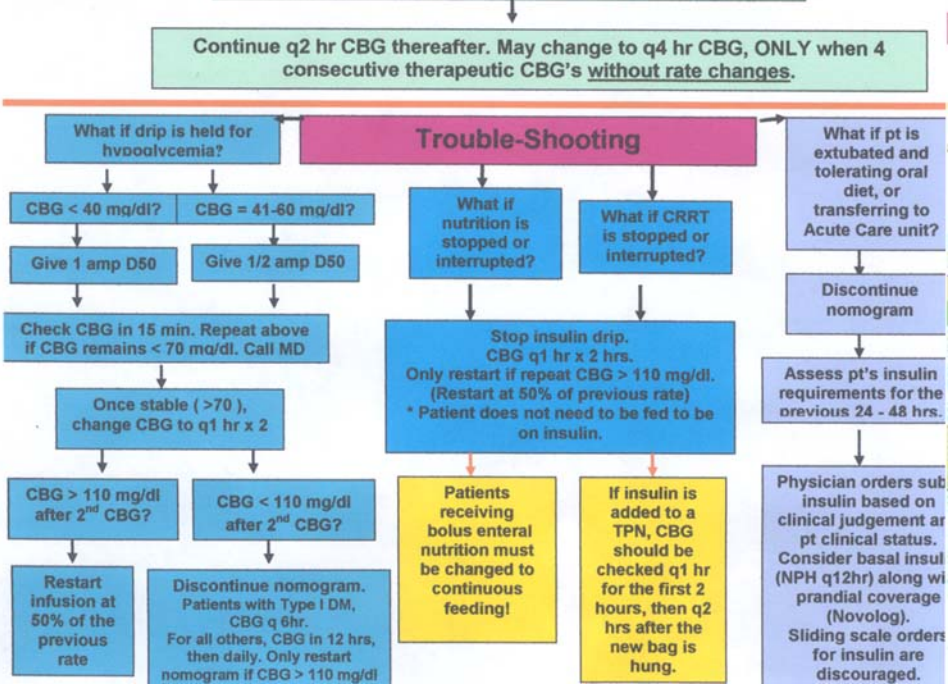
Stop infusion daily, if possible to allow wake-up.

If patient is a candidate, stop infusion each morning and allow patient to wake up.
Do not stop sedation in the following patients:
-Paralyzed with NMBA
-Status epilepticus
-Specialized mechanical ventilation – pressure control

Consider BIS monitoring for patients requiring NMBA and sedation/analgesia. Goal BIS level 60.

Critical Care Algorithm for Insulin Nomogram –09/02/2004
Harper University Hospital



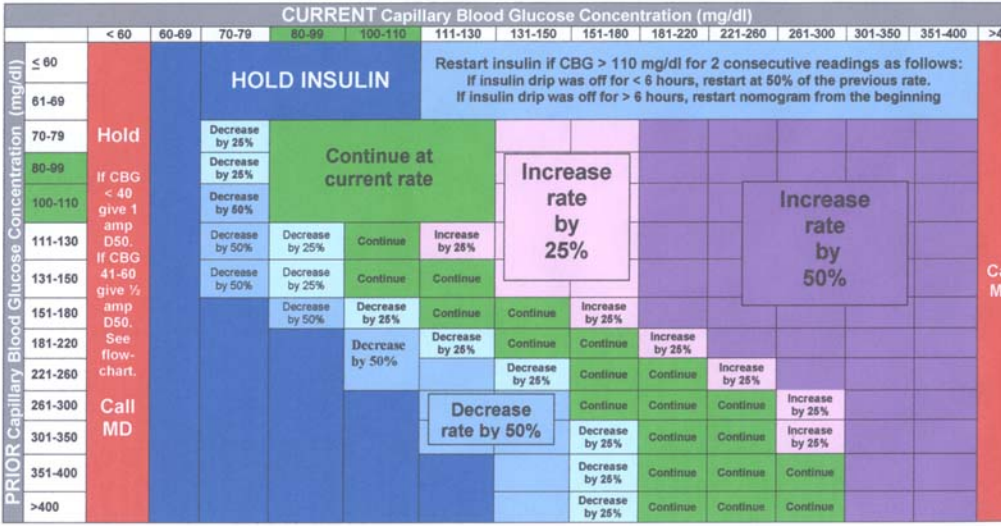


Goal is to maintain capillary blood glucose concentration between 80 and 110 mg/dl.

Exclusion criteria: diabetic ketoacidosis, hyperosmolar non-ketotic states, oral diet, expected ICU LOS < 24 hrs, hematocrit < 20% or > 55%., absence of central line

Maximum rate increase per hour is 4 Units!

Glucose	111-140 mg/dl	140-200 mg/dl	201-250 mg/dl	251-300 mg/dl	301-350 mg/dl	351-400 mg/dl	≥ 400 mg/dl
Regular Insulin	No bolus Start 2 Units/hour	2 units IVP Start 2 units/hour	4 units IVP Start 2 units/hour	6 units IVP Start 2 units/hour	8 units IVP Start 4 units/hour	10 units IVP Start 4 units/hour	Call MD



- Chart all capillary blood glucose on a dedicated column, and chart all changes in the insulin dose on the medication portion of the Critical Care Flow Sheet
- Refer to, "ALGORITHM FOR INSULIN NOMOGRAM" for guidance.

KAW: 9/02/04

This nomogram was developed as a nursing titration guide and is not to supersede clinical judgment

Harper University Hospital

Continuous Intravenous Insulin Nomogram - NURSING TITRATION GUIDE

Maximum hourly rate increase is 4 Units/hr. No limit on hourly rate reductions.

DECREASE		CURRENT INSULIN RATE	INCREASE	
Decrease by 50%	Decrease by 25%	units/hour	Increase by 25%	Increase by 50%
OFF	OFF	0.5	1	1
0.5	0.5	1	1.5	1.5
1	1	1.5	2	2
1	1.5	2	3	3
2	2	3	4	5
2	3	4	5	6
3	4	5	7	8
3	5	6	8	9
4	6	7	9	11
4	6	8	10	12
5	7	9	12	13
5	8	10	13	14
6	9	11	14	15
6	9	12	15	16
7	10	13	16	17
7	11	14	18	18
8	12	15	19	19
8	12	16	20	20
9	13	17	21	21
9	14	18	22	22
10	15	19	23	23
10	15	20	24	24
11	16	21	25	25
11	17	22	26	26
12	18	23	27	27
12	18	24	28	28
13	19	25	29	29
13	20	26	30	30
14	21	27	31	31
14	21	28	32	32
15	22	29	33	33
15	23	30	34	34
16	24	31	35	35
16	24	32	36	36
17	25	33	37	37
17	26	34	38	38
18	27	35	39	39
18	27	36	40	40
19	28	37	41	41
19	29	38	42	42
20	30	39	43	43
20	30	40	44	44

Do not exceed a <u>4 unit/hour</u> increase in the infusion rate and round up to the nearest unit/hour

Insulin infusion rates that exceed 40 Units/hr are not covered by this nomogram. Please refer to physisicans orders.

KAW 09/02/2004

Detroit Medical Center
Wayne State University

PHYSICIAN'S ORDER SHEET
Preprinted Protocol Orders
Critical Care
Neuromuscular Blockade Protocol

Draft

ALLERGIES:_____ **HEIGHT** _____ **WEIGHT** _____

MEDICATION ORDERS ONLY	ALL OTHER ORDERS
DATE/TIME	**DATE/TIME**

1. Pancuronium:

a. ☐ Loading dose pre-infusion:
Pancuronium _____ mg/kg IVP
(Range 0.04 – 0.10 mg/kg

b. ☐ Pancuronium 100 mg in 250ml D5W and infuse at _____mcg/kg/min (Range 1.0 – 1.7 mcg /kg/min) Titrate to goal.

OR

c. ☐ Pancuronium 0.1 – 0.2 mg/kg q 1-3 hours IVP PRN

2. Vecuronium:

a. ☐ Loading dose pre-infusion-
Vecuronium _____mg/kg IVP
(Range 0. 08 – 0.10 mg/kg)

b. ☐ Vecuronium 100mg in 250ml D5W and infuse at _____mcg/kg/min (Range 0.8 – 1.2 mcg /kg/min) Titrate to goal.

OR

c. ☐ Vecuronium _____mg/kg q 1 -3 hour IVP PRN
(Range 0.01-0.5mg/kg)

3. Cisatracurium:

a. ☐ Loading dose pre-infusion -
Cisatracurium _____mg/kg IVP
(Range 0.15 – 0.2mg/kg)

b. ☐ Cisatracurium 100 mg in 250ml D5W and infuse at _____mcg/kg/min (Range 0.5 - 10 mcg /kg/min) Titrate to goal.

OR

c. ☐ Cisatracurium 0.3mg/kg q 1 hour IVP PRN

3. Lubricate both eyes:

a. Lacrilube q 8 hours PRN

4. Hold NMBA q am

a. Hold until patient responds.
b. Assess.
c. Rebolus ½ of the loading dose IVP.
d. Infuse at previous rate.

Patient must also receive concurrent and adequate sedation and analgesia.

Pancuronium is the first agent of choice. Tachycardia, alone is not a contraindication to pancuronium.

If vecuronium or cisatracurium is considered, check the appropriate critieria:

1. **Vecuronium:**
   a. Hemodynamically significant increases in heart rate or blood pressure

2. **Cisatracurium:**
   a. Pancuronium and vecuronium contraindicated.
   b. Concurrent corticosteroid administration.
   c. Significant renal & hepatic dysfunction.

3. Manage NMBA using goals as follows:
   a. 1 to 3 thumb twitches with Train of Four.
   b. Promote ventilator synchrony.
   c. Decrease oxygen consumption.
   d. Reduce AutoPEEP, peak inspiratory pressure, and expiratory pressure.
   e. Lower intracranial pressure.
   f. Minimal or No patient movement.
   g. Other_____

4. Perform train of four at before initiating NMBA as a baseline, q 4 hours, and 15 minutes after each change in rate/dose.

5. Hold NMBA q am for assessment of neurological status, adequacy of sedation and analgesia, and if paralysis is necessary to meet clinical goals.

6. Assess patient for pain.

7. Intermittent pneumatic compression sleeves for DVT prophylaxis.

Physician Signature	Date/Time	Physician Signature	Date/Time

Clerk Signature	Date/ Time	Nurse Signature	Date/Time	Clerk Signature	Date/ Time	Nurse's Signature	Date/Time