# Psychological and Neurological changes in ICU patients

An essay submitted for the partial fulfillment of the Master degree in Anesthesia and Intensive Care

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# بسم الله الرحمن الرحيم

"اقرأ بسم ربك الذى خلق، خلق الانسان من علق، اقرأ و ربك الأكرم، الذى علم بالقلم، علم الانسان ما لم يعلم"

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# التغيرات النفسية و العصبية فى مرضى الرعاية المركزة

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## *List of Abbreviations*

| Abbreviation | Meaning |
|---|---|
| **AIDP** | **Acute inflammatory demylinating polyradiculopathy** |
| **AIS** | **Acute ischemic stroke** |
| **BUN** | **Blood urea nitrogen** |
| **CAM** | **Confusion assessment method** |
| **CCU** | **Coronary care unit** |
| **CEA** | **Carotid end arterectomy** |
| **CNS** | **Central nervous system** |
| **CSF** | **Cerebrospinal fluid** |
| **CT** | **Computed tomography** |
| **DBP** | **Diastolic blood pressure** |
| **DSM-IV** | **Diagnostic and statistical manual of mental disorders, fourth edition** |
| **DVT** | **Deep venous thrombosis** |
| **ECT** | **Electroconvulsive therapy** |
| **EEG** | **Electroencephalogram** |
| **EPS** | **Extrapyramidal syndrome** |
| **FDA** | **Food and Drug Association** |
| **GABA** | **Gamma amino butyric acid** |
| **GBS** | **Guillain- Barre` syndrome** |
| **GCS** | **Glasgow coma scale** |
| **HIG** | **Human immunoglobulin** |
| **HIV** | **Human immunodeficiency virus** |
| **ICA** | **Internal carotid artery** |
| **ICH** | **Intracerebral hemorrhage** |
| **ICP** | **Intracranial pressure** |
| **ICU** | **Intensive care unit** |
| **ICVD** | **Ischemic cerebrovascular disease** |
| **IM** | **Intramuscular** |
| **IV** | **Intravenous** |
| **MAOI** | **Monoamine oxidase inhibitor** |
| **MRI** | **Magnetic resonance imaging** |

| | |
|---|---|
| **NMBA** | **Neuromuscular blocking agent** |
| **NPO** | **Nothing per os** |
| **NS** | **Nervous system** |
| **PE** | **Pulmonary embolism** |
| **PO** | **Per os** |
| **RASS** | **Richmond Agitation Sedation scale** |
| **rt-PA** | **Recombinant tissue plasminogen activator** |
| **SAH** | **Subarachnoid hemorrhage** |
| **SBP** | **Systolic blood pressure** |
| **SNRI** | **Serotonin norepinephrine reuptake inhibtor** |
| **SSRI** | **Selective serotomin reuptake inhibitor** |
| **TCA** | **Tricyclic antidepressant** |
| **TENS** | **Transcutaneous electrical nerve stimulation** |
| **TIA** | **Transient ischemic attack** |
| **VC** | **Vital capacity** |

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# Introduction

Patients admitted to an intensive care unit (ICU) generally present an unexpected life-threatening condition, with the exception of those admitted after scheduled surgery. These patients will remain in their critical condition for various lengths of time and will need several types of life support, such as ventilation, cardiovascular or renal support. They will also receive various types of sedatives and analgesics to ensure compliance with ventilation and to induce some comfort. As the event that takes these critical patients to the ICU was unexpected, most patients will not be aware of their condition until late in their ICU stay and some of them only after their discharge to the ward. However, during their ICU stay they continue to have an emotional life, in a mixture of dreams, delusions and emotional experiences related to real events **(Sukantarat and Brett, 2003).**

Although various degrees of anxiety or depression that might delay and impair their recovery have been described in critical illness survivors, little is known about this and other neuropsychological sequelae of critical illness; cognitive impairment and memory disturbances are those more frequently described **(Jackson and Ely, 2001).**

Neuropsychological consequences in ICU survivors have been described as being related either to environmental factors (characteristic of the ICU, which can lead to an overwhelming of sensory stimuli) or factors related to memory problems (namely delusional memories and amnesia). These findings should suggest a need not only to review our concepts of optimal analgesia and sedation but also to evolve strategies to reinforce and help maintain factual memories, such as dialogue with the patients, explanation of all procedures, maintenance of the day/night cycle, minimisation of sensory stimuli and minimisation of noise and lights. Although for

some patients the noise of alarms and seeing staff around them may be reassuring, trying to make the ICU a quiet place, at least during the night, is a good strategy **(Granja, 2002).**

The term psychosis does not adequately reflect the range of symptoms seen in confused ICU patients. Traditionally, the term ICU psychosis has been used to designate florid abnormalities of mood and behavior in ICU patients. The term is outmoded and misleading because it implies a cause-and-effect relationship between being in an ICU and becoming psychotic **(Skirrow, 2002).**

Psychosis is defined as a loss of contact with reality because of a functional (i.e., nonorganic) disturbance in which the sensorium is normal but thinking is abnormal and associated with abnormal perceptions (e.g., auditory hallucinations) and systematic delusions (i.e., fixed, false beliefs) **(Jackson and Ely, 2001).**

Neurologic problems present in the intensive care unit (ICU) in two modes, primary neurologic problems such as stroke, Guillain-Barré syndrome, head trauma, or myasthenia gravis who are admitted to the ICU for close observation and management of vital functions, such as respiration or control of ICP. The other type of patients includes those with secondary neurologic complications, occurring in patients with other medical or surgical disorders **(Wijdicks, 2001).**

Patients with primary neurologic problems most commonly have conditions with an identified cause.. Such patients are admitted to the ICU for close observation and management of vital functions, such as respiration or control of ICP. These patients represent the minority of neurologic problems seen in the ICU. Far more frequently the neurologist is called on to evaluate the neurologic complications of medical disease: impairment of consciousness in a patient who has undergone cardiopulmonary resuscitation, development of delirium in an elderly

individual with a serious infection, or occurrence of focal neurologic deficits in a patient with a ponderous medical record that reveals long-standing diabetes, renal failure, hypertension, and pulmonary disease **(Nunes et al., 2003).**

The patient with the most common of ICU neurologic problems, a depressed state of consciousness, ranging from lethargy to coma, raises a host of questions. Does the patient have a focal brainstem lesion or diffuse cerebral involvement? Is there an anatomic lesion or a metabolic disorder? Have vital brainstem functions been impaired? Is ICP increased? **(Hopkins et al., 1999).**

The most common primary neurologic causes of depressed consciousness include head trauma, intracranial hemorrhage, and, less common, inapparent seizures. The secondary conditions seen most often are metabolic, such as anoxia, drug intoxication, or diabetic acidosis. Sometimes the diagnosis is evident, as in head trauma; other times determination of the cause of depressed consciousness may present a diagnostic challenge, demanding a race against the clock to avoid irreversible changes. In every case, it is crucial to establish whether depressed consciousness is due to intrinsic brainstem damage, increased ICP, toxins, widespread anoxia or ischemia, or some other less common cause. It is particularly important to sort out rapidly the component(s) that may be treatable **(Granja, 2002).**

# Psychological changes in ICU Patients

An acute change in behavior or mental status in the intensive care unit (ICU) patient requires rapid recognition and treatment. The confused patient is often restless and disorganized, and the illusions, hallucinations, and paranoid ideation that accompany confusion can precipitate intense agitation and combativeness **(Irwin and Rippe, 2003).**

The term psychosis does not adequately reflect the range of symptoms seen in confused ICU patients. Traditionally, the term ICU psychosis has been used to designate florid abnormalities of mood and behavior in ICU patients. The term is outmoded and misleading because it implies a cause-and-effect relationship between being in an ICU and becoming psychotic **(Ely, 2001).**

Although some patients may become psychotic in an ICU or enter the ICU with a preexisting psychotic condition (e.g., schizophrenia, manic-depressive psychosis), most patients with mental status changes are delirious because of one or more factors that disrupt the integrity of the central nervous system (CNS) **(Jacobi et al, 2002).**

Psychosis is defined as a loss of contact with reality because of a functional (i.e., nonorganic) disturbance in which the sensorium is normal but thinking is abnormal and associated with abnormal

perceptions (e.g., auditory hallucinations) and systematic delusions (i.e., fixed, false beliefs). In fact, mental status changes in ICU patients are usually characterized by an abnormal sensorium, illusions, delusions that are fleeting and disorganized, and all varieties of hallucinations (i.e., olfactory, tactile, visual, and auditory) **(Jackson and Ely, 2001).**

The onset of confusion in an ICU patient generally signifies an important change in the patient's medical status that warrants evaluation for systemic and metabolic abnormalities, drug toxicity, withdrawal states, and other reversible factors (**Nasraway, 2001).**

The most common Psychological changes in the ICU are:-

- **Delirium.**
- **Agitation.**
- **Anxiety.**
- **Depression.**

## • DELIRIUM

## (Acute confusional state)

Delirium in the Intensive care unit (ICU) is a common and problematic condition that leads to higher morbidity and mortality and extended hospital stays. Delirium is a condition that can be either unrecognized or misdiagnosed. Delirium is considered to be a global manifestation of brain dysfunction. It is defined as a reversible, global impairement of cognitive processes, usually of sudden onset, coupled with disorientataion, impaired short-term memory, altered sensory perceptions (hallucinations), abnormal thought processes and inappropriate behavior **(Elly et al., 2001).**

Delirium is a reversible organic mental disorder whose hallmarks are an acute onset of confusion and an altered level of consciousness. Therefore, it has also been referred to as an acute confusional state. Abnormal consciousness distinguishes delirium from dementia, which is also characterized by confusion but is associated with a normal level of consciousness. Although delirium is usually reversible within a period of days to weeks, some cases progress to irreversible brain failure **(Jacobi et al., 2002).**

Sixty six percent to 84% of delirium in hospitalized patients is unrecognized by clinicians. Delirium has been described as a sundown

syndrome, ICU psychosis, acute confusion, ICU syndrome, encephalopathies, and cognitive impairment **(Ely et al., 2001).**

**Incidence:-**

The highest incidences of delirium have been reported in the surgical ICU, followed by the medical ICU, the coronary care unit (CCU), and the general medical and surgical wards **(Marcantonio et al., 2003).**

Thirty percent of patients in the surgical ICUs and 40% to 50% of patients after hip surgery manifest delirium. A mortality rate between 23% and 33% is documented, three months after a patient is diagnosed with delirium. In a 1 year follow up, there was up to 50 % mortality rate of patients diagnosed with delirium. Up to 60 % of older hospitalized patients(especially those exposed to anesthesia and surgery) develop delirium as a complication during their hospital course **(Pisani, 2003).**

**Clinical Features:-**

The delirious patient exhibits a global impairment of cognitive function characterized by abnormal attention and arousal, impaired short-term memory, and disorientation. Typically, levels of consciousness and activity fluctuate throughout the day and achieve peak intensity at night **(Herridge, 2002).**

Delirium is indicative of cerebral dysfunction. The beginning stages of this process are seen in the prodromal symptoms. These symptoms

include anxiety, restlessness, insomnia, and disturbing dreams and these usually start at night. Delirium can manifest in 2 varieties, hypoactive and hyperactive. Patients can have a mixture of both types, which means at one point they can appear hypoactive and then at another point appear to be hyperactive. Hypoactive delirium includes slowed speech, slowed movements, sluggishness, apathy, depression, and lethargy. Hyperactive delirium includes excessive activity, rapid pressured speech, rage, fear, rapid movements and increased reaction to any stimuli. The hypoactive type may not be recognized because it does not have the physical danger of injury that the hyperactive type has **(Stephens et al., 2004).**

**Etiology:-**

Delirium is considered as a dysfunction in multiple brain regions. Numerous organic disturbances have been implicated in the etiology of delirium and can be listed under one of four major categories,

- primary intracranial disease, which includes infections, stroke, and trauma
- systemic diseases that secondarily affect the brain, which are metabolic diseases, infections, and cardiovascular disease
- exogenous toxic agents
- withdrawal from substances on which the patient has become dependent (e.g., alcohol, sedative-hypnotic agents)(Table 1-1) **(Irwin and Rippe, 2003).**

These conditions are accompanied by a reduction in cerebral oxidative metabolism which is the causative for cognitive impairment. Any disease or toxic agent capable of reducing the supply or utilization of substrates for brain metabolic activity could produce delirium. A reduced rate of cerebral oxidative metabolism reduces acetylcholine synthesis resulting in cholinergic deficiency and thus leads to delirium. Acute confusional states in the elderly are a reaction to stress with elevated levels of cortisol and deleterious effects on anatomical substrates of attention and information processing **(Shintani et al., 2004).**

***(Table 1-1): Differntial Diagnosis of Delirium (Irwin and Rippe, 2003).***

| System Problem | Etiologic Factor |
|---|---|
| **-Primary intracranial disease** | ***Infection**<br>**-HIV encephalopathy**<br>**-Meningitis/encephalitits**<br>**-Neurosyphilis**<br>***Neoplasm**<br>**-Space- occupying lesion**<br>***seizure**<br>**-Postictal state**<br>**-Complex partial seizures/status**<br>***Vascular**<br>**-Hypertensive encephalopathy**<br>**-Intracranial hemorrhage**<br>**-Vasculitis**<br>**-Stroke**<br>***Miscellaneous**<br>**-Normal pressure hydrocephalus** |
| **-Secondary diseases that secondary affect the brain** | ***Cariopulmonary**<br>**-Cardiac arrest**<br>**-Congestive heart failure**<br>**-Respiratory failure**<br>**-Shock** |

| | |
|---|---|
| | ***Endocrine/metabolic** |
| | **-Acid-base disturbances** |
| | **-Adrenal dysfunction** |
| | **-Fluid /electrolyte imbalance** |
| | **-Diabetic ketoacidosis** |
| | **-Hypoglycemia** |
| | **-Hepatic failure (encephalopathy)** |
| | **-Renal failure (uremia)** |
| | **-Parathyroid dysfunction** |
| | **-Thyroid dysfunction** |
| | **-Porphyria** |
| | ***Infection** |
| | **-Sepsis** |
| | **-Subacute bacterial endocarditis** |
| | ***Neoplasm** |
| | **-Paraneoplastic syndromes** |
| | ***Nutritional deficiency** |
| | **-Folic acid** |
| | **-Niacin (pellagra)** |
| | **-Thiamine(Wernicke's encephalopathy, Wernicke-Korsakoff psychosis)** |
| | **-Vitamin B12 (pernicious anemia)** |
| **-Exogenous toxic agents** | ***Drugs of abuse** |
| | **-Alcohol** |
| | **-Amphetamines** |
| | **-Cocaine** |
| | **-LSD** |
| | **-Phencyclidine** |
| | ***Nonmedicinal** |
| | **-Carbon monoxide** |
| | **-Heavy metals** |
| **-Drug withdrawal** | ***Alcohol** |
| | ***Propanediols** |
| | **-Chloral hydrate** |
| | **-Meprobamate** |
| | ***Sedative-hypnotic agents** |
| | **-Barbiturates** |
| | **-Benzodiazipines** |
| | ***Narcotics** |

Table (1-2) shows some of the drugs which are commonly used in the ICU and are known to cause delirium **(Irwin and Rippe, 2003).**

***(Table1-2): Common Delirium-Inducing Drugs Used in the ICU (Irwin and Rippe, 2003).***

| Drug group | Agent |
|---|---|
| • **Antiarrhythmics** | **Lidocaine**<br>**Mexiletine**<br>**Procainamide hydrochloride**<br>**Quinidine sulfate** |
| • **Antibiotics** | **Pencillin**<br>**Rifampin** |
| • **Antichloinergics** | **Atropine sulfate** |
| • **Antihistamines** | **Nonselective**<br>**Diphenhydramine hydrochloride**<br>**Promethazine hydrochloride**<br>**H2 blockers**<br>**Cimetidine**<br>**Ranitidine** |
| • **Beta-blockers** | **Propranolol hydrochloride** |
| • **Narcotic analgesics** | **Meperidine hydrochloride**<br>**Morphine sulfate**<br>**Pentazocine** |

**Risk Factors:-**

Delirium is extremely common in the ICU because of many characteristics of patients in the ICU, including advanced age, critical illness, and multiple medical procedures and interventions. The ICU environment differs significantly from other units; it is noisier and more active at night and there is, continuous contact by the medical staff. This results in the increased potential for inducing fear, anxiety psychologic stress, sleep deprivation, and delirium **(Herridge, 2002).**

Environmental noise and light, frequent nursing assessments, and diagnostic and therapeutic procedures are important causes of sleep disturbances in the ICU. Although sleep deprivation has often been quoted to be a potential cause of delirium in the ICU, no definitive studies have established this (Table 1-3) **(Pisani et al., 2003).**

***(Table 1-3): Risk factors for delirium (Pisani et al., 2003).***

- **Older than 70 years of age**
- **Previous history of depression or dementia**
- **History of congestive heart failure, stroke, or epilepsy**
- **Alcohol abuse within a month**
- **Administration of psychoactive drugs**
- **Drug overdose/illicit drug use**
- **Hypo- or hypernatremia**
- **Hypo- or hyperglycemia**
- **Hypo- or hyperthyroidism**
- **Hypothermia or fever**
- **Serum urea nitrogen:creatinine ratio that is 18 or more**
- **Renal failure (creatinine >2.0 mg/dL)**
- **Liver disease (bilirubin >2.0 mg/dL)**
- **Cardiogenic or septic shock**
- **HIV infection**
- **Tube feeding**

- **Rectal or bladder catheters**
- **Central venous catheters**
- **Malnutrition**
- **Use of physical restraints**
- **Visual or hearing impairment**

Psychoactive drugs are the leading iatrogenic risk factor for complications in hospitalized patients. Moreover, psychoactive drugs are an important contributor to delirium, which represents the leading complication of hospitalization for older persons. Benzodiazipines, narcotics, and other psycho-active drugs are associated with a 3 to 11 fold increased relative risk for the development of delirium. The half life of narcotics can increase six-fold in critically ill patients and the elderly **(Rothschild et al., 2000).**

The elderly are more at risk for delirium. In those patients older than 70, 30% to 50% show signs of delirium while hospitalized. In the elderly, delirium can be the presenting symptom of acute physical illness, and if not recognized, can lead to death. The elderly are more prone to this disorder because of the effects of aging, disease of the brain, reduced neurotransmitters, particularly acetylcholine, reduced vision and hearing, chronic diseases, sleep deprivation, stress, and failure to adapt to residing in unfamiliar environments. Those older than 65 years usually have other medical conditions, they are usually on

at least 6 to 8 medications before coming into hospital. These drugs include agents such as digoxin, antiparkinsonian, antipsychotics, antidepressants, diuretics and sedative hypnotics. Polypharmacy and drug interactions can induce delirium **(Mercantonio et al., 2001).**

Physical conditions that induce delirium include congestive heart failure, pneumonia, urinary tract infections, cancer, uremia, dehydration, sodium depletion, and cerebral infarction **(Stephens et al., 2004).**

**Diagnosis:-**

The *Diagnostic and Statistical Manual of Mental Disorders, fourth edition* (DSM-IV) criteria for the diagnosis of delirium are as follows:

(1) disturbance of consciousness, with reduced ability to focus, sustain, or shift attention;

(2) a change in cognition or the development of a perceptual disturbance that is not better accounted for by a pre-existing dementia;

(3) the disturbance develops after a short period of time and tends to fluctuate;

(4) evidence from history, physical examination, or laboratory findings that the disturbance is caused by the physiologic consequences of a general medical condition **(Meade and Herridge, 2001).**

Delirium is often misdiagnosed as dementia, depression, psychiatric illness, or normal aging. In the ICU setting, lethargy and confusion are viewed as expected outcomes of the ICU stay. Recent research showed that ICU delirium is associated with higher mortality and adverse outcomes even when controlling for baseline and illness variables **(McNicoll et al., 2002).**

The first step in assessing delirium is to determine the patient's baseline cognitive function. Second, the level of consciousness is assessed. The Glasgow Coma Scale (GCS) (Table 1-4) is often used because it is well known and widely-used clinically, however, this scale does not assess agitation, which is often present in delirium The Richmond Agitation Sedation Scale (RASS)(Table 1-5) was developed to incorporate the assessments of agitation and sedation into one scale. It works well for the assessment of altered level of consciousness in delirium, whether it is agitation and hyperalertness or lethargy and somnolence **(Sessler et al., 2002)**

***(Table 1-4): The Glasgow coma scale (Sessler et al., 2002).***

| **Glasgow Coma Score** | | |
|---|---|---|
| **Eye Opening (E)** | **Verbal Response (V)** | **Motor Response (M)** |
| ***4=Spontaneous***<br>***3=To voice***<br>***2=To pain***<br>***1=None*** | ***5=Normal conversation***<br>***4=Disoriented conversation***<br>***3=Words, but not coherent***<br>***2=No words.....only sounds***<br>***1=None*** | ***6=Normal***<br>***5=Localizes to pain***<br>***4=Withdraws to pain***<br>***3=Decorticate posture***<br>***2=Decerebrate***<br>***1=None*** |
| | | **Total = E+V+M** |

***(Table 1-5): The Richmond Agitation Sedation Scale (Sessler et al., 2002).***

| **Richmond Agitation Sedation Scale(RASS)** | | |
|---|---|---|
| **Score** | **Term** | **Description** |
| **4** | **Combative** | ***Combative or violent, immediate danger to staff*** |
| **3** | **Very agitated** | ***Pulls on or removes tube(s) or catheter(s) or has aggressive behavior toward staff*** |
| **2** | **Agitated** | ***Frequent nonpurposeful movement or patient-ventilator dyssynchrony*** |
| **1** | **Restless** | ***Anxious or apprehensive but movements not aggressive or vigorous*** |
| **0** | **Alert and calm** | |
| **-1** | **Drowsy** | ***Not fully alert, but has sustained (more than 10 seconds) awakening, with eye contact, to voice*** |
| **-2** | **Light sedation** | ***Briefly (less than 10 seconds) awakens with eye contact to voice*** |
| **-3** | **Moderate sedation** | ***Any movement (but no eye contact) to voice*** |
| **-4** | **Deep sedation** | ***No response to voice, but any movement to physical stimulation*** |
| **-5** | **Unarousable** | ***No response to voice or physical stimulation*** |

***Procedure for RASS Assessment:-***

**1-Observe patient.**
**a. Is patient alert, restless, or agitated? (score 0 to+4)**
**2-If not alert, state patient's name and instruct to open eyes and look at speaker.**
**b. Does patient awaken, with sustained eye opening and contact? (score -1)**
**c Does patient awaken, with eye opening and contact, but not sustained? (score-2)**
**d. Does patient fail to awaken (no eye contact), but has eye opening or movement in response to voice? (score-3)**
**3. Physically stimulate patient by shaking shoulder or rubbing sternum.**
**e. No response to voice, but response (movement) to physical stimulation. (score -4)**
**f. No response to voice or physical stimulation. (score-5)**

In the third step, a formal cognitive assessment is performed. The special circumstances of the ICU prohibit most direct cognitive testing because the tests are largely language-based and can be difficult to administer in mechanically-ventilated patients. Thus, nonverbal tasks have been developed for the assessment of cognition in the ICU as the basis for the assessment of delirium. The CAM-ICU uses the abbreviated version of the Cognitive Test for Delirium and combines it with the widely used and validate Confusion Assessment Method (CAM). The tasks were designed for nonverbal, mechanically-ventilated, or restrained patients in ICU settings (Table 1-6) **(Ely et al., 2001).**

***(Table 1-6): CAM-ICU features, and assessments (Ely et al., 2001).***

| CAM feature | Description | Method |
|---|---|---|
| 1-Acute onset and Fluctuating course | Is there evidence of an acute change in mental status based on family or nurse observations?<br>Did it fluctuate during the day, come and go, or increase and decrease in severity? | Baseline assessment (MBDRS or IQCODE)<br>Information from nurses and family members<br>Direct observation |
| 2- Inattention | Did the patient have difficulty focusing attention, was easily distractible, had difficulty keeping track of what was said? | Attention Screening Examinations<br>Picture Recognition Test<br>Vigilance A Random Letter Test |
| 3-Disorganized Thinking | Was there disorganized thinking incoherence, rambling, irrelevant conversation, unclear or illogical flow of ideas, or unpredictable switching of ideas? | Yes/no logic questions<br>Simple commands<br>Conversation-if verbal |
| 4-Alttered level of concioussness | Any level of consciousness other than alert and awake (ie, vigilant, lethargic, stuporous or comatose) | Glasgow Coma Scale or Richmond Agitation Sedation Scale |

The CAM-ICU was validated in a large cohort study of patients in the ICU patients against delirium expert assessments; it had a sensitivity of 95% to 100%, a specificity of 89% to 93%, and high inter-observer reliability. Using the CAM-ICU, the prevalence of delirium in the ICU has ranged from 70% to 87% **(Ely et al., 2001).**

## • Agitation

Agitation is most often described as excessive restlessness, which is characterized by nonpurposeful mental and physical activity due to internal tension and anxiety. However, no clear, concise, and universally accepted definition of agitation in ICU patients exists. Patients with agitation have continual movement such as fidgeting, moving from side to side, pulling at dressings and bed sheets, and attempting to remove catheters or other tubes. Patients with agitation are usually disoriented and cannot readily follow commands. Agitation occurs often in the critically ill and may result in unplanned extubation, increased oxygen consumption, hemodynamic instability, injury to self or care providers, and inability to participate in therapeutic interventions. The syndrome complicates management in the ICU, often leading to further morbidity and complications **(Riker et al., 1999).**

Agitation is associated with inappropriate verbal behavior, physical aggression, and increased motor activity on the part of the patient. Agitation may lead to harm to the patient or caregivers. Agitation is considered to be further along a continuum of emotional turmoil and upset than is anxiety. Agitation is a common finding in the ICU **(Bair et al., 2000).**

**Clinical Features:-**

Agitated patients exhibit continual movement, characterized by constant fidgeting, moving from side to side, pulling at dressings and bed sheets, and attempting to remove catheters or other tubes. There may be a total lack of awareness as to name, place, or time. Alternatively, patients may know who they are, but have no idea of their current location **(Wise and Cassem, 1997).**

The agitated patient will often exaggerate complaints of pain, when, in actuality, other factors such as the need to urinate or have a bowel movement are the causes of the complaints **(DeJonghe et al., 2000).**

None of the above descriptions characterize a patient undergoing neuromuscular blockade who is agitated because of lack of sedation and analgesia. This condition, which often results in patients having vivid recall while under pharmacologic paralysis, is a particularly disturbing occurrence to critical care unit personnel, and may have long-term negative effects on the patient **(Weinart et al, 2001).**

Vital signs are generally abnormal in the agitated patient. Blood pressure may increase to dangerously high ranges, respiratory rate may be elevated, and heart rate may increase, with potential for ischemia .An elevated metabolic rate results in an increase in overall oxygen requirements and, if left to continue for a protracted period of time, an

increase in caloric demand. The agitated patient with a rapid respiratory rate may not be able to synchronize respirations with the mechanical ventilator, resulting in high airway pressures, inadequate ventilation, and decreases in $P_{O_2}$ with either increases or decreases in $P_{CO_2}$, all of which further propagate the tendency toward agitation **(Harvey et al., 1996).**

**Etiology:-**

In the postoperative patient, the multiple pharmacologic agents typically administered during the perioperative stage can result in significant and often unpredictable interactions, leading to agitation and confusion. These agents include benzodiazepines, opioids, inhalation agents, anticholinergics, antibiotics, and muscle relaxants; they can interact in unpredictable ways and may lead to a difficult management situation, especially in the elderly. In addition to drug-drug interactions, some agents alone, including lorazepam and anticholinergics, have been associated with the development of agitation; once again, the aged are particularly at risk (Table 1-7) **(Haskell et al., 1997).**

*(Table 1-7): Medications associated with agitation in patients in the intensive care unit (Haskell et al, 1997).*

| Antibiotics | Cardiac drugs |
|---|---|
| Acyclovir | Captopril |
| Amphotericin B | Clonidine |
| Cephalosporins | Digoxin |
| Ciprofloxacin | Dopamine |
| Imipenen—cilastatiri | Labetalol |
| Ketoconazole | Lidocaine |
| Metronidazole | Nifedipine |
| Penicillin | Nitroprusside |
| Rifampin | Procainamide |
| Trimethoprim—sulfamethoxazole | Propranolol |
| | Quinidine sulfate |
| **Anticonvulsants** | **Corticosteroids** |
| Phenobarbital | Dexamethasone |
| Phenytoin | Methylprednisolone |
| **Miscellaneous drugs** | **Narcotic analgesics** |
| Hydroxyzine | Codeine |
| ketamine | Meperidine |
| Metoclopramide | Morphine sulfate |
| Theophylline | |
| Anticholinergics | |
| Benzodiazepines | |
| Nonsteroidal anti-inflammatory agents | |

A significant factor in the development of agitation in critically ill patients, predominantly in the postoperative period, is failure to provide adequate pain control **(Sessler et al., 2001).**

Hypoxemia has long been associated with agitation. ICUs in most hospitals have documented numerous clinical incidences in which hypoxemia had been misdiagnosed as agitation. PO2 levels of 60 mm Hg or less (or oxygen saturations below 90%) can contribute to agitation secondary to hypoxemia. Hypotension has also been associated with agitation and is considered a form of brain injury resulting from hypoperfusion. Likewise, hyper- and especially hypoglycemia can promote severe agitation. Uremia and the presence of elevated levels of heavy metals such as lead, mercury, and manganese also have been identified as causes of significant agitation in the critically ill patient **(Cooper et al., 2001).**

Another cause of minor to severe agitation is brain injury, including closed head trauma and bleeds from a ruptured aneurysm with resulting subarachnoid hemorrhage. Thrombotic stroke may cause agitation as well. Brain abscesses, seizures, infections such as meningitis, and air embolism have all been associated with persistent and severe degrees of agitation **(Haskell et al., 1997).**

Withdrawal from alcohol or from other agents including cocaine, opioids, and sedatives such as benzodiazepines all contribute to brain injury and agitation **(Jenkins , 2000).**

Agitation can occur in patients who develop significant ventilator desynchronization. This is frequently caused by a poorly performing ventilator, with a delay in responding to the patient's efforts at spontaneous breathing. Patients who require short- or long-term intubation may also develop agitation, because of the stimulus of the endotracheal tube itself **(Hassan et al., 1998).**

**Diagnosis:-**

Agitated patients require that the clinician undertake a detailed work-up to find and eliminate the various possible causes. At the top of any list, because of its accompanying danger, should be hypoxemia, which can be readily detected by both arterial blood gas analysis and measurement of oxygen saturation **(Kress et al., 2000).**

Metabolic abnormalities can usually be detected by laboratory analysis, including a basic electrolyte panel and determination of specific factors including phosphate, calcium, and glucose levels. It is often necessary to order additional tests, not routinely performed, such as a thyroid panel and liver function studies. Deficiencies in vitamin B-12, niacin, and thiamine should be considered, as well as heavy metal intoxication with lead, mercury, or manganese **(Young et al., 2000).**

Neurologic abnormalities often require not only a detailed examination but also a computed tomography (CT) scan and, in some cases, a magnetic resonance imaging (MRI) scan **(Jacobi et al., 2002).**

Patients with chronic pain syndromes, such as low back pain, may become quite uncomfortable when confined to one position in a hospital bed in the ICU. Obtaining an adequate history will assist in making this specific diagnosis **(Mercantonio et al., 2001).**

Consequences of numerous drug interventions—drug reactions, drug interactions, and drug withdrawal—increase the incidence of agitation in the ICU**.** To diagnose an adverse drug interaction, it is often necessary to sequentially eliminate one or more agents, or in some cases all agents **(Harvey, 1996).**

Infections can lead to agitation, but are more likely to manifest as increased lethargy, with the patient becoming less responsive to stimuli and commands. Endotoxin release from an ongoing illness may directly affect brain function. It has been demonstrated in patients with sepsis that amino-acid levels are commonly altered both in plasma and cerebrospinal fluid. Furthermore, normal brain metabolism can be impaired in septic patients **(Haskell et al., 1997).**

Renal and hepatic failure may also lead to various levels of agitation. Diagnostic features of hepatic failure include neurologic dysfunction with signs of encephalopathy and triphasic waveforms seen

on the EEG. Similar EEG changes can also be present in renal failure; however they are not necessarily specific **(Crippen, 1990).**

**Scales to Monitor Agitation:-**

The most commonly used scale in current is the Ramsay Sedation Scale. The Ramsay scale identifies six levels of sedation ranging from frank agitation to deep coma (Table 1-8) **(Delvin et al., 1999).**

***(Table1-8): Ramsay scale for assesseing level of sedation (Delvin et al., 1999).***

| Level | Response |
|---|---|
| 1 | Patient awake and anxious, agitated, and/or restless |
| 2 | Patient awake, cooperative, accepting ventilation, oriented, and tranquil |
| 3 | Patient awake, responds to commands only |
| 4 | Patient asleep; brisk response to light glabellar tap or loud auditory stimulus |
| 5 | Patient asleep; sluggish response to light glabellar tap or loud auditory stimulus but does respond to painful stimulus |
| 6 | Patient asleep, no response to light glabellar tap or loud auditory stimulus |

Another scale is the Richmond Agitation Sedation Scale (RASS) (Table 1-5) **(Sessler et al., 2002).**

## • Anxiety

Anxiety is a psychophysiological phenomenon experienced as a foreboding dread or threat to a human organism whether the threat is generated by internal, real or imagined dangers. Anxiety has been described as a subjective feeling of distress and anguish that has affective, motivational, behavioral, and physiological components. A key feature of anxiety is its subjective nature **(Ely et al., 2001).**

Anxiety is a diffuse and unpleasant emotion of apprehension that is not associated with a specific threat. It is a condition characterized by increased motor activity and autonomic arousal. Anxiety also may be manifested by fearful withdrawal. The combination of pain, altered sensory inputs, and an unfamiliar environment can lead to abnormal psychologic manifestations in hospitalized patients, particularly in patients in the critical care setting. These patients have the most severe illnesses, the most intensive monitoring, and are exposed to a myriad of strange faces. For the mechanically ventilated patient the inability to talk and express fear may be the most agonizing state of all. Anxiety can lead to a situation in which weaning of mechanical ventilation becomes difficult or even impossible because the patient experiences repeated episodes of breathlessness **(Fraser et al., 2000).**

Anxiety in the critical care setting may be expected as a transient response to the stress of hospitalization; however, excessive or pathologic anxiety has a negative impact on patient morbidity, mortality, and compliance with treatment. It has been reported that anxiety disorders have a prevalence of 6% to 10% in primary care settings, 10% to 14% in cardiology practices, and 5% to 20% among medical inpatients **(Baker, 2000).**

Following certain types of major elective surgery, patients routinely spend the immediate post-operative period in the ICU, and these planned post-operative patients constitute a large percentage of intensive care patients. For many such patients, the ICU environment can be a 'wildly unfamiliar' one, depriving them of normal interactions and sensations while constantly bombarding them with strange sensory stimuli.. This situation can exacerbate the feelings of anxiety that the patient may already be experiencing from the surgery and, consequently, trigger psychological abnormalities collectively referred to as 'intensive care syndrome' **(Cole-King and Harding, 2001).**

Patients hospitalized in the intensive care unit (ICU) encounter internal and external dangers: fear of death, separation from loved ones and familiar surroundings, loss of control, intimacy with strangers, sleep loss, and frequent procedures that are painful or restrict mobility (e.g., placement of an intraaortic balloon pump). Patients experience anxiety about their illness and about their capacity to work and maintain social

and family relationships in the future **(Shi et al., 2003).**

Anxiety and fear can be clinically indistinguishable; however, their causes are different. Fear is the sense of dread and foreboding that may occur in response to an external threatening event (e.g., being attacked). Anxiety is the same distressing experience of apprehension and foreboding as fear except that it derives from an unknown internal stimulus, inappropriate or excessive to the reality of the external stimulus or concerned with a future one **(Shuldham et al., 2002).**

**Clinical Features:-**

The physical signs and symptoms of anxiety are generally those associated with autonomic arousal (e.g., tachycardia, tachypnea, diaphoresis, lightheadedness). Many physical symptoms of anxiety are also manifestations of critical illness; attention to the characteristics of anxiety is often necessary to minimize diagnostic confusion **(Arthur et al., 2000).**

The behavioral consequences of anxiety include the avoidance of distressing situations, noncompliance with procedures, or flight from the hospital. The cognitive aspects include worry, apprehension, and thoughts about emotional or bodily damage **(McDonald et al., 2004).**

**Causes of Anxiety:-**

A patient's known medical illness, its complications, and its treatment should be suspected as causes of anxiety. For example, hypoxia, hyperventilation, and sympathomimetic bronchodilators may all contribute to anxiety in a patient with chronic obstructive pulmonary disease. In addition, risk factors such as a family history of a disorder thought to be anxiety related (e.g., hyperthyroidism) may provide important information to guide further assessment. **(Scott, 2004).**

The differential between an organic anxiety syndrome and a primary anxiety disorder may be clarified by systematic consideration of the following six factors that suggest the presence of an organic cause:

- onset of anxiety symptoms after the age of 35 years.
- lack of personal or family history of an anxiety disorder.
- lack of childhood history of significant anxiety, phobias, or separation anxiety.
- absence of a significant life event generating or exacerbating the anxiety symptoms.
- lack of avoidance behavior.
- poor responses to standard antipanic agents (i.e., antidepressants or benzodiazepines) **(Shuldham, 2001).**

The emergence of anxiety symptoms within 48 to 72 hours after admission raises the suspicion of withdrawal from alcohol or other drugs (e.g., sedative-hypnotics, opiates) **(Wong and Arthur, 2000).**

Complex partial seizures secondary to limbic system irritability may cause anxiety symptoms. Patients may present with episodic anxiety or panic associated with a variety of physical symptoms, including chest pain, tachyarrhythmias, syncope, abdominal distress, changes in level of consciousness, and staring spells, as well as hallucinations **(Ely et al., 2001).**

Patients with a number of primary psychiatric disorders may present with anxiety in the ICU. Usually, a history of psychiatric illness precedes the patient's entry into the ICU and is exacerbated by the acute medical or surgical condition. Examples of primary psychiatric disorders associated with anxiety are panic disorder, generalized anxiety disorder, simple phobia, social phobia, posttraumatic stress disorder, and obsessive compulsive disorder **(Sessler et al., 2002).**

## • Depression

Intense emotions are evoked routinely in intensive care units (ICUs). In the ICU, depression occurs as a psychological reaction to an acute medical illness or as a manifestation of a primary affective disorder detected at the time of medical evaluation **(Irwin and Rippe, 2003).**

The term depression is often used to describe clinical signs and symptoms (e.g., transient feelings of discouragement, disappointment, sadness, grief) of a disorder with neurovegetative symptoms (i.e., major depressive disorder) that may involve psychotic features (e.g., hallucinations, delusions). The term depression is defined in the fourth edition of Diagnostic and Statistical Manual of Mental Disorders as a syndrome that affects neurovegetative functions (e.g., sleep, appetite, concentration) as well as mood **(Aronson and Ayres, 2005).**

## Diagnostic Criteria of Depression:-

Important questions for the clinician who works in the ICU are "What is depression?" and "What does a patient experiencing depression look like in the ICU?" To qualify for a diagnosis of major depression, a patient must have a sustained period of depressed or hopeless mood for a period of at least 2 weeks in association with at least four of the following eight neurovegetative symptoms:

- a change in sleep patterns
- a decrease in one's interests or drives in life
- a sense of guilt
- a decrease in energy
- a decrease in concentration ability (e.g., not being able to read a newspaper article all the way through or follow a television show).
- a change in appetite (either an increase or decrease)
- a change in psychomotor activity [i.e., either decreased (psychomotor retardation) or increased (psychomotor agitation)]
- suicidal ideation (e.g., with an active plan to commit suicide) or thoughts of death **(Murray et al., 2004).**

**Causes:-**

Various medications and medical illnesses can cause affective disorders (Table 1-9). Endocrine disorders (especially hypothyroidism, Cushing's disease, and parathyroid disturbances), neurologic disorders (e.g., poststroke states), and human immunodeficiency virus (HIV) infections are frequently accompanied by depression. HIV infection is a common cause of depression in critically ill patients. Depression may be the first manifestation of HIV infection as well as the first manifestation of an endocrinopathy or a carcinoma **(Aronson and Ayres, 2005).**

***(Table1-9): Medical Conditions Associated with Depressive Symptoms (Aronson and Ayres, 2005).***

***Cardiovascular**
- **-Cardiac tumors**
- **- Congestive heart failure**
- **- Hypertensive encephalopathy**

***Collagen vascular**
- **-Polyarteritis nodosa**
- **-Systemic lupus erythematosus**

***Endocrine**
- **-Diabetes**
- **-Hyperadrenalism**
- **-Hypoadrenalism**
- **-Hyperparathyroidism**
- **-Hypoparathyroidism**
- **-Hyperthyroidisim**
- **-Hypothyroidism**

***Infection**
- **-Hepatitis**
- **-HIV**
- **-Mononucleosis**
- **-Postinfluenza**

***Metabolic**
- **-Acid-base problems**
- **-Hypokalemia**
- **- Hypernatremia**
- **- Hyponatremia**
- **-Renal failure**

***Neoplasms**
- **- Carrinoid**
- **-Pancreatic carcinoma**

***Neurologic**
- **-Brain tumor**
- **-Multiple sclerosis**
- **-Parkinson's (especially with on/off phenomenon)**
- **-Temporal lobe epilepsy**

There are several drugs that may cause depressive symptoms (Table 1-10). The agents most often responsible for depression in the coronary care unit are antihypertensives, beta-blockers, antiarrhythmics, antihistamines (e.g., cimetidine, ranitidine), and steroids. If a drug regimen or dosage appears to be temporally related to the patient's depression, the dose should be lowered or eliminated entirely **(Thomas et al., 1997).**

***(Table 1-10): Drugs associated with Depressive Symptoms (Irwin and Rippe, 2003).***

**-Acydovir (especially at high doses)**
**-Alcohol**
**-Amphetamine-like drugs (withdrawal): phenylpropanolamine, phenmetrazine, fenfluramine**
**-Anabolic steroids: methandrostenolone, methyltestosterone**
**-Anticonvulsants (at high doses or plasma levels):carbamazepine (Tegretol),**
**-phenytoin, primidone**
**-Antihypertensives: reserpine, methyldopa, thiazides, clonidine, hydralazine hydrochloride**
**-Asparaginase**
**-Barbiturates**
**- Benzodiazepines: triazolam, alprazolam (Xanax), clonazeparn, chlorazepate,**
**diazepam, lorazepam**
**-Beta-blockers: .atenolol, betaxolol, propranolol, timolol**
**-Bromide**
**- Bromocryptine**
**- Carbon monoxide**
**-Cimetidine**
**- Cocaine (withdrawal)**
**-Oral contraceptives**
**-Corticosteroids**
**-Cyclosporine**

**-Dapsone**
**-Digitalis**
**-Diltiazem**
**-Disopyramide**
**-Ethionamide**
**-Halothane (postoperatively)**
**-Heavy metals**
**-H2 receptor antagonists: cimetidine, ranitidine**
**-Interferone-alpha**
**-Isoniazid**
**-Isotretinoin**
**-Levodopa (especially in the elderly)**
**-Mefloquine**
**-Metoclopromide**
**-Metrizamide**
**-Metronidazole**
**-Nalidixic acid**
**-Narcotics: morphine,meperidine, methadone, pentazocine, propoxyphene**
**-Nifedipine**
**-Nonsteroidal anti-inflammatory drugs**
**-Norfloxacin**
**Phenylephrine**
**-Prazosin**
**-Procaine derivatives: penicillin G procaine, lidocaine, procainamide**
**-Thyroid hormone**

# Neurological Changes in ICU patients

Neurologic problems present in the intensive care unit (ICU) in two modes, primary neurologic problems such as stroke, Guillain-Barré syndrome, head trauma, or myasthenia gravis who are admitted to the ICU for close observation and management of vital functions, such as respiration or control of ICP. The other type of patients includes those with secondary neurologic complications, occurring in patients with other medical or surgical disorders **(wijdicks, 2001).**

The most common neurological problems encountered in the ICU are

- **Metabolic encephalopathy.**
- **Generalized anoxia/ischemia of the nervous system (N.S).**
- **Cerebrovascular Disease.**
- **Neuropathy and Mypoathy in the ICU.**

## • Metabolic Encephalopathy

Metabolic encephalopathy is a general term used to describe any process that affects global cortical function by altering the biochemical function of the brain. It is the most common cause of altered mental status in the intensive care unit (ICU) setting, either medical or surgical, and is also the most treatable condition in the ICU **(Azim and Walker, 2003).**

Early recognition of metabolic encephalopathy, therefore, is critical to the management of the ICU patient. The patients who are most at risk for development of a metabolic encephalopathy are shown in (Table 2-1)**( Hung et al., 2001).**

***Table(2-1): Risk Factors for development of metabolic encephalopathy (Hung et al., 2001).***

- **Those with single or multiple organ failure**
- **Those receiving multiple central nervous system (CNS) toxic agents**
- **Those with severe nutritional deficiencies such as cancer patients and alcoholics**
- **Infection**
- **Temperature dysregulation (hypothermia and fever)**
- **Chronic degenerative neurologic or psychiatric diseases such as dementia or schizophrenia**
- **Endocrine disorders**

Metabolic encephalopathy is always suspected when there is an altered cognitive status in the absence of focal neurologic signs or an obvious anatomic lesion such as an acute cerebrovascular accident or head injury **(Thomson et al., 2002).**

**Clinical Features:-**

Initial observation of the patient's level of arousal, posture in bed, breathing pattern, vital signs, and behavioral fluctuations is highly suggestive of a metabolic disturbance in many cases. Often signs of sympathetic overactivity (tachycardia, elevated blood pressure, tremulousness) and abnormal sleep patterns or "sun-downing" are present **(Parsons et al., 2002).**

Changes in the respiratory pattern are the next most important findings for the diagnosis of metabolic encephalopathy, also providing a clue as to its etiology. In the mildly confused patient, breathing may be normal, but lethargic or mildly obtunded patients tend to hyperventilate, with brief spells of apnea. This is due to transient lowering of the partial pressure of carbon dioxide ($PCO_2$)below 15 mm Hg without the appropriate CNS drive to breathe more rapidly at a lower tidal volume **(Robins et al., 2001).**

Abnormal motor activity is characteristic of many metabolic encephalopathies and is quite varied in appearance; tremors, myoclonus, rigidity, and choreoathetosis may be seen. Tremors are rhythmic, involuntary oscillatory movements seen in all limbs and often

exaggerated during voluntary movement **(Van den Berghe et al., 2005).**

Seizures are another significant symptom of metabolic encephalopathy, especially in uremia, hypoglycemia, pancreatic failure, and various types of metabolic acidosis (e.g., ethylene glycol and salicylates). They occur most often at the onset of the metabolic disturbance, for example as the blood urea nitrogen (BUN) is climbing acutely, and as a preterminal expression of severe neuronal injury in a comatose patient. Management of the seizures is typically ineffective until the underlying cause is corrected **(Wilmer et al., 2006).**

The laboratory investigation of patients with delirium or coma is crucial in defining the cause of a metabolic encephalopathy. Blood tests for glucose, electrolytes, and blood gases should be drawn immediately along with a panel of hepatic function tests [ratio of serum alanine aminotransferase to serum aspartate aminotransferase, lactate dehydrogenase, ammonium ion ($NH_4^+$)], BUN, and creatinine. Serum and urine osmolality, cerebrospinal fluid (CSF) analysis, serum magnesium and phosphate levels, and specific hormone levels may be needed to define the cause of encephalopathy further **(Young et al., 2003).**

**Etiology:-**

- **Hepatic Failure:-**

The clinical onset of hepatic encephalopathy may be subtle, with a

blunting of affect and lethargy, or dramatic in 10% to 20%, with mania or an agitated delirium . It is easy to recognize hepatic encephalopathy in an individual with the obvious stigmata of chronic liver disease, such as ascites, varices, or jaundice. In those without apparent liver disease, the mental changes may only appear after an additional metabolic demand on the liver. Such stressors are a high-protein meal, gastrointestinal bleeding with increased blood absorption from the gut, or hepatically metabolized drugs **(Ahboucha and Butterworth, 2004).**

Asterixis is the next most common clinical sign, appearing in all limbs, the jaw, and the tongue. As the patient progresses into a coma, it may be replaced by muscle spasticity and decorticate or decerebrate posturing to stimulation **(Cordoba et al., 2004).**

The pathophysiology of hepatic coma is not certain, but it is thought to be caused by portacaval shunting of neurotoxic substances **(Ferenci et al., 2002).**

The serum transaminases are usually elevated two to three fold, and serum ammonia is at least in the high normal range once the patient is lethargic **(Mas et al., 2003).**

- **Renal Failure:-**

Uremic encephalopathy may develop acutely, be superimposed on chronic renal insufficiency, or occur as a consequence of chronic dialysis. It is often a complication of systemic diseases that

independently affect the kidneys and the CNS—collagen-vascular disease, malignant hypertension, drug overdoses, diabetes, or bacterial sepsis **(Fraser and Arieff, 1997).**

The first sign of encephalopathy in uremia is delirium or a decrease in level of consciousness; hyperventilation and increased motor activity follow as the patient becomes obtunded. Also, there is a high frequency of generalized convulsions at the outset and a metabolic acidosis with low serum bicarbonate. The motor component is prominent in many patients with multifocal myoclonus, hypertonus or asterixis, and tremors, together producing a picture of "twitch- convulsif"—as if the patient had fasciculations **(Zweifler, 2003).**

- **Pulmonary Failure:-**

A combination of hypoxemia and hypercarbia can produce typical changes of a metabolic encephalopathy in patients with underlying pulmonary failure **(Collins et al., 2006).**

This may be precipitated by systemic infection with fatigue of ventilatory muscles, paralysis of these muscles by neuromuscular disease or Guillain-Barré syndrome, and sedative drugs with their depressant effect on the medullary respiratory center **(Maisel et al., 2002).**

The critical factor in the development of pulmonary encephalopathy is a rapid increase in serum $PCO_2$. This may be complicated by the presence of sedatives, hypoxemia, cardiac failure, and renal hypoperfusion **(Mueller et al., 2006).**

- **Hypoglycemic Encephalopathy:-**

Hypoglycemia can occur as an isolated problem or as a complication of liver failure, of tumors producing insulin-like substances, or of urea cycle defects **(Altuntas et al., 2005).**

An initial insulin reaction occurs when the serum glucose drops below approximately 40 mg/dL, producing flushing, sweating, faintness, palpitations, nausea, and anxiety. This persists for several minutes before the patient becomes confused and either agitated or drowsy. Focal neurologic signs such as hemiparesis, cortical blindness, or dysphasia may appear at this point, mimicking an acute stroke. If the serum glucose drops below 30 mg/dL, generalized convulsions may occur in flurries followed by a postictal coma **(Bourcigaux et al., 2005).**

When severe hypoglycemia is sustained for more than 10 minutes, stepwise progression of neurologic signs occurs. Finally, decerebrate rigidity is seen before the so-called medullary phase of hypoglycemia. The medullary phase describes a state of deep coma with dilated pupils, bradycardia, hypoventilation, and generalized flaccidity **(Ragland, 1996).**

- **Electrolyte Disturbances:-**

Hyponatremia and hypernatremia cause fluid shifts and critical changes in serum osmolality. Mild to moderate hyponatremia (120 to

130 mEq/L) is evidenced by confusion or delirium with asterixis and multifocal myoclonus. If the serum sodium goes below 110 mEq/L, or drops at a rate greater than 5 mEq/L /hour to 120 mEq/L and below, seizures and coma are likely to follow. Common causes of hyponatremia are the syndrome of inappropriate antidiuretic hormone excretion, excess volume expansion with hypotonic IV solutions; and renal failure with a decreased glomerular filtration rate . Other less common causes include psychogenic polydipsia, severe congestive heart failure, and Addison's disease **(Laffey and Kavanagh, 1999).**

Hypernatremia is not seen very often outside the hospital setting except in children with severe diarrhea and inadequate fluid intake. Excess diuretic therapy, hyperosmolar tube feedings, and restricted access to fluids are reflected in a serum sodium of greater than 155 mEq/L in institutionalized patients. With levels of sodium greater than 170 mEq/L developing acutely, subdural hematomas can occur as a result of stretching of the dural vessels off the dehydrated cortex. These patients may complain of headache, develop seizures, or simply drift into a stupor. Catastrophic complications such as venous sinus thrombosis and irreversible coma are seen with a serum sodium level of greater than 180 mEq/L due to the marked hyperosmolality that accompanies it **(Rose and Post, 2001).**

- **Acid-Base Disturbances:-**

Metabolic acidosis by itself produces only mild delirium or confusion

but may be accompanied by organ failure, direct CNS toxicity from drug metabolites, or volume depletion. The first sign of an encephalopathy caused by metabolic acidosis is hyperpnea followed by mental status changes and mild muscular rigidity **(Kaller et al., 2000).**

- **Endocrine Disorders:-**

Addison's disease or secondary adrenocortical deficiency occurs acutely in the setting of septicemia, surgery, and most frequently, sudden withdrawal of chronically administered steroids, presenting with hypotension, a mild hyponatremia, hypoglycemia, and hyperkalemia, together with a delirium or stupor that fluctuates. Unlike many metabolic encephalopathies, adrenocortical insufficiency is associated with decreased muscle tone and deep tendon reflexes. Seizures and papilledema may appear when the patient has a profound adrenocorticotropic hormone deficiency and coma **(Laureti et al., 2000).**

Excess steroids produce different forms of encephalopathy depending on whether the source is endogenous or exogenous. In Cushing's disease, psychomotor depression and lethargy are the norm,

whereas high doses of prednisone usually cause elation, delirium, or frank psychosis . The latter is not uncommon in the ICU setting due to the administration of stress levels of steroids and multiple other CNS toxins **(Rivers et al., 2001).**

Hypothyroidism is now a rare cause of encephalopathy and coma. It may be confused initially with other causes of hypotension, hypoventilation, and hyponatremia, such as septic shock, brainstem infarcts, or an overdose of sedatives. The diagnosis should be considered in any patient with hypothermia, pretibial edema, pseudomyotonic stretch reflexes (e.g., delayed relaxation of the knee jerk), and coarse hair or facies **(Ringel, 2001).**

Thyrotoxicosis is more difficult to recognize because it can present as a thyroid storm or in a subacute form. In a thyroid storm, the patient with hyperthyroidism may be stressed by an infection or surgery and responds with marked signs of hypermetabolism: tachycardia, fever, profuse sweating, and pulmonary or congestive heart failure. Neurologically, the individual becomes acutely agitated and delirious and then progresses into a stupor. The subacute picture that precedes this is one of mild irritability, nervousness, tremors, and hyperactivity and is often misdiagnosed as an affective disorder rather than endocrine in origin **(Ringel, 2001).**

Hyperparathyroidism may be manifest neurologically with asthenia or a vague change in personality. The patient is mildly depressed, lacks energy, and fatigues easily. A serum calcium greater than 12 mg/dL and elevated parathormone levels are important diagnostic findings. Occasionally, psychiatric symptoms predominate, starting with delirium and psychosis, or obtundation and coma when the serum calcium exceeds 15 mg/dL **(Burman and Wartofsky, 2001).**

Hypocalcemia due to hypoparathyroidism produces an encephalopathy that parallels the depression of serum calcium levels. At less than 4.0 mEq/L calcium, a blunted affect and seizures are common and may be confused with a dementing process or epilepsy. The motor signs of hypocalcemia, that is, tetany or neuromuscular irritability, should make one suspicious of a metabolic disturbance. Another diagnostic dilemma is the occasional presentation of hypocalcemia with papilledema and headache **(Vasa and Molitch, 2001).**

- **Generalized Anoxia/Ischemia of the Nervous System**

Anoxic brain injury results from inadequate oxygen supply to the brain. The clinical picture ranges from mild confusion to deep coma with loss of brainstem responses. Anoxic damage can be caused by circulatory collapse, respiratory failure, or inadequate hemoglobin binding to oxygen **(Zandbergen et al., 1998).**

**Pathogenesis:-**

The brain is unique in that it uses almost exclusively aerobic metabolism of glucose. The continuous availability of oxygen is secured by the cerebral vasculature's autoregulatory mechanism, which controls the rate of blood flow over a wide range of blood pressures. If blood pressure drops too low for autoregulatory mechanisms to operate, oxygen extraction from the blood increases. Failure of this compensatory mechanism results in a changeover from aerobic to anaerobic metabolism **(Arbelaez, 1999).**

In cardiac arrest, depletion of brain oxygen reserves occurs within 10 seconds, thereby eliminating the major source of neuronal adenosine triphosphate and phosphokinase. Excessive glutamate release and reduced reuptake lead to activation of the N-methyl- D-aspartate receptors and consequent ischemic cascade. The resulting intracellular

(cytotoxic) edema leads to increased intracranial pressure. The changeover to anaerobic metabolism results in neuronal catabolism. In cardiovascular collapse, loss of venous outflow leads to the accumulation of lactic acid and pyruvate, the end-products of anaerobic metabolism. Buildup of these catabolites potentiates the cellular damage **(Moonis and Fisher, 2001).**

**Diagnosis:-**

The first question to address when evaluating a comatose or obtunded patient with a possible hypoxic insult is whether the impaired consciousness is the result of a metabolic insult or a structural brain lesion. Coma caused by a mass lesion is usually associated with focal neurologic signs. Computed tomography (CT) or magnetic resonance imaging scans usually reveal focal lesions in this setting **(Schoerkhuber et al., 1999).**

The diagnosis is often suggested by the clinical setting (e.g., cardiac arrest in patients with arrhythmias or myocardial infarctions or severe episodes of intraoperative hypotension). Arterial blood gas determination, if obtained during the causal event, can confirm the diagnosis. A partial pressure of oxygen of less than 40 mm Hg causes confusion and less than 30 mm Hg results in coma. Associated abnormalities that potentiate anoxic damage include anemia, acidosis, hypercapnia, hyperthermia, and hypotension **(Rosen et al., 1998).**

**Clinical Features:-**

The symptomatology and clinical outcome of patients with sustained anoxic injuries depend on the degree and duration of oxygen deprivation to the brain as well as the maintenance of blood flow. With complete cessation of blood flow to the brain, consciousness is lost after several seconds. If the duration of oxygen deprivation is moderately prolonged, the patient awakens but may have residual deficits, such as cognitive impairment, or later sequelae, including extrapyramidal movement disorders or seizures, that may not develop for days to weeks **(Bernard et al., 2002).**

With prolonged, severe hypoxia the patient is comatose with loss of brainstem reflexes. Many patients with severe anoxic changes die within 48 hours; others live in vegetative states. In patients who survive, the rate of improvement slows after the first few weeks or months; return of cognitive function late in the clinical course is rare, particularly in elderly individuals **(Gunn and Gunn, 1998).**

**Prognosis:-**

The overall prognosis for a meaningful recovery in patients with nontraumatic coma is poor. The longer patients are in coma, the worse the outcome . Most improvement occurs within the first 30 days. A good outcome is seen in 50% of patients who awaken within 24 hours. Few patients who remain in a coma beyond 1 day regain normal

function. The occurrence of seizures or myoclonus is not related to ultimate recovery. Myoclonic status is, however, a grave prognostic sign in comatose patients and implies severe neuronal damage and likely poor recovery **(Van Bel et al., 1998).**

In cases of nontraumatic coma, the most valuable prognostic information is obtained from the physical examination(Table2-2) **(Bernard et al., 2002).**

***(Table 2-2): Prognostic indicators (Bernard et al., 2002).***

| **Favorable prognostic indicators** | **Poor prognostic indicators** |
|---|---|
| 1-Recovery of multiple brainstem responses within 48 hours (pupillary, oculocephalic, and corneal).<br>2-Return of purposeful responses to painful stimuli by 24 hours.<br>3-Primary pulmonary event leading to coma.<br>4.-Hypothermia at the time of the anoxic event may be protective; patients who have experienced near-drowning submerged in cold water up to 40 minutes may return to normal neurologic function.<br>5-Younger age (children and young adults). | 1-Absence of pupillary or motor response to pain by the third day.<br>2-The loss of vestibuloocular responses at 12 hours and the presence of decerebrate or decorticate posturing at 24 hours.<br>3-Electroencephalogram (EEG) patterns: nonreactive EEG; burst suppression; alpha coma. Serial EEGs documenting improvement are associated with a better prognosis.<br>5-The presence of either diffuse edema or watershed infarctions on CT scans.<br>6-Loss of gray-white matter distinction on CT scan and severe abnormalities on diffusion-weighted imaging. |

## • Cerebrovascular Disease

Cerebrovascular disease encompasses stroke due to thrombotic or embolic ischemia, intracerebral hemorrhage (ICH), and subarachnoid hemorrhage **(Brown and Morgenstern, 2005).**

### • I-Ischemic Cerebrovascular Disease:-

ICVD is the most common neurologic problem that leads to acute hospitalization. Admission to the ICU is indicated in patients with impaired consciousness; associated co-morbid conditions, particularly myocardial infarction; stroke after coronary artery bypass grafting; symptomatic secondary hemorrhagic conversion with neurologic deterioration; and for the initial 24 hours after administration of intravenous (IV) recombinant tissue plasminogen activator (rt-PA) **(Fiebach et al., 2004).**

Two broad clinical, anatomic categories of ICVD syndromes are recognized, based on division of the cerebrovascular supply into those areas supplied by the carotid system and those supplied by the vertebral-basilar system. Symptoms commonly encountered in carotid-system disease include aphasia, monoparesis or hemiparesis, monoparesthesias or hemiparesthesia, or monocular visual loss. Symptoms seen in vertebral-basilar system disease include binocular visual disturbance, vertigo, diplopia, ataxia, dysarthria, paresis, and

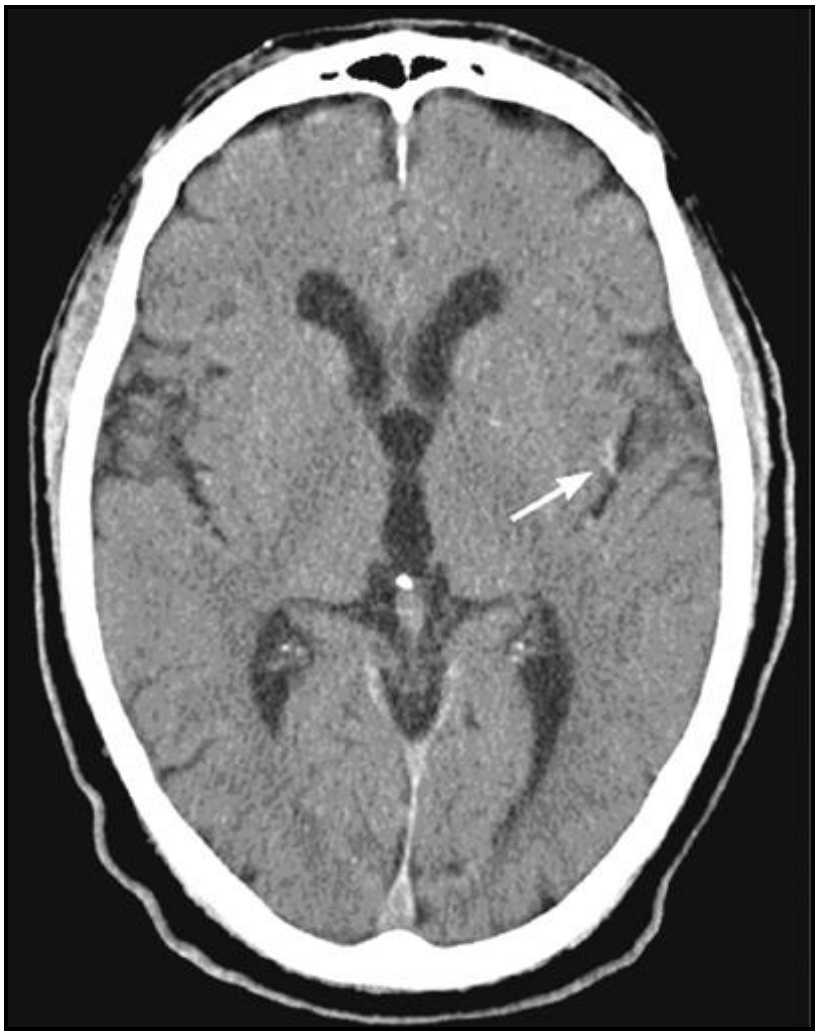
paresthesias, frequently with involvement of one side of the face and the contralateral body **(Kidwell et al., 2004).**

**Mechanism:-**

Acute ICVD can be categorized as large vessel thrombosis, small vessel thrombosis, embolism, or watershed infarction **(Mader and Mandel, 2002).**

Large vessel atherothrombotic occlusion is due to atherosclerosis in the carotid or vertebralbasilar arteries and is a common cause of acute ICVD. The pattern and severity of the neurologic deficit depend on the arterial territory, completeness of occlusion, and collateral flow (Fig. 2-1) **(Mayer et al., 2005).**

Small vessel occlusion occurs due to lipohyalinosis of the lenticulostriate arteries or basilar penetrators and results in a small area of cerebral infarction called a lacune. If a lacune is strategically placed in the internal capsule, thalamus, or basis pontis, substantial neurologic deficits occur. The most common lacunar syndromes are pure motor hemiparesis, pure sensory loss, ataxic hemiparesis, and clumsy-hand dysarthria **(Mendelow et al., 2005).**



***(Fig2-1): Noncontrast axial head CT showing hyperdense signal of third-order MCA branches in the left Sylvian fissure (Mayer et al., 2005).***

The most common cardiac sources associated with cerebral embolic events are outlined in (Table 2-3) **(Irwin and Rippe, 2003).**

***(Table 2-3): Cardiac sources for cerebral emboli (Irwin and Rippe, 2003).***

| Common |
| --- |
| **Nonvalvular atrial fibrillation** |
| **Acute anterior wall myocardial infarction** |
| **Ventricular aneurysms and dyskinetic segments** |
| **Rheumatic valvular disease** |
| **Prosthetic cardiac valves** |
| **Right-to-left shunts** |
| **Bacterial endocarditis** |
| **Less common** |
| **Mitral valve prolapse** |
| **Cardiomyopathy** |
| **Bicuspid aortic valve** |
| **Atrial rfiyxoma** |
| **Nonbacterial endocarditis** |
| **Mitral annulus calcification** |
| **Idiopathic hypertrophic subaortic stenosis** |
| **Atrial septal aneurysm** |

Watershed infarction is due to globally diminished cerebral blood flow resulting from cardiac arrest or systemic hypotension, with focal infarction and deficits occurring in well described patterns. In the carotid circulation, watershed infarcts occur between the distribution of the middle cerebral artery and both the anterior and posterior cerebral arteries. The usual anterior infarction causes contralateral weakness and sensory loss sparing the face; in posterior watershed infarcts, homonymous hemianopsia with little or no weakness is most common. Quadriparesis, cortical blindness, or bilateral arm weakness may also be seen **(Quershi et al., 2001).**

**Differntial Diagnosis:-**

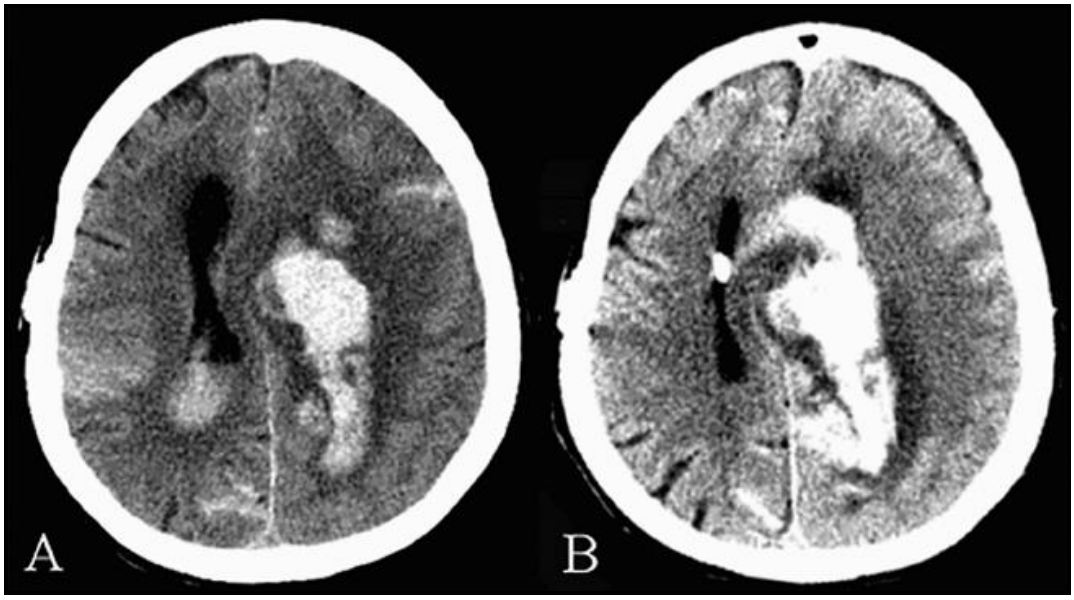
It is especially important to differentiate ICVD patients from those with primary ICH. Patients with cerebral hemorrhage typically have a progressive course, with evolution of symptoms over hours. Early obtundation, coma, seizures, headache, and vomiting are more common in patients with ICH. If this diagnosis is suspected, early imaging with computed tomography (CT) or magnetic resonance imaging (MRI) scan is imperative. Emergent noncontrast head CT scanning is mandatory for rapidly distinguishing ischemic from hemorrhagic infarction and for defining the anatomic distribution of stroke. Head CT scan is a fundamental branch point in the evaluation of stroke, since patients with acute ischemic stroke may be triaged to receive thrombolytic therapy, while patients with hemorrhagic stroke are taken down a completely different diagnostic and therapeutic pathway. The changes in CT scan over the time course of acute cerebral infarction must be understood. Most patients who have had onset of ischemic stroke symptoms within 6 hours initially will have normal findings on CT scan. After 6-12 hours, sufficient edema is recruited into the stroke area to produce a regional hypodensity on CT scan. A large hypodense area present on CT scan within the first 3 hours of symptom onset should prompt careful requestioning regarding the time of stroke symptom onset. MRI is useful for patients with acute ischemic stroke involving cerebellar or lacunar pathology. Disadvantages include its high cost, lack

of ready availability at most centers, and insensitivity for detecting early hemorrhages. Conditions other than cerebrovascular events can occasionally cause acute focal neurologic deficits and must be considered. Primary or metastatic brain tumors can present with acute focal neurologic signs due to hemorrhage into the tumor or other mechanisms. Subdural hematomas may rarely present with acute focal neurologic deficits but must be considered in elderly patients, even without a history of head trauma. Patients with migraine headaches commonly develop focal neurologic symptoms either before or during the early phase of the headache. Rarely, these deficits may occur in the absence of a headache (acephalgic migraine) or may persist (migrainous stroke) **(Zweifler et al., 2003).**

- **II-Intracerebral Hemorrhage:-**

Nontraumatic ICH occurs less frequently than ICVD but often requires management in the ICU. The majority of cases are due to spontaneous (primary) ICH or rupture of saccular aneurysms and arteriovenous malformations **(Clavero et al., 2004).**

Primary ICH is defined as bleeding within the brain parenchyma without an underlying cause, such as neoplasm, vasculitis, bleeding disorder, prior embolic infarction, aneurysm, vascular malformation, or trauma. One-half of cases of primary ICH result from long-standing hypertension. Due to the aggressive control of hypertension, the incidence of ICH has decreased (Fig.2-2) **(Leonard et al., 2001).**




***(Fig 2-2): Axial noncontrast head CT showing growth of intracerebral hemorrhage between (A) and (B) (Leonard et al., 2001).***

**Clinical Manifestations:-**

The clinical presentation of ICH is distinctive. In most cases, the onset is during the waking state when the patient is active; it is unusual for ICH to occur during sleep. The onset is abrupt, and the development of neurologic deficits occurs progressively over minutes to hours. This contrasts with the fluctuating or stepwise progression of deficits commonly seen in atherothrombotic infarcts. In addition, prior TIA is rare with ICH and relatively common with ischemic stroke. The average age of onset of ICH, 50 to 70 years, is younger than that of other types of stroke. Patients may report lateralized headache, and vomiting is common. Nuchal rigidity may be present. Seizures are seen more frequently at the onset of ICH than in ICVD and are more likely

to occur if the bleeding involves the cerebral cortex . Forty-four percent to 72% of patients are comatose when first seen by a physician **(Miyazaki et al., 2001).**

The diagnosis of ICH can be made by CT scan, which provides accurate information about the size and site of the hematoma as well as the degree of extension, midline shift, and development of cerebral edema **(Yorifuji et al., 2002).**

## • Neuropathy and Myopathy in the ICU

Several disorders of nerve and muscle causing acute weakness are encountered in the intensive care unit (ICU). The most common disorder requiring ICU admission and monitoring is the Guillain-Barré syndrome (GBS). In more recent years, disorders of nerve and muscle acquired after admission to the ICU—acute myopathy of intensive care and critical illness polyneuropathy—have been recognized. Less commonly encountered are patients with weakness due to toxic/infectious neuropathies or a metabolic myopathy. In most of these disorders, weakness occurs before admission to the ICU **(Newswanger and Warren, 2004).**

- **Guillain-Barre` Syndrome:-**

GBS is an acute inflammatory demyelinating polyradiculoneuropathy (AIDP) affecting nerve roots and cranial and peripheral nerves of unknown cause that occurs at all ages. It was described by Guillain et al. in 1916 as an acute flaccid paralysis with areflexia and elevated spinal fluid protein without pleocytosis **(Odaka et al., 2005).**

GBS often occurs 2 to 4 weeks after a flulike or diarrheal illness caused by a variety of infectious agents , including cytomegalovirus, Epstein-Barr and herpes simplex viruses, mycoplasma, chlamydia, and Campylobacter jejuni. It can also be an early manifestation of human

immunodeficiency virus (HIV) infection before the development of an immunosuppressed state. Other antecedent events include immunization, general surgery and renal transplantation, Hodgkin's disease, and systemic lupus erythematosus **(Pandey et al., 2005).**

**Clinical Features (**Table 2-4 **):-**

The major feature is weakness that evolves rapidly (usually over days) and classically has been described as ascending from legs to arms and, in severe cases, to respiratory and bulbar muscles. The extent and distribution of weakness in GBS are variable. Within a few days, a patient may become quadriparetic and respirator dependent or the illness may take a benign course and after progression for 3 weeks produce only mild weakness of the face and limbs **(Seneviratne, 2000).**

In a typical case of moderate severity, the physical examination discloses symmetric weakness in proximal and distal muscle groups associated with attenuation or loss of deep tendon reflexes . In the early stage of illness, there is no muscle wasting or fasciculation. If the attack is particularly severe and axons are interrupted, then after a number of months, muscles undergo atrophy and scattered fasciculations may be seen. Sensory loss is usually mild, although a variant of GBS is described in which sensory loss (involving large fiber modalities) is widespread, symmetric, and profound. Respiratory muscles are often involved; between 10% and 25% of patients require ventilaton assistance initiated within 18 days (mean of 10 days) after onset **(Seta et al., 2005).**

***(Table 2-4):Features of Guillain-Barre` Syndrome(Pandey et al, 2005).***

| Clinical Features | Laboratory Features |
|---|---|
| **-Rapidly progressive weakness** | **- Elevated cerebrospinal fluid protein** |
| **-Loss of reflexes** | **- Acellular cerebrospinal fluid** |
| **-Mild dysesthesias** | **-Electromyogram:slow conduction** |
| **-Autonomic dysfunction** | **velocities, conduction block,** |
| **-Respiratory compromise** | **dispersed responnses** |

There is often mild to moderate bilateral facial weakness. Mild weakness of tongue muscles and the muscles of deglutition may also develop. Ophthalmoparesis from extraocular motor nerve involvement is unusual in the typical patient with GBS. In the Miller-Fisher variant, however, there is ophthalmoplegia in combination with ataxia and areflexia, with little limb weakness. Pupillary abnormalities have been noted in GBS and in the Miller-Fisher variant . Papilledema is exceedingly rare **(Van Koningsveld and Van Doorn, 2005).**

Autonomic dysfunction takes the form of excessive or inadequate activity of the sympathetic nervous system or the parasympathetic nervous system, or both. Common findings include cardiac arrhythmias (e.g., persistent sinus tachycardia, bradycardia, ventricular tachycardia, atrial flutter, atrial fibrillation, and asystole), orthostatic hypotension, and transient and persistent hypertension. Other changes include transient bladder paralysis, increased or decreased sweating, and paralytic ileus. These changes are not completely understood but may

be due to inflammation of the thinly myelinated and unmyelinated axons of the peripheral autonomic nervous system **(Winer, 2002).**

The most characteristic laboratory features of GBS are an abnormal cerebrospinal fluid (CSF) profile showing albuminocytologic dissociation (elevated protein without pleocytosis) and abnormal nerve conduction studies. CSF examination is most helpful in reaching the diagnosis of GBS. Although the CSF profile is usually normal during the first 48 hours after onset , by 1 week into the illness, the CSF protein is elevated in most patients, sometimes to levels as high as 1g/dL. Rarely, even several weeks after onset of GBS, the CSF protein remains normal and the diagnosis must rest on the presence of otherwise typical clinical features. The cell count may be slightly increased but rarely exceeds 10 cells per mm3; the cells are mononuclear in nature. The CSF glucose is expected to be normal. **(Wijdicks et al., 2003).**

A number of well-defined conditions cause an acute or subacute onset of generalized weakness and must be differentiated from GBS (Table 2-5 )**(Walk, 1997).**

*(Table2-5):Conditions that may mimic Guillain-Barre` Syndrome (Walk,1997)*

| Disorder | Major distinguishing features |
|---|---|
| -Myasthenia gravis | Reflexes are spared |
| | Ocular weakness predominates |
| | Positive response to edrophonium |
| | EMG: decremental motor response |
| -Botulism | Predominant buibar involvement |
| | Autonomic abnormalities (pupils) |
| | EMG: normal velocities, low amplitudes, incremental response (with high-frequency repetitive nerve stimulation) |
| -Tick paralysis | Rapid progression (1-2 d) |
| | Tick present |
| -Shellfish poisoning | Rapid onset (face, finger, toe numbness) |
| | Follows consumption of mussels/clams |
| -Toxic neuropathies | EMG: usually axon loss |
| -Organophosphorus | Acute cholinergic reaction toxiciry |
| -Porphyric neuropathy | Mental disturbance |
| | Abdominal pain |
| -Diphteritic neuropathy | Prior pharyngitis |
| | Slower evolution |
| | Palatal/accommodation paralysis |
| | Myocarditis |
| -Poliomyelitis | Weakness, pain, and tenderness |
| | Preserved sensation |
| | Cerebrospinal fluid: protein and cell count |
| | Elevated |
| -Periodic paralysis | Reflexes normal |
| | Cranial nerves and respiration spared |
| | Abnormal serum potassium concentration |
| -Critical illness neuropathy | Sepsis and multiorgan failure >2 wk |
| | EMG: axon loss |
| -Acute myopathy of intensive care | Tetraparesis and areflexia |
| | Follows prolonged treatment with neuromuscular blocking agent and corticosteroids |
| | Trauma, status asthmaticus, and organ transplantation associated |
| | Clinical and EMG features of myopathy |

**Intensive Care Unit Related Weakness:-**

In recent years, neuromuscular disorders acquired in the ICU have become increasingly important. Unlike neuromuscular emergencies such as GBS, myasthenia gravis, or porphyria, in which rapidly progressive weakness develops before admission to the ICU, these conditions (polyneuropathy, myopathy, and neuromuscular junction disease) affect patients already in the ICU because of severe systemic illnesses **(Donofrio, 2005).**

- **Critical Illness Polyneuropathy:-**

Critical illness polyneuropathy is present in at least 50% of patients who have been septic and critically ill with multiorgan system failure longer than 2 weeks. It is characterized by difficulty in weaning from the ventilator, distal greater than proximal muscle weakness, and reduced or absent reflexes. In many patients there is an associated encephalopathy. The electrophysiologic findings point to a sensory-motor, axon-loss polyneuropathy. Most patients recover over weeks to months after appropriate treatment of the underlying sepsis or critical illness has begun. The development of weakness in the midst of critical illness as seen in critical illness polyneuropathy helps differentiate this disorder from axonal GBS, in which weakness develops days to weeks after an infection **(Erdmann et al., 2005).**

- **Acute Myopathy Of Intensive Care:-**

Similar to peripheral nerve tissue in critical illness polyneuropathy, the muscle fiber may be adversely affected in the wake of severe systemic illness **(Hobson-webb and Donofrio, 2005).**

An acute myopathy of intensive care was described in some patients receiving high-dose corticosteroids (equal to or greater than 1000 mg methylprednisolone) in combination with neuromuscular-blocking agents (NMBAs) . Although initially observed in patients treated for status asthmaticus, this entity has also been encountered in the setting of trauma, organ transplantation, burns, and critical illness. Clinically, patients are found to have variable degrees of weakness, typically generalized, including respiratory muscles and rarely affecting extraocular muscles. The condition is recognized when a patient who has been critically ill fails to wean from the ventilator because of respiratory muscle weakness **(Leger and Behin, 2005).**

# Prevention

- ***Prevention Of Delirium:-***

In a recently conducted trial of 852 general medical patients over the age of 70, strategies for primary prevention of delirium resulted in a 40% reduction in the odds of developing delirium (15% in controls vs 9.9% in the intervention patients). The main focus was on optimization of risk factors via the following methods: repeated reorientation of the patient by trained volunteers and nurses, provision of cognitively stimulating activities for the patient three times per day, a nonpharmacological sleep protocol to enhance normalization of sleep/wake cycles, early mobilization activities and range of motion exercises, timely removal of catheters and physical restraints, institution of the use of eyeglasses and magnifying lenses, hearing aids and earwax disimpaction, and early correction of dehydration **(O'Keeffe and Lavan, 2005).**

However, this study of primary prevention did not focus on critically ill patients, and excluded mechanically ventilated patients. Considering that pilot studies to date have estimated an incidence of delirium approaching 50 to 90%, one might view the "room for improvement" in delirium management in the ICU or after ICU discharge as far greater than for non-critically ill medical patients. Although primary prevention of delirium is preferred, some degree of

delirium is likely to be inevitable in the ICU. In these cases, the above-mentioned basic tenets of patient management, some of which have already been studied, should be applied to reduce the duration of delirium and its associated complications. Preventive and management strategies for delirium in the ICU represent an important area for future investigation **(Meagher et al., 2005).**

Reversal or avoidance of the risk factors of delirium helps in primary prevention of delirium (Table 1-3) **(O'Keeffe and Lavan, 2005).**

Primary prevention of drug-induced delirium requires the prescription of alternative lower risk medications and the minimisation of polypharmacy. Anticholinergic, hypnosedative and opioid medications should be used sparingly in the elderly **(Vallverdu et al, 1999).**

Secondary prevention may be achieved through improved recognition of the condition. It has been recommended that all acutely ill patients should have a brief mental test on admission to increase the rate of detection of delirium **(Heffner, 2000).**

- ***Long Term Therapy To Prevent Stroke:-***

Cerebrovascular disease is the third leading cause of mortality and the leading cause of long-term neurological disability in the world. Most strokes are of ischemic origin and, other than cardioembolic or small

vessel strokes, are caused by the development of platelet-fibrin thrombi on an atherosclerotic plaque. It has been estimated that up to 80% of ischemic strokes could be prevented with application of currently available treatments for blood pressure, cholesterol, and antithrombotic therapies **(Spagnoli et al., 2004).**

Current prevention strategies for ischemic stroke center around the management of modifiable risk factors through a combination of lifestyle modifications, including diet, exercise, smoking cessation, carotid artery surgery in high-risk patients, and pharmacologic treatment with antihypertensive, antihyperlipidemic, anticoagulant, and/or anti-platelet agents. Anticoagulation is indicated definitely only for patients with atrial fibrillation, less definitely in a few other conditions. Antiplatelet therapies that have shown the most promise in secondary stroke prevention include aspirin, clopidogrel, and low-dose aspirin plus extended-release dipyridamole. Given the ongoing risk of secondary atherothrombotic events in stroke survivors, the continuum of care from hospital discharge to the primary care setting must ensure that secondary prevention measures are initiated early and maintained long-term **(Vickrey et al., 2002).**

## Primary Prevention of Ischemic Stroke

Prophylactic strategies for ischemic stroke center largely on the management of modifiable risk factors (Table 3-1). Guidelines recommend that patients adopt healthy lifestyle habits such as

avoidance of tobacco (including passive smoking), healthy eating patterns (including consumption of fruits, vegetables, low-fat dairy products, and lean meat), regular appropriate exercise, and minimization of alcohol intake. Carotid endarterectomy or carotid stenting may be considered for patients with carotid stenosis, at high risk of stroke **(Volpato et al., 2004).**

Patients at risk can be treated with ensembles of therapies or pharmacotherapy that may include antihypertensive agents, statins, and antithrombotic therapies. Patients with atrial fibrillation benefit from anticoagulation. In primary prevention in men, aspirin prevents MI but not stroke (American Physicians Heart study), but in women, there seems to be a reduced risk of stroke as well in both middle aged and elderly subjects **(Ridker et al., 2005).**

***(Table3-1): Modifiable Risk Factors For Stroke (Volpato et al.,2004).***

| |
|---|
| **Hypertension** |
| **Smoking (including passive smoking)** |
| **Diabetes** |
| **Asymptomatic carotid stenosis** |
| **Increased blood lipid levels** |
| **Atrial fibrillation (nonvalvular)** |
| **Obesity** |
| **Physical inactivity** |

# Management of Psychological and Neurological Changes in the ICU

## • Part I:-Management of Psychological changes

Sedation is an essential component of care for the critically ill patient. An ideal regimen should control pain, anxiety, agitation, and delirium while minimizing adverse effects. Practices of ICU sedation vary widely. Inappropriate therapy may result in adverse drug reactions, prolonged mechanical ventilation, extended ICU stays, and increased costs **(Jacobi et al., 2002).**

Selection of drug therapy is based on identification and differentiation of pain, anxiety, agitation, and delirium.

Clinical practice guidelines for critically ill adults recommend routine assessment for the presence of delirium as well as pharmacologic management strategies with neuroleptic agents. Although no neuroleptic agent is FDA-approved for the treatment of delirium, haloperidol is considered to be the preferred agent in critically ill patients. Newer atypical antipsychotic agents have also been suggested due to the potential for decreased adverse effects **(Ostermann et al., 2000).**

Benzodiazepines are considered first-line agents for the management of anxiety and agitation. Barbiturates are not recommended because of their high addictive potential, marked side effects, slow onset of action, and low therapeutic indices. Beta-blockers do not reduce intrinsic anxiety although they do reduce anatomic components (eg, tachycardia, diaphoresis). They are helpful for cardiac, endocrine, and other medical conditions commonly associated with stress and anxiety. Serotonin reuptake inhibitors (eg Paroxetine) generally are preffered as the drug of choice for long term treatment of panic disorders **(Shintani et al., 2004).**

## DELIRIUM

- ***Neuroleptics:-***

***-Haloperidol (Haldol)***

Haloperidol, a butyrophenone neuroleptic drug, is the agent of choice for treatment of delirium in critically ill patients. Clinical effects are observed within 30-60 mins after IV administration and last for as long as 4-8 hrs. The usual starting dosage is 2-10 mg IV, repeated every 2-4 hrs. Most patients being treated for ICU delirium require much larger doses of the drug than noncritically-ill patients. Haloperidol does

not cause major respiratory depression. The drug blocks dopaminergic transmission at postsynaptic receptor sites in the central nervous system. Patients treated with haloperidol generally seem to be more calm and are better able to make appropriate responses **(Skrobik et al., 2004).**

The adverse effects associated with haloperidol include occasional hypotension resulting from the a-blocking properties of the drug. Although rare with IV administration, haloperidol may cause extrapyramidal effects such as drowsiness, lethargy, a fixed stare, rigidity, and akathisia. These symptoms are usually mild and reversible with discontinuation of the drug. High doses of the drug are associated with QT interval prolongation and development of torsades de pointes, which is a cardiac arrhythmia (a rhythmic pattern of sinusoidal ventricular complexes that lead to ventricular fibrillation and cardiac arrest) associated with administration of high doses (100-1200 mg/d). The QT interval should be monitored closely, and administration of haloperidol should be discontinued if the QT interval is prolonged by more than 25% or is >450 msecs. Rarely, a patient may experience neuroleptic malignant syndrome, a rare complication of haloperidol therapy with a mortality rate of 20% to 30%. Neuroleptic malignant syndrome develops slowly over 24-72 hrs and can last for up to 10 days after discontinuation of the drug. Characteristics of neuroleptic malignant syndrome include fever, muscle rigidity, altered conciousness,

and elevated concentrations of creatinine phosphokinase. This condition is a medical emergency and requires immediate attention. The recommended dose of haloperidol is 1-5 mg oral and 2-5 mg IV/IM. In elderly or debilitated patients the dose is 0.5-2 mg IV/IM **(Truman et al ., 2004).**

***-Droperidol (Inapsine)***

It is better than haloperidol for control of severely disturbed and/or violent patients. Somewhat faster acting and more sedating than haloperidol, but more likely to cause hypotension. May exert antipsychotic activity through dopaminergic system. May alter dopamine action in CNS. The recommended dose for droperidol is 0.625-5 mg IM/IV (5 mg standard adult dose for chemical restraint) **(McNicoll et al., 2003).**

***-Atypical antipsychotics***

These are newer neuroleptics with a lowered risk of extrapyramidal syndrome (EPS) and improved efficacy for the negative symptoms (withdrawal, apathy) of psychosis because of their enhanced serotonergic activity as compared to older-style neuroleptics. These medications have largely supplanted older neuroleptics for sedation and treatment of psychosis in elderly patients with dementia. **Risperidone (Risperdal):** It is now considered drug of choice for sundowning in elderly patients. Binds to dopamine D2 receptor with 20

times lower affinity than serotonin 5-HT2 receptors. Improves negative symptoms of psychosis and reduces incidence of EPS. Also may have antidepressant effects, probably because of its serotonin activity. The recommended dose for risperidone is 1-8 mg/d oral. Intial dosing for delirium or sundowning in elderly persons: 0.25-0.5 mg/d, titrated upwards **(Pisani et al., 2003).**

## AGITATION AND ANXIETY

- ***Sedatives***

Sedatives are the mainstays of supportive patient care in the ICU. Critically ill patients are frequently in pain as a result of their medical condition or surgery. Mechanical ventilation and environmental factors cause additional stresses. Delirium and other adverse effects of the ICU stay necessitate the use of sedation to prevent or alleviate the agitation that commonly results. Analgesia is important for the same reason: severe pain is a frequent cause of agitation and delirium **(Inouye et al., 2001).**

The choice of an appropriate sedative is often difficult, and depends on the individual needs of the patient. For example, if rapid awakening to a state of alertness is required, as in the neurologic patient who requires frequent monitoring, propofol is the preferred agent. For

long-term sedation, lorazepam is considered the drug of choice **(Margolin et al., 2001).**

Maintenance of adequate sedation is a key component of ICU care. Ventilatory support frequently induces anxiety and asynchrony. Appropriate sedatives and analgesics can alleviate much of this discomfort, and can lessen stress-induced increases in oxygen consumption. In patients with respiratory failure, the administration of sedatives at appropriate doses helps increase chest wall compliance, allows the manipulation of inspiratory to expiratory ratio and other variables, improves oxygenation, and reduces desynchronized breathing **(Bogardus et al.,2000).**

Alleviation of pain is an equally important component of care in the ICU. An increased level of pain activates the sympathetic nervous system, placing additional demands on the cardiovascular system in critically ill patients. When pain is prolonged, it contributes to severe anxiety and even delirium **(Fleiss et al., 2003)**

The primary goals of sedative therapy, once a pain-free state is achieved, are anxiolysis, hypnosis, and amnesia. Not all sedative agents used in the ICU can achieve these goals. Similar plasma concentrations of a given sedative can have varied results in different individuals with respect to drug disposition and pharmacodynamic effect. The doses of drug required for adequate sedation also change during the ICU stay based on the nature and course of the disease, interaction of the

sedative with other pharmacologic agents, and the response to therapy **(Foreman et al., 2001).**

Sedatives are not used only for sedation in the ICU; other indications include management of drug withdrawal syndromes and treatment of seizures. Proper use of these agents can enhance patient comfort and safety, but, if inappropriately chosen or incorrectly administered, the occurrence of side effects can lead to increased morbidity, mortality, and costs (Table 4-1) **(Jackson and Ely, 2001).**

***(Table 4-1): Properties of an ideal sedative (Jackson and Ely, 2001)***

- **Easily titratable level of adequate sedation**
- **Rapid onset of action**
- **Short acting, allowing patient assessment, easy weaning from mechanical ventilation, and early extubation**
- **No adverse effects**
- **No nausea, vomiting, phlebitis**
- **No anaphylaxis or allergic reaction**
- **Minimal metabolism; not dependent on normal hepatic, renal, or pulmonary function**
- **No active or toxic metabolites**
- **No suppression of cortisol production by the adrenal cortex**
- **No interactions or incompatibilities with other commonly prescribed intensive care unit drugs**
- **Ease of administration**
- **Lack of accumulation with prolonged adminstration**
- **Does not promote growth of pathogens**
- **Cost effective**
- **Easily prepared and long shelf-life**

The levels of sedation have been defined as follows:

• Minimal sedation is a drug-induced state during which patients respond normally to verbal commands, although cognitive function and coordination may be impaired; ventilatory and cardiovascular functions are unaffected.

- Moderate sedation is a drug-induced depression of consciousness during which patients respond purposefully to verbal commands, either alone or accompanied by light tactile stimulation. No interventions are required to maintain a patent airway, and spontaneous ventilation is adequate. Cardiovascular function is usually maintained.
- Deep sedation is a drug-induced depression of consciousness during which patients cannot be easily aroused but respond purposefully following repeated or painful stimulation. The ability to independently maintain ventilatory function may be impaired. Patients may require assistance in maintaining a patent airway, and spontaneous ventilation may be inadequate. Cardiovascular function is usually maintained. **(Gautam et al., 2001).**

## ***-Benzodiazipines***

The class of agents most widely used for sedation in the ICU is the benzodiazepines (Table 4-2). These drugs provide anxiolysis and amnesia, but they have no analgesic properties. The mechanism of action of benzodiazepines within the nervous system involve activity at gamma-aminobutyric acid (GABA) receptors. Potentiation of GABA-mediated transmission by benzodiazepines is apparently responsible for the somnolent, anxiolytic, and anticonvulsant actions, whereas the amnestic property seems to correlate with GABA agonist activity in the limbic cortex. The benzodiazepines currently used in the ICU setting

are diazepam, lorazepam, and midazolam. The primary difference between these agents relates to their pharmacokinetics **(Bogardus et al., 2003).**

***(Table 4-2): Pharmakokinetics of Diazepam, Lorazepam, Midazolam and Propofol in healthy volunteers (Bogardus et al., 2003).***

| | Diazepam | Lorazepam | Midazolam | Propofol |
|---|---|---|---|---|
| **Half-life,min** | **30-66** | **3-20** | **6-15** | **2-3** |
| **Volume of distribution, L/Kg** | **0.7-1.7** | **1.14-1.3** | **1.1-1.7** | **5.4-7.8** |
| **Clearance, mL/Kg/min** | **0.24-0.53** | **1.05-1.1** | **6.4-11.1** | **26-29** |
| **Protein binding, %** | **96-99** | **86-93** | **97** | **98** |
| **Active metabolites** | **Yes** | **No** | **Yes** | **No** |

The liver extensively clears benzodiazepines. The effects of these drugs may be prolonged in critically ill patients because of decreased metabolism or in the presence of severe liver disease. Because benzodiazepines are sequestered in fat stores, prolonged sedation may occur, with chronic administration. The effects of benzodiazepines can be reversed by flumazenil, a competitive antagonist with a rapid onset and relatively short duration of action in comparison with the prolonged effects of benzodiazepines **(Coursin, 2002).**

Withdrawal syndromes are known to occur after continued use of benzodiazepines, and tachyphylaxis can develop within hours to days. The latter requires either dose escalation or use of another sedative agent. After several weeks of continued use, the acute cessation of

therapy can give rise to a syndrome that manifests as tremors, diaphoresis, photophobia, insomnia, abdominal discomfort, hypertension, and seizures **(Nasrawy, 2001).**

**1-Diazepam:-**

Diazepam is a long-acting lipophilic benzodiazepine that rapidly penetrates the central nervous system, so that sedative effects are seen within 2-3 mins. Although diazepam is no longer recommended for routine use in the ICU, there are reports of its use for long-term sedation in selected patients. This recommendation is the result of a scheduled intermittent dosing regimen that may easily lead to excessive and prolonged sedation. Also, dilution is needed for continuous infusion, and this usually requires large volumes of fluid administration. Other disadvantages of diazepam are the common occurrence of pain and thrombophlebitis when the drug is administered by peripheral vein injection. Diazepam has an active metabolite, dimethyl-diazepam, which is only slightly less potent than diazepam and has an elimination half-life of 96 hrs, longer than that of the parent compound **(Cawley, 2001).**

**2-Lorazepam:-**

Lorazepam, an intermediate-acting benzodiazepine, is less lipophilic than diazepam and therefore has less potential for accumulation. The drug is usually administered by intermittent IV injection, but continuous infusion may be used. Because there is a slight delay in the onset of action of lorazepam, it is acceptable to administer a single dose of a

more rapidly acting benzodiazepine when achievement of rapid sedation is necessary. Compared with midazolam, lorazepam is longer acting, causes less hypotension, produces equally effective anterograde amnesia, and, with prolonged administration, produces more rapid awakening **(Thompson and Goodale, 2000).**

The new *Clinical Practice Guidelines* recommend lorazepam for the sedation of most patients by intermittent IV doses or continuous infusion. The drug has no active metabolites and its metabolism is less affected by advanced age or liver dysfunction compared with midazolam. Lorazepam is associated with a stable hemodynamic profile, even when opioids are concurrently administered. It may, however, be unstable in solution and can precipitate in IV catheters and tubing, particularly if infusions last longer than 12 hrs. This can add to the cost of therapy. Propylene glycol toxicity, marked by acidosis and renal failure, has occurred with higher doses of lorazepam or prolonged infusion of the drug **(Cremer et al., 2001).**

**3-Midazolam:-**

Midazolam is a short-acting, water-soluble benzodiazepine that is transformed to a lipophilic compound in the blood. The drug rapidly penetrates the central nervous system to produce a short onset of sedation of 2-5 mins. Its duration of effect is brief because it is rapidly redistributed, a property that favors continuous infusion for maintenance of sedation. Use of midazolam for chronic sedation is limited

because, in some patients, there is prolonged elimination half-life of up to 30 hrs and associated variability in the time of return to consciousness after discontinuation; however, few adverse hemodynamic and respiratory effects are seen with the short-term use of midazolam. To minimize the incidence of withdrawal phenomena after long-term duration infusions, the drug should be properly tapered **(Hall et al., 2001).**

The new *Clinical Practice Guidelines* recommend midazolam for rapid sedation of acutely agitated patients. It is recommended for short-term use only, as it produces unpredictable awakening and/or time to extubation when infusions continue for more than 48-72 hrs. Midazolam exhibits dose-related hypnotic, anxiolytic, amnestic, and anticonvulsant actions. The drug also causes dose-related respiratory depression, and at large doses can cause hypotension and vasodilatation. When midazolam is administered as a continuous infusion, however, these effects are minimal. The drug is biotransformed to an active metabolite in the liver that is not as potent and is shorter-lasting than the parent compound. Because only small quantities are formed during continuous infusion of midazolam, this metabolite does not contribute significantly to the pharmacologic activity of the drug (except in patients with severe renal failure) **(Shafer, 1998).**

## -Propofol

Propofol is a sedative-hypnotic with no analgesic action; it has sedative, hypnotic, and anxiolytic properties .Other effects of propofol are bronchodilation, seizure suppression, muscle relaxation, and possible anti-inflammatory and antiplatelet effects. Propofol is highly fat soluble, and hence is formulated in an intralipid, a 1% emulsion containing 10% soya bean oil, 2.25% glycerol, and 1.2% purified egg phosphatide **(Sandiumenge Camps et al., 2000).**

After a single IV dose, the onset of action of propofol is rapid (1-2 mins) and its effect is brief (10-15 mins) because of rapid central nervous system penetration and subsequent redistribution. Therefore, propofol is administered only by continuous infusion when used for sedation. Long-term infusion results in accumulation within lipid stores, so that there is a prolonged elimination phase with a half-life of up to 300-700 mins **(Barrientos-Vega et al., 2001).**

Although the mechanism of action of propofol is still not completely understood, the drug appears to activate the GABA-A receptor within the central nervous system. Propofol alters the sensorium in a dose-dependent manner, from light sedation to general anesthesia. The drug is also a potent respiratory depressant, causing a reduction in systemic vascular resistance and possibly hypotension, especially when administered as a bolus. Parallel with its action on the

level of arousal, propofol decreases cerebral metabolism, which results in a coupled decline in cerebral blood flow and a decrease in intracranial pressure. Sedative infusion doses of this agent typically result in minimal hemodynamic alteration with no change in perfusion pressure as long as adequate intravascular volume status is maintained **(Thompson and Goodale, 2000).**

Propofol is considered an ultra short-acting agent for two reasons. Because it is highly lipophilic, the drug redistributes to fatty tissues to such an extent that its volume of distribution approaches 600-800 L. Second, drug clearance is calculated to be more than 1.5-2.0 L/min, exceeding hepatic blood flow and suggesting possible extrahepatic metabolism. These Kinetics result in a very rapid uptake and elimination from plasma with little accumulation and a low likelihood of delayed recovery from sedation. Despite maintenance of propofol sedation for up to several days, recovery to an awake and responsive state after discontinuation of therapy occurs within 10-15 mins. The pharmacokinetics of propofol are not altered in patients with renal or hepatic disease **(Herr et al., 2000).**

The use of propofol is not currently recommended for pediatric patients in the ICU because of reports of metabolic acidosis with accompanying lipemic serum, bradyarrhythmias, and fatal myocardial failure; this occurred in patients being treated with excessively high doses. In adults, prolonged high-dose infusion may also lead to cardiac failure **(Higgins et al., 2000).**

## ***-Dexamedetomidine***

Dexmedetomidine, a selective alpha-2 adrenergic receptor agonist, exhibits sympatholytic, sedative, and analgesic effects, and is eight times more potent for alpha-2 receptor than clonidine. The drug has been approved by the FDA as a short-term sedative (<24 hrs) and analgesic in the critical care setting, specifically for use in the early postoperative period **(Shapiro et al., 1995).**

Dexmedetomidine acts at two adrenergic sites. On the one hand, the drug works by presynaptic activation of the alpha-2 adrenoceptor, thereby inhibiting the release of norepinephrine and terminating the propagation of pain signals. Also, by postsynaptic activation of these receptors in the central nervous system, dexmedetomidine inhibits sympathetic activity with a resultant decrease in blood pressure and heart rate. Together, these two effects can produce sedation, anxiolysis, sympatholysis, and analgesia **(Gertler et al., 2001).**

Dexmedetomidine has several advantages for use as a sedative in the ICU. Because the drug does not cause respiratory depression, a patient can be extubated without prior discontinuation. Because a dexmedetomidine infusion can be continued during the postextubation period, the drug provides flexibility in the timing of extubation and may be useful during the weaning process. Another advantage of the drug is easy arousability of treated patients—i.e., they can be calmly and easily awakened. The adverse effects of dexmedetomidine include

hypotension, hypertension (with the loading dose), and bradycardia **(Bhana et al., 2000).**

## DEPRESSION

Patients who meet the criteria for major depression are usually treated with a somatic therapy alone or in combination with psychotherapy. In critical care units, somatic therapies are the most widely used treatments for depression. Somatic therapies include pharmacotherapy and electroconvulsive therapy (ECT). Pharmacotherapy may also be used in critical care units for patients who have an adjustment disorder with depressed mood, particularly when these patients have several neurovegetative symptoms. A patient who is neither eating nor sleeping and who lacks the energy to participate in his or her rehabilitation may be helped considerably by antidepressants **(Apter et al., 2001).**

Each type of pharmacotherapy has its own indications and contraindications, but general rules are available when selecting an antidepressant. The most common rule is to choose a medication with a side-effect profile that best fits the patient's symptoms. For instance, a patient who is having trouble sleeping will benefit from a sedating antidepressant. Conversely, a patient who has severe psychomotor retardation may benefit from a more stimulating antidepressant. The

older polycyclic antidepressants, as well as the selective serotonin reuptake inhibitors (SSRIs), take approximately 4 to 6 weeks until full antidepressant effects are noted, although effects can occur in 1 to 2 weeks. In critical care units, quicker effects are generally needed. Stimulants and ECT work more quickly, usually within 1 week. Lithium carbonate is used to stabilize mood (both highs and lows). Monoamine oxidase inhibitors (MAOIs) are used to treat atypical depressions and may also take several weeks to reach their full effectiveness; their use is rarely associated with cardiac conduction difficulties. Patients with depression may also manifest considerable anxiety and may be helped by the use of an anxiolytic (e.g., a benzodiazepine) while awaiting response to an antidepressant. Psychotically depressed patients (with delusions or hallucinations) may need antipsychotics (e.g., haloperidol) for control of symptoms **(Angst et al., 1999).**

**Pharmacotherapy:-**

- **Selective Serotonin Reuptake Inhibitors(SSRIs):-** Include fluoxetine (Prozac), paroxetine (Paxil), sertraline (Zoloft), fluvoxamine (Luvox), citalopram (Celexa), and escitalopram (Lexapro). These treatments, which were developed in the 1970s and introduced in the mid-1980s, act like TCAs by inhibiting the reuptake of neurotransmitters by the presynaptic cell. However, their activity is specific to the serotonin reuptake transporter protein, resulting in more available serotonin in the synapse. Their serotonin-specificity is believed to result in a decreased side effect profile, as well as reduced toxicity.

Because of their pharmacologic properties, SSRI doses do not need to be monitored as closely as other drugs. Common side effects associated with SSRIs include nausea, nervousness, insomnia, sexual dysfunction, and headache **(Aronson and Ayres, 2005).**

- **Serotonin/Norepinephrine Reuptake Inhibitors (SNRIs):**

Include venlafaxine (Effexor) and duloxetine (Cymbalta). Safety, tolerability, and side effect profiles are similar to that of the SSRIs, with the exception that the SNRIs have been associated (rarely) with a sustained rise in blood pressure. SNRIs can be used as first-line agents, particularly in patients with significant fatigue or pain syndromes associated with the episode of depression. The SNRIs also have an important role as second-line agents in patients who have not responded to SSRIs **(Detke et al., 2002).**

- **Atypical Antidepressants:-** Include bupropion (Wellbutrin),

nefazodone (Serzone), mirtazapine (Remeron), and trazodone (Desyrel). This group also shows low toxicity in overdose and may have an advantage over the SSRIs by causing less sexual dysfunction and GI distress.

-Bupropion is associated with a risk of seizure at higher doses, especially in patients with a history of seizure.

-Mirtazapine is a potent antagonist at 5-HT2, 5-HT3, alpha2, and histamine (H1) receptors and, thus, can be very sedating. Adverse effects such as drowsiness and weight gain may tend to improve over time and with higher doses.

-Trazodone is very sedating and usually is used as a sleep aid rather than as an antidepressant **(Gumnick and Nemeroff, 2000).**

- **Tricyclic Antidepressants(TCA):-** Include amitriptyline

(Elavil), nortriptyline (Pamelor), desipramine (Norpramin), clomipramine (Anafranil), doxepin (Sinequan), protriptyline (Vivactil), trimipramine (Surmontil), and imipramine (Tofranil).

  - This group has a long record of efficacy in the treatment of depression and has the advantage of lower cost. They are used less commonly now because of the need to titrate the dose to a therapeutic level and because of their considerable toxicity in overdose.
  - Adverse effects largely are due to their anticholinergic and antihistaminic properties and include sedation, confusion, dry mouth, orthostasis, constipation, urinary retention, sexual dysfunction, and weight gain. Caution should be used in patients with cardiac conduction abnormalities **(Martinez and Marangell, 2004).**

- **Mono Amine Oxidase Inhibitors(MAOIs):-** Include phenelzine (Nardil) and tranylcypromine (Parnate).
    - MAOIs are widely effective in a broad range of affective and anxiety disorders.
    - Because of the risk of hypertensive crisis, patients on these medications must follow a low-tyramine diet. Other adverse effects can include insomnia, anxiety, orthostasis, weight gain, and sexual dysfunction **(Keller, 2003).**

**Nonpharmacologic therapy:-**

-Electroconvulsive therapy (ECT) is a highly effective treatment for depression and may have a more rapid onset of action than drug treatments. Advances in brief anesthesia and neuromuscular paralysis have improved the safety and tolerability of this modality. Risks include those associated with brief anesthesia, postictal confusion, and, more rarely, short-term memory difficulties. ECT is used when a rapid antidepressant response is needed, when drug therapies have failed, when there is a history of good response to ECT, or when there is patient preference. ECT is particularly effective in the treatment of delusional depression **(Amsterdam, 2003).**

-Transcranial magnetic stimulation: This modality is in investigational stages for the treatment of depression. Initial results suggest that it may be an effective intervention without the risks and

adverse effects of ECT. Vagus nerve stimulation also is in investigational stages and has shown some efficacy in treatment resistant depression **(Goldberg and Truman, 2003).**

- Consultation can be important at many stages of the treatment process. Certainly, consultation should be sought if treating physicians exhaust the options with which they feel comfortable. A psychiatrist must be involved in the care of patients in whom more severe symptoms develop and for whom a more intensive level of care will be needed (eg, suicidal ideation, psychosis, mania, severe decline in physical health) **(Kessler et al., 2003).**

**-**Dietary restrictions are necessary only when prescribing MAOIs. Foods high in tyramine, which can produce a hypertensive crisis in the presence of MAOIs, should be avoided. These foods include soy sauce, aged chicken or beef liver, aged cheese, fava beans, air-dried sausage, and similar meats, pickled or cured meat or fish, overripe fruit, canned figs, raisins, avocados, yogurt, sour cream, yeast extracts, caviar, and shrimp paste **(Mann, 2005).**

- ***Part II-Management of Neurological problems***

## Metabolic Encephalopathy:-

- **Hepatic encephalopathy**

Therapy for hepatic encephalopathy is directed toward decreasing the amount of toxic substances that are being shunted to the brain. Neomycin and lactulose help to sterilize and flush the gut. A protein-restricted diet and the exclusion of hepatically cleared drugs decrease the metabolic load, and IV glucose effectively maintains the serum glucose level. Neurologic recovery then depends on the capacity of the liver to regenerate at least 25% of its full function. With prolonged or repeated bouts of hepatic coma, there may be residual signs of basal ganglia dysfunction evidenced by chorea, postural tremors, or a parkinsonian picture (acquired hepatocerebral degeneration) **(Butterworth, 2004).**

- **Pulmonary failure**

Treatment is directed toward slow correction of hypercarbia while maintaining an adequate Po2 and good cerebral flow. Prognosis for full neurologic recovery is good if the patient is not subjected to cerebral ischemia as well **(Mueller et al., 2006).**

- **Hypoglycemic encephalopathy**

One should not delay treatment with a bolus of 50 mL 50% glucose (one ampule) if there is doubt about the cause of a rapidly evolving coma, because hypoglycemic encephalopathy can result in permanent neurologic deficits if not reversed in 20 minutes or less. The first bolus of glucose must be followed by close monitoring of blood glucose levels, because most agents that lead to symptomatic hypoglycemia are long acting **(Bourcigaux et al., 2005).**

- **Electrolyte Disturbances:-**

Treatment of hyponatremia is directed toward the underlying cause with fluid restriction in mild cases unless total body sodium is depleted. In moderate cases (i.e., a serum sodium of 105 to 115 mEq/L), PO sodium supplementation may be needed as well. A serum sodium below 100 mEq /L is lifethreatening. This requires treatment with IV hypertonic saline at a rate calculated to replace about one-half of the total sodium deficit in 3 to 6 hours (averaging less than or equal to 0.5 mg Na / hour). The remainder of the deficit should be administered in the next 24 to 48 hours. Excessively rapid correction of severe hyponatremia, can be associated with another serious neurologic complication known as central pontine myelinolysis. Central pontine myelinolysis starts with a flaccid quadriparesis and inability to chew, swallow, or talk over a period of days. Patients who recover from the

underlying systemic disorder are left with a spastic paraparesis and pseudobulbar speech for a number of months **(Laffey and Kavanagh, 1999).**

The treatment of symptomatic hypernatremia depends on its cause: dehydration alone or complicated by additional sodium depletion due to hyperosmolar diuresis or excessive sweating. Fluid replacement is accomplished with 5% dextrose and water at a rate dependent on the total body water deficit—half of the water needed being administered IV in the first 12 to 24 hours and no faster. Saline solutions of one-half normal strength (0.45%) are used in most other cases. The exception is hyperosmolar diabetic coma, in which insulin and normal saline are both necessary to correct the severe serum hypertonicity **(Rose and Post, 2001).**

- **Endocrine disorders**

The neurologic picture of adrenocortical deficiency does not clear until cortisone replacement is given along with treatment of the electrolyte imbalances. These patients are also particularly sensitive to sedative medications and may lapse into coma with small doses of narcotics or barbiturates **(Laureti et al., 2000).**

The treatment of excess steroids or cushing's disease consists of withdrawal of the steroids and sometimes temporary use of tranquilizers or lithium for the psychiatric features as well. Full

neurologic recovery may lag behind the treatment by several days to weeks **(Rivers et al., 2001).**

Treatement of hypothyroidism consists of replacement therapy with triiodothyronine or thyroxine. The constitutional symptoms may take several weeks to respond, but the neurologic picture clears promptly with proper treatment **(Ringel, 2001).**

Therapy for thyrotoxic encephalopathy is aimed at ablation of the gland, but supportive care may require beta-blockers, digoxin, diuretics, and sometimes dexamethasone and sedatives for the associated hypermetabolic state **(Ringel, 2001).**

Treatment of hyperparathyroidism is directed toward the underlying disease rather than addressing the hypercalcemia alone. Primary hyperparathyroidism is effectively managed by ablation of the overactive gland. This is not always possible, because the glands often are ectopic and may escape discovery on selective angiography or exploratory surgery **(Burman and Wartofsky, 2001).**

## Generalized Anoxia/Ischemia of the Nervous System

Treatment approaches for cardiac arrest and perioperative hypoxic encephalopathy are similar. Optimal therapy is directed at preventing the recurrence of hypoxia. To ensure that the oxygen-carrying capacity of the blood is restored, excess oxygen administration is suggested for several hours after anoxic events. There is recent evidence that mild or moderate hypothermia may improve outcome after cardiac arrest. Blood pressure is maintained at normotensive or mildly elevated levels. Mean arterial pressure should be 90 to 110 mm Hg in patients who are usually normotensive. The partial pressure of oxygen should be greater than 100 mm Hg. The partial pressure of carbon dioxide is kept at the patient's baseline (usually 40 mm Hg), unless there are active signs of herniation. If herniation is suspected, the patient should be hyperventilated. Mild hypovolemia and elevation of the head of the bed to 30 degrees reduce intracranial pressure **(Moonis and Fisher, 2001).**

Seizures occur in 25% of patients in anoxic coma. They are treated with loading and then maintenance doses of phenytoin (loading dose, 15 to 20 mg/kg, rate not to exceed 100 mg / minute; maintenance dose, 5 mg/kg/day). Phenobarbital is usually avoided because of its sedative effects. Occasionally, comatose patients are in status epilepticus without

any obvious motor signs after an anoxic event **(Schoerkhuber et al., 1999).**

Steroid administration is of little help in cases of postanoxic encephalopathy because the increased intracranial pressure is due to cytotoxic edema. Steroids, mannitol, and glycerol result in elevated serum blood sugar levels, which increase the brain's production of lactic acid, possibly potentiating preexisting damage **(Bernard et al., 2002).**

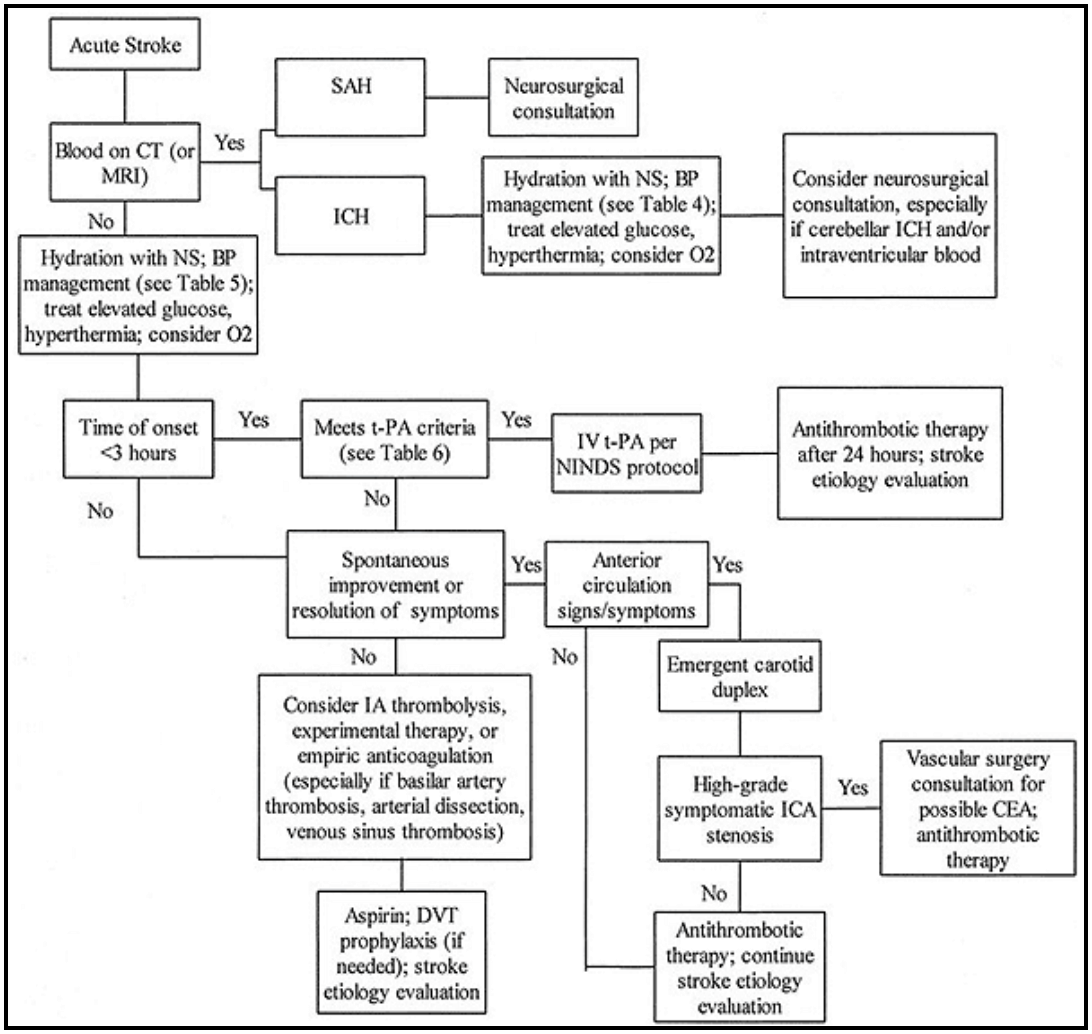
One experimental therapeutic approach has been the administration of high-dose barbiturates. By reducing intracranial pressure and diminishing requirements for osmotic agents, they reduce the metabolic requirements and oxygen requirements. They are ineffectual in anoxia because intracranial pressure rises rapidly after withdrawal of the drug. Similarly, calcium-channel blockers are not effective in improving outcome **(Moonis and Fisher, 2001).**

If the patient awakens, mobilization is initiated early to minimize the risk of bedsores and deep venous thrombosis **(Arbelaez, 1999).**

## Cerebrovascular Stroke

**Intial management:-** Once the diagnosis of acute stroke is suspected, the duration of symptom onset must be determined, as time from stroke onset remains the single most important determinant of therapeutic options (Fig. 4-1). Patients with symptom onset of less than 3 hours should be evaluated for potential treatment with intravenous tissue plasminogen activator (t-PA) **(Black-Schaffer, 2002).**

All patients should receive intravenous hydration with normal saline, hypoxia should be corrected with supplemental oxygen, hyperglycemia should be treated with insulin, and fever should be treated aggressively with antipyretics. The head of the bed may be placed in the horizontal position for patients with ischemic stroke and no elevation of intracranial pressure (ICP). An electrocardiogram should be performed and patients should receive continuous cardiac monitoring. (Table 4-3): a general management of patients with acute stroke) **(Coull et al., 2002).**




**(Fig.4-1): Algorithm for the Management of Acute Stroke (Schwarz et al., 2003).**

***(Table 4-3): General Management of Patients With Acute Stroke (Coull et al., 2002).***

| | |
|---|---|
| Blood glucose | Treat hypoglycemia with D50<br>Treat hyperglycemia with insulin if serum glucose >200 mg/dL |
| Blood pressure | See recommendations for thrombolysis candidates and noncandidates (Table 4-6) |
| Cardiac monitor | Continuous monitoring for ischemic changes or atrial fibrillation |
| Intravenous fluids | Avoid D5W and excessive fluid administration<br>IV isotonic sodium chloride solution at 50 mL /h unless otherwise indicated |
| Oral intake | NPO initially; aspiration risk is great, avoid oral intake until swallowing assessed |
| Oxygen | Supplement if indicated ($Sa0_2$ <90%, hypotensive, etc) |
| Temperature | Avoid hyperthermia, oral or rectal acetaminophen as needed |

- Hypoglycemia and hyperglycemia need to be identified and treated early in the evaluation. Not only can both produce symptoms that closely mimic ischemic stroke, but both also can aggravate ongoing neuronal ischemia. Administration of glucose in hypoglycemia produces profound and prompt improvement,

while insulin should be started for patients with stroke and hyperglycemia

- Hyperthermia is infrequently associated with stroke but can increase morbidity. Administration of acetaminophen, by mouth or per rectum, is indicated in the presence of fever.
- Supplemental oxygen is recommended when the patient has a documented oxygen requirement. To date, evidence exists that supernormal oxygenation improves outcome.
- Blood pressure management is delicate and controversial. Many patients are hypertensive on arrival. Recent American Stroke Association guidelines have reinforced the need for caution in lowering blood pressures acutely. (Table 4-4) shows current recommendations for both candidates and noncandidates for thrombolytic therapy.

- In the small proportion of patients with stroke who are relatively hypotensive, pharmacologically increasing blood pressure may improve flow through critical stenoses **(Adams, 2002).**

**Management of Blood Pressure.** During brain ischemia, cerebral autoregulation is impaired and cerebral blood flow becomes pressure passive (ie, blood flow declines with declining perfusion pressure). Blood pressure should therefore not be treated unless one of the following exists: 1) systolic blood pressure (SBP) exceeds 220 mm Hg or diastolic blood pressure (DBP) exceeds 120 mm Hg after repeated

measurements; 2) cardiac ischemia, heart failure, or aortic dissection is present; 3) thrombolytic therapy is planned; or 4) intracerebral hemorrhage is identified. In the latter situation, blood pressure should be maintained below 180/105 mm Hg, with more aggressive control reserved for patients with no prior history of hypertension. Specific treatment recommendations for the management of blood pressure after acute stroke are presented in (Table 4-4) and (Table4-5) **(Cummins, 2004).**

***(Table 4-4): Antihypertensive Therapy for Acute ischemic Stroke (Cummins, 2004).***

| Blood Pressure | Treatment |
|---|---|
| **Nonthrombolytic candidates** | |
| **DBP>140 mm Hg** | **Sodium nitroprusside(0.5 mcg/kg/min). Aim for 10 to 20 % reduction in DBP** |
| **SBP> 220, DBP> 120, or MAP> 130 mm Hg** | **10 to 20 mg labetalol IV push over 1 to 2 min. May repeat or double labetalol every 20 min to a maximum dose of 150 mg.** |
| **SBP <220, DBP>120, or MAP> 130mm Hg** | **Emergency antihypertensive therapy is deferred in the absence of aortic dissection, acute myocardial infarction, severe congestive heart failure, or hypertensive encephalopathy.** |
| **Thrombolytic candidates Pretreatment** | |
| **SBP >180mm Hg or DBP > 110 mm Hg** | **1 to 2 inches of nitropaste or 1 to 2 doses of 10 to 20 mg labetalol IV push. If BP is not reduced and maintained to <185/110 mm Hg, the patient should not be treated with tPA.** |
| **During and after treatment** | |
| **Monitor BP** | **BP is monitored every 15 min for 2 houres, then every 30 min for 6 hours, and then very 1 hour for 16 hours.** |
| **DBP >140 mm Hg** | **Sodium nitroprusside (0.5 mcg/kg/min)** |
| **DBP >230 or DBP 121 to 140 mm Hg** | **(1) 10 mg labetalol IVP over 1 to 2 min. May repeat or double labetalol every 10 min to a maximum dose of 150 mg or give the initial labetalol bolus and then start a labetalol drip at 2 to 8 mg/min. (2) If BP not controlled by labetalol, consider Sodium nitroprusside.** |
| **SBP 180 to 230 or DBP 105 to 120 mm Hg** | **10 mg labetalol IVP. May repeat or double labetalol every 10 to 20 min to a maximum dose of 150 mg or give initial labetalol bolus and start a labetalol drip 2 to 8 mg/min.** |

- ***DBP, diastolic blood pressure: SBP, systolic blood pressure: MAP, mean arterial pressure: BP, blood pressure: min, minutes: tPA, tissue plasminogen activator: IV, intravenous.***
- ***All initial blood pressures should be verified before treatment by repeating reading in 5 min.***
- ***Labetalol should be avoided in patients with asthma, cardiac failure, or severe abnormalities in cardiac conduction. For refractory hypertension, alternative therapy may be considered with sodium nitroprusside or enalopril.***

***(Table 4-5): Antihypertensive therapy for hemorrhagic stroke (Cummins, 2004).***

| Blood pressure[b] | Treatment |
|---|---|
| 1. SBP >230 or DBP >120 mm Hg | Sodium nitroprusside (0.5–10 μg/kg/min) or nitroglycerine drip (at 10–20 μg/min). |
| 2. SBP >180 or DBP >105 mm Hg | Consider 10 mg labetalol[c] IVP. May repeat or double labetalol every 10 to 20 min to a maximum dose of 300 mg. Alternatively, administer initial labetalol bolus and then start labetalol drip at 2 to 8 mg/min. |
| 3. Hypertension relative to prestroke condition | If prehemorrhage BP is estimated to have been considerably lower (eg, 120/80 mm Hg), then antihypertensive therapy may be appropriate to approximate premorbid pressures, particularly in the first hours after subarachnoid hemorrhage. |

**Intravenous Thrombolysis.** Intravenous thrombolysis with tissue plasminogen activator (t-PA) is indicated for selected patients within 3 hours of ischemic stroke onset. Inclusion and exclusion criteria for t-PA are listed in (Table 4-6). If blood pressure exceeds 185/110 mm Hg, a single dose of an antihypertensive can be administered; the patient qualifies for therapy if blood pressure declines below this level. Blood pressure should be monitored every 15 minutes for 2 hours after the start of infusion, then every 30 minutes for 6 hours, and then every 60 minutes for 16 hours. Blood pressure must be maintained below 185/110 mm Hg and antithrombotic agents must be avoided for the first 24 hours post-thrombolysis (Table4-5) **(Furlan et al., 2003).**

***(Table 4-6): Inclusion and Exclusion Criteria for Administration of Intravenous Tissue Plasminogen Activator for Acute Stroke ( Furlan et al., 2003).***

| |
|---|
| **Inclusion** |
| **Age > 18 yr** |
| **Ischemic stroke** |
| **Persistent neurologic deficit beyond an isolated sensory deficit or ataxia** |
| **Cranial computed tomography negative for hemorrhage** |
| **Initiation of treatment within 3 hours after symptom onset** |
| **Exclusion** |
| **Treatment initiated > 3 hours after symptom onset** |
| **Neurologic deficit that is rapidly improving based on history or observation** |
| **CT scan shows major early infarct signs (eg, substantial edema, mass effect, midline shift)** |
| **Patient taking oral anticoagulants or with PT >15 seconds (INR > 1.7)** |
| **Patient receiving heparin within the preceding 48 hours who has a prolonged PTT** |
| **Platelet count <100.000/mm 3** |
| **Pretreatment systolic blood pressure >185 mm Hg or diastolic pressure > 110 mm Hg or if aggressive treatment is required to reduce blood pressure to the specified limits before thrombolytic therapy** |
| **Prior stroke or any serious head trauma in the preceding 3 months** |
| **Major surgery within the preceding 21 days** |
| **Prior intracerebral hemorrhage** |
| **Gastrointestinal or urinary tract hemorrhage within the preceding 14 days** |
| **Seizure at the onset of stroke** |
| **Symptoms suggestive of SAH** |
| **Arterial puncture at a noncompressible site within the previous 7 days** |

Patients with ischemic stroke who do not qualify for intravenous t-PA should be administered aspirin (160-325 mg/d) as it has been shown to modestly reduce the risk of recurrent stroke and death when administered within the first 48 hours poststroke (**Bernard et al., 2002).**

**Emerging Therapies:** For patients with ischemic stroke in whom intravenous thrombolysis is not indicated, consideration can be given to the administration of intra-arterial thrombolysis if the appropriate facilities and personnel are available. A prospective, randomized controlled trial of intra-arterial prourokinase showed a treatment benefit for selected patients with middle cerebral artery stroke, but prourokinase is not currently available for use. These data have led to the adoption of protocols for the administration of intra-arterial t-PA at some centers. The safety and efficacy of the combination of a lower dose of intravenous t-PA followed by intra-arterial t-PA are currently under investigation. Other antithrombotic agents under clinical investigation for ischemic stroke include intravenous heparin administered within 12 hours of stroke onset, a platelet glycoprotein IIb/IIIa antagonist (abciximab), and a direct thrombin inhibitor (argatroban) **(Furan et al., 2003).**

**Surgical Care:** Surgical intervention is rarely required urgently in AIS; however, current recommendations suggest that neurosurgical care should be available within 2 hours when needed, eg, to evaluate surgical options in symptomatic hemorrhagic conversion following t-PA or in the management of life-threatening elevations of ICP.

- Increased ICP is a life-threatening event occurring in as many as 20% of all strokes; it is more common in large, hemispheric

strokes. Edema and herniation are the most common causes of early death in patients with hemispheric stroke.

  - Patient position, hyperventilation, hyperosmolar therapy, and rarely, barbiturate coma may be used, as in patients with increased ICP secondary to closed head injury.

  - Recent reports of hemicraniectomy to treat life-threatening ICP have suggested that these patients have shorter ICU stays and a lower mortality rate, if surgery is performed before clinical deterioration.

- Selected patients with either hemorrhagic transformation or intracerebral hemorrhage after thrombolytic therapy may benefit from surgical evacuation of the hematoma, but this has not been proven prospectively in randomized, double-blind trials **(Schneider et al., 2004).**

## Neuropathy and myopathy in the ICU

- **Guillain-Barre` Syndrome:-**

The three major treatment issues in GBS are controlling respiration and deciding when to intubate the patient, recognizing and managing autonomic dysfunction, and determining which patients are candidates for plasmapheresis or human immune globulin (HIG) (Table4-7) **(Bersano et al., 2005).**

***(Table 4-7): Management of Guillain-Barre` Syndrome (Irwin and Rippe, 2003),***

| | |
|---|---|
| **General** | **Monitor respiratory parameters: VC, arterial blood gas.**<br>**Intubate if:**<br>**VC <12-15 ml/kg.**<br>**Oropharyngeal paresis with aspiration.**<br>**Falling vital capacity over 4-6 h**<br>**Respiratory fatigue with VC 15 ml/kg.**<br>**Use short-acting medications to control autonomic dysfunction.**<br>**Nursing care: frequent turns to avoid pressure sores.**<br>**Place pads at elbows and fibular head to avoid compression neuropathies.**<br>**Physical therapy.**<br>**Subcutaneous heparin**. |
| **Treatment** | |
| **Plasmapharesis** | **Exchange a total of 200 mL plasma/kg body weight over 7-14 d (40-50 mL/kg for 3-5 sessions)."** |

| | |
|---|---|
| | **Albumin is used as replacement solution, not fresh-frozen plasma.**<br>**During plasmapheresis, monitor blood pressure and pulse every 30 min.**<br>**Obtain complete blood cell count (baseline and before each exchange to calculate plasma volume).**<br>**Obtain immunoglobulin levels before first exchange and after last exchange: if immunoglobulin G <200 mg/dL after last plasma exchange, infuse 400 mg/kg HIG.** |
| **HIG** | **2 g/kg divided over 5 consecutive d (0.4 g/kg/d for 5 d).** |

Good supportive care is critical in the treatment of patients with GBS. As most deaths related to GBS are associated with complications of ventilatory failure and autonomic dysfunction, many patients with GBS need to be monitored closely in ICUs by physicians experienced in acute neuromuscular paralysis and accompanying complications. Competent intensive care includes such things as respiratory therapy, cardiac monitoring, safe nutritional supplementation, and monitoring for infectious complications such as pneumonia, urinary tract infections, and septicemia **(Dalakas, 2004).**

Approximately one third of patients with GBS require ventilatory support. Monitoring for respiratory failure, bulbar weakness, and

difficulties with swallowing help to anticipate complications. Proper positioning of the patient to optimize lung expansion and secretion management for airway clearance is required to minimize respiratory complications. Serial assessment of ventilatory status is needed, including measurements of vital capacity and pulse oximetric monitoring. Respiratory assistance should be considered when the expiratory vital capacity decreases to <18 mL/kg or a decrease in oxygen saturation is noted (arterial $PO_2$ < 70 mm Hg) **(Newswanger and Warren, 2004).**

Close monitoring of heart rate, blood pressure, and cardiac arrhythmias allows early detection of life-threatening situations. Antihypertensives and vasoactive drugs should be used with caution in patients with autonomic instability. The nursing and medical team must also be aware of the many autonomic nervous system disturbances that can occur. Fluctuating blood pressure with transient hypertensive episodes sometimes associated with extreme degrees of agitation may be present. Other manifestations of sympathetic nervous system overactivity include sudden diaphoresis, general vasoconstriction, and sinus tachycardia. Evidence of underactivity of the sympathetic nervous system includes presence of marked postural hypotension and heightened sensitivity to dehydration and sedative-hypnotic agents. Excessive parasympathetic nervous system activity is reflected in facial flushing associated with a feeling of generalized warmth and bradycardia. Electrocardiographic changes, consisting of ST- and Twave

changes, also occur.Hypertension may be managed with short-acting alpha adrenergic blocking agents, hypotension with fluids, and bradyarrhythmias with atropine. Hyponatremia may occur and is probably best managed by fluid restriction **(Seta et al., 2005).**

Enteric or parental feedings are required for patients on mechanical ventilation to ensure that adequate caloric needs are met when the metabolic demand is high. Even patients off the ventilator may require nutritional support if dysphagia is severe. Precautions against dysphagia and dietary manipulations should be used to prevent aspiration and subsequent pneumonias in patients at risk. **(kokontis and Gutmann, 2000).**

Prevention of secondary complications of immobility, such as deep venous thrombosis (DVT), pressure sores, and development of contractures, also is required. This preventative action entails careful positioning, frequent postural changes to prevent the latter 2 complications. Subcutaneous heparin and thromboguards often are used in the treatment of immobile patients to prevent lower extremity DVTs and secondary pulmonary embolisms (PE). Pain management with analgesics and adjunct medications also may be needed. Modalities such as transcutaneous electrical nerve stimulation (TENS) and heat may be of benefit in the management of complaints of myalgia. Desensitization techniques can be used to improve the patient's tolerance for activities **(Pandey et al., 2005).**

Although bowel and bladder dysfunction is generally transitory, management of these functions is needed to prevent other complications. Initial management should be directed toward safe evacuation and prevention of overdistension. Monitoring for secondary infections, such as a urinary tract infection, is also an area of concern **(Van Koningsveld and Van Doorn, 2005).**

Hospitalized patients with GBS may experience mental status changes, including hallucinations, delusions, vivid dreams, and sleep abnormalities. These occurrences are thought to be associated with autonomic dysfunction and are more frequent in patients with severe symptoms. The issue resolves as the patient recovers **(Winer, 2002).**

**Surgical Intervention:** Tracheotomy may be required in the patient with prolonged respiratory failure, especially if mechanical ventilation is required for more than 2 weeks. Percutaneous feeding tubes also may be required to meet the nutritional needs of patients with severe and prolonged dysphagia. A central venous line needs to be placed for patients undergoing plasmapheresis **(Pandey, 2005).**

## Slide 1

بسم الله الرحمن الرحيم

أول خمس ايات من سوره العلق

## Slide 2

**Acknowledgements**

## Slide 3

Psychological Problems in the ICU

## Slide 4

Patients admitted to an intensive care unit (ICU) generally present an unexpected life-threatening condition, with the exception of those admitted after scheduled surgery

## Slide 5

These patients will remain in their critical condition for various lengths of time and will need several types of life support, such as ventilation, cardiovascular or renal support. They will also receive various types of sedatives and analgesics to ensure compliance with ventilation and to induce some comfort.

## Slide 6

Psychosis is defined as a loss of contact with reality because of a functional
disturbance in which the sensorium is normal but thinking is abnormal and associated with abnormal perceptions and systematic delusions

## Slide 7

The term psychosis does not adequately reflect the range of symptoms seen in confused ICU patients. Traditionally, the term ICU psychosis has been used to designate florid abnormalities of mood and behavior in ICU patients. The term is outmoded and misleading because it implies a cause-and-effect relationship between being in an ICU and becoming psychotic.

## Slide 8

The most common psychological changes in the ICU are

## Slide 9

1-Delirium
(Acute confusional state)

## Slide 10

Delirium is considered to be a global manifestation of brain dysfunction. It is  defined as a reversible, global impairement of cognitive processes, usually of sudden onset, coupled with disorientataion, impaired short-term memory, altered sensory perceptions (hallucinations), abnormal thought processes and inappropriate behavior

## Slide 11

Clinical Features

Delirium can manifest in 2 varieties

- Hypoactive delirium:  This includes slowed speech, slowed movements, sluggishness, apathy, depression, and lethargy.
- Hyperactive delirium: This includes excessive activity, rapid pressured speech, rage, fear, rapid movements and increased reaction to any stimuli.

## Slide 12

Etiology

Numerous organic disturbances have been implicated in the etiology of delirium and can be listed under one of four major categories

## Slide 13

1. primary intracranial disease, which includes infections, stroke, and trauma

2. systemic diseases that secondarily affect the brain, which are metabolic diseases, infections, and cardiovascular disease

3. exogenous toxic agents

4. withdrawal from substances on which the patient has become dependent

## Slide 14

Risk Factors

- **Older than 70 years of age**
- **Previous history of depression or dementia**
- **History of congestive heart failure, stroke, or epilepsy**
- **Alcohol abuse within a month**
- **Administration of psychoactive drugs**
- **Drug overdose/illicit drug use**
- **Hypo- or hypernatremia**
- **Hypo- or hyperglycemia**
- **Hypo- or hyperthyroidism**

- **Hypothermia or fever**
- **Serum urea nitrogen:creatinine ratio that is 18 or more**
- **Renal failure (creatinine >2.0 mg/dL)**
- **Liver disease (bilirubin >2.0 mg/dL)**
- **Cardiogenic or septic shock**
- **HIV infection**
- **Tube feeding**
- **Rectal or bladder catheters**
- **Central venous catheters**
- **Malnutrition**
- **Use of physical restraints**
- **Visual or hearing impairment**

## Slide 15

The DSM-IV criteria for the diagnosis of delirium are as follows:
(1) disturbance of consciousness, with reduced ability to focus, sustain, or shift attention;
(2) a change in cognition or the development of a perceptual disturbance that is not better accounted for by a pre-existing dementia;
(3) the disturbance develops after a short period of time and tends to fluctuate;
(4) evidence from history, physical examination, or laboratory findings that the disturbance is caused by the physiologic consequences of a general medical condition

## Slide 16

## 2-Agitation

## Slide 17

Agitation is most often described as excessive restlessness, which is characterized by nonpurposeful

mental and physical activity due to internal tension and anxiety. However, no clear, concise, and universally accepted definition of agitation in ICU patients exists

**Slide 18**

Agitation occurs often in the critically ill and may result in unplanned extubation, increased oxygen consumption, hemodynamic instability, injury to self or care providers, and inability to participate in therapeutic interventions. The syndrome complicates management in the ICU, often leading to further morbidity and complications

**Slide 19**

**3-Anxiety**

**Slide 20**

Anxiety is a psychophysiological phenomenon experienced as a foreboding dread or threat to a human organism whether the threat is generated by internal, real or imagined dangers. It is a diffuse and unpleasant emotion of apprehension that is not associated with a specific threat.

**Slide 21**

Anxiety and fear can be clinically indistinguishable; however, their causes are different. Fear is the sense of dread and foreboding that may occur in response to an external threatening event. Anxiety is the same distressing experience of apprehension and foreboding as fear except that it derives from an unknown internal stimulus, inappropriate or excessive to the reality of the external stimulus or concerned with a future one.

**Slide 22**

Clinical Features

**Slide 23**

- The physical signs and symptoms of anxiety are generally those associated with autonomic arousal.
- The behavioral consequences of anxiety include the avoidance of distressing situations, noncompliance with procedures, or flight from the hospital.
- The cognitive aspects include worry, apprehension, and thoughts about emotional or bodily damage.

**Slide 24**

Causes of Anxiety in the ICU

**Slide 25**

Patients hospitalized in the ICU encounter internal and external dangers: fear of death, separation from loved ones and familiar surroundings, loss of control, intimacy with strangers, sleep loss and frequent procedures that are painful or restrict mobility. Patients experience anxiety about their illness and about their capacity to work and maintain social and family relationships in the future.

**Slide 26**

**4- Depression**

**Slide 27**

Intense emotions are evoked routinely in intensive care units. In the ICU, depression occurs as a psychological reaction to an acute medical illness or as a manifestation of a primary affective disorder detected at the time of medical evaluation.

## Slide 28

The term depression is defined in the DSM-IV as a syndrome that affects neurovegetative functions as well as mood

## Slide 29

Diagnostic criteria of depression

To qualify for a diagnosis of major depression, a patient must have a sustained period of depressed or hopeless mood for a period of at least 2 weeks in association with at least four of the following eight neurovegetative symptoms

## Slide 30

1. a change in sleep patterns
2. a decrease in one's interests or drives in life
3. a sense of guilt
4. a decrease in energy
5. a decrease in concentration ability
6. a change in appetite
7. a change in psychomotor activity
8. suicidal ideation or thoughts of death

## Slide 31

Causes of depression

- Various medications and medical illnesses can cause depression. Endocrine disorders, neurologic disorders , and human immunodeficiency virus (HIV) infections are frequently accompanied by depression
- There are several drugs that may cause depressive symptoms .The agents most often responsible for depression are antihypertensives, beta-blockers, antiarrhythmics, antihistamines , and steroids.

## Slide 32

One may wonder why it is important to attend to a patient's mood in the ICU when vital organs are not working and survival is not assured. Moreover, many physicians believe that depression is appropriate in the ICU because severe illness devastates and disrupts a person's life.

However, it is always important to treat depression. In fact, there is compelling evidence that untreated depression decreases survival and increases morbidity and mortality from cardiac conditions.

## Slide 33

## Management of Psychological problems in the ICU

## Slide 34

An ideal regimen should control pain, anxiety, agitation, and delirium while minimizing adverse effects.

## Slide 35

Clinical practice guidelines for critically ill adults recommend routine assessment for the presence of delirium as well as pharmacologic management strategies with neuroleptic agents. Haloperidol is considered to be the preferred agent in critically ill patients. Newer atypical antipsychotic agents have also been suggested due to the potential for decreased adverse effects.

## Slide 36

Sedatives are the mainstays of supportive patient care in the ICU. Critically ill patients are frequently in pain as a result of their medical condition or surgery. Mechanical ventilation and environmental factors cause additional stresses. Benzodiazipines are considered first line agents for the management of anxiety and

agitation. These drugs provide anxiolysis and amnesia but they have no analgesic properties.

## Slide 37

## Properties of an ideal sedative

## Slide 38

- **Easily titratable level of adequate sedation**
- **Rapid onset of action**
- **Short acting, allowing patient assessment, easy weaning from mechanical ventilation, and early extubation**
- **No adverse effects**
- **No nausea, vomiting, phlebitis**
- **No anaphylaxis or allergic reaction**
- **Minimal metabolism; not dependent on normal hepatic, renal, or pulmonary function**
- **No active or toxic metabolites**
- **No suppression of cortisol production by the adrenal cortex**
- **No interactions or incompatibilities with other commonly prescribed intensive care unit drugs**
- **Ease of administration**
- **Lack of accumulation with prolonged adminstration**
- **Does not promote growth of pathogens**
- **Cost effective**
- **Easily prepared and long shelf-life**

## Slide 39

Levels of sedation

- Minimal sedation
- Moderate sedation
- Deep sedation

## Slide 40

Patients who meet the criteria for major depression are usually treated with a somatic therapy alone or in combination with psychotherapy. In critical care units, somatic therapies are the most widely used treatments for depression. Somatic therapies include pharmacotherapy and electroconvulsive therapy (ECT).

## Slide 41

The most common rule is to choose a medication with a side-effect profile that best fits the patient's symptoms. A patient who is having trouble sleeping will benefit from a sedating antidepressant. A patient who has severe psychomotor retardation may benefit from a more stimulating antidepressant.

## Slide 42

The older polycyclic antidepressants, as well as the selective serotonin reuptake inhibitors (SSRIs), take approximately 4 to 6 weeks until full antidepressant effects

are noted, although effects can occur in 1 to 2 weeks. In critical care units, quicker effects are generally needed. Stimulants and ECT work more quickly, usually within 1 week.

## Slide 43

MAOIs are used to treat atypical depressions and may also take several weeks to reach their full effectiveness; their use is rarely associated with cardiac conduction difficulties.

## Slide 44

Neurologica problems in the ICU

## Slide 45

Neurologic problems present in the intensive care unit (ICU) in two modes

- primary neurologic problems such as stroke, Guillain-Barré syndrome, head trauma, or myasthenia gravis who are admitted to the ICU for close observation and management of vital functions, such as respiration or control of ICP.
- The other type of patients includes those with secondary neurologic complications, occurring in patients with other medical or surgical disorders.

## Slide 46

## 1-Metabolic Encephalopathy

## Slide 47

Metabolic encephalopathy is one of the most frequently seen neurologic disorders in the ICU. It is also one of the most diverse in its clinical presentations and requires a systematic approach to define the etiology and to institute effective treatment.

## Slide 48

The features that distinguish most metabolic encephalopathies from structural lesions are a nonfocal neurologic examination, increased motor activity, intact ocular and pupillary reflexes, and laboratory abnormalities that support the clinical picture. Additional tests such as an EEG, head CT, or toxicology screen are useful in ruling out other possible causes.

## Slide 49

2-Generalized anoxia / ischemia of the Nervous system

## Slide 50

The effects of oxygen deprivation depend on many factors; the degree and duration of hypoxia are the most important. In cases of cardiac arrest, brain damage is proportional to the amount of time without perfusion. The patient's age, underlying medical conditions, infection, and other metabolic imbalances also play a role in the body's ability to withstand oxygen deprivation. Treatment strategies for the acute phase focus on supportive care. Elevation of the head of the bed, maintaining a relatively hypovolemic state, and avoidance of hypotension may be of benefit. A vigorous search should be made for concurrent metabolic abnormalities. . Prognosis is best determined by the early return of brainstem and cranial nerve function. Absence of brainstem functions 72 hours after the event is associated with irreversible coma.

## Slide 51

3-Cerebrovasular disease

## Slide 52

Stroke is the clinical term for acute loss of circulation to an area of the brain, resulting in ischemia and a corresponding loss of neurologic function. Classified as either hemorrhagic or ischemic, strokes typically manifest with the sudden onset of focal neurologic deficits, such as weakness, sensory deficit, or difficulties with language. Ischemic strokes have a heterogeneous group of causes, including thrombosis, embolism, and hypoperfusion, whereas hemorrhagic strokes can be either intraparenchymal or subarachnoid.

## Slide 53

4-Neuropathy & Myopathy in the ICU

## Slide 54

Although there are many neuromuscular disorders producing acute weakness, the most commonly encountered is GBS. Of increasing importance are the ICU-acquired disorders of nerve and muscle. Less commonly encountered disorders are toxic/ infectious neuropathies, porphyria, and metabolic myopathies. Careful evaluation in determining whether the weakness started before or after admission to the ICU is important in making the correct diagnosis and providing the

appropriate treatment and prognosis. HIG and plasmapheresis may hasten recovery in patients with GBS, whereas the avoidance of corticosteroids and NMBAs may prevent acute myopathy of intensive care. Recognition of these disorders early in the illness is the key in providing optimal care and treatment of these entities.

# References


- **Adams HB Jr** (2002): Emergent use of Anticoagulants in treatment of patients with ischemic stroke. Stroke; 33: 856-61.
- **Ahboucha S and Butterworth RF (2004**): Pathphsiology of hepatic encephalopathy: a new look at GABA from the molecular standpoint. Metab Brain Dis; 19: 331-43.
- **Altuntas Y, Bilir M, Ucak S and Gundogdu S (2005):** Reactive hypoglycemia in lean young women with PCOS and correlations with insulin sensitivity and with beta cell function. Eur J Obstet Gynecol Reprod Biol; 119: 198-205.
- **Amsterdam DJ (2003):** A double-blind, placebo-controlled trial of the safety and efficacy of selegiline transdermal system without dietary restrictions in patients with major depressive disorder. J Clin Psychiatry; 64: 208-14.
- **Angst J, Angst F and Stassen HH (1999):** Suicide risk in patients with major depressive disorder. J Clin Psychiatry; 60:57.
- **Apter A, Horesh N, Gothfel D, et al (2001):** Relationship between self disclosure and serious suicidal behavior. Compr Psychiatry; 42: 70-5.
- **Arbelaez A (1999):** Diffusion Weighted MR imaging of global cerebral anoxia. AM J Neuroradiol; 20: 999.

- **Aronson SC and Ayres VE (2005):** Depression: A treatment algorithm from the family physician. Hospital Physician; 33:12-4.
- **Arthur HM, Daniels C, McKelvie R, et al (2000**): Effect of preoperative intervention on preoperative and postoperative outcomes in low-risk patients awaiting elective coronary artery by-pass graft surgery. A randomized, controlled trial. Ann Int Med; 133: 253-62..
- **Azim W and Walker R ( 2003):** Wernickes encephalopathy: a Freaquently Missed Problem. Hospital Medicine; 64: 326-7.
- **Bair N, Bobeck MB, Hoffman-Hogg L, et al (2000):** Introduction of sedative, analgesic, and neuromuscular blocking agent guidelines in medical intensive care unit: Physician and nurse adherence. Crit Care Med; 28: 707-11.
- **Baker M (2000):** Modernising the NHS: Patients Care (empowerment): the view from national society. British Medical Journal; 320: 1660-2.
- **Barrientos-Vega R, Sanchez-Sorio MM, Morales-Garcia C,et al (2001):** Pharmachoeconomic assessment of propofol 2% used for prolonged sedation. Crit Care Med; 29:317-22.
- **Bernard SA, Gray TW, Buist MD, et al (2002):** Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. N Eng J Med; 346: 549.

- **Bersano A, Carpo M, Allaria S, et al (2005):** Long term disability and social status change after Guillain-Barre` syndrome. J Neurol; 21:330-45..
- **Bhana N, Goa KL and McClellan KJ (2000):** Dexmedetomidine. Drugs; 59: 263-8.
- **Black-Schaffer RM, Osberg JS (2002):** Return to work after stroke: Development of a predictive model. Arch Phys Med Rehabi; 71: 285-90.
- **Bogardus ST, Desai MM, Williams CS, et al (2003):** The effect of a targeted milticomponent delirium intervention on post discharge outcomes for hospitalized older adults. Am J Med; 114:383-90.
- **Bourcigaux N, Arnault-Ouary G, christol R, et al (2005):** Treatment of hypoglycemia using combined glucocorticoid and recombinant human growth hormone in a patient with a metastatic non-islet cell tumor hypoglycemia; 27: 246-51.
- **Brown DL and Morgenstern LB (2005):** Stopping the bleeding in intracerebral hemorrhage. N ENG J Med; 352: 828-30.
- **Burman K and Wartofsky L (2001):** Thyroid function in the intensive care unit setting. Crit Care Clin; 17: 43-57.
- **Butterworth RF (2004):** pathogenesis of hepatic encephalopathy: new insights from neuroimaging and molecular studies. J Hepatol; 39: 279-85.

- **Cawley MJ (2001):** Short -term lorazepam infusion and concern for propylene glycol toxicity: Case report and review. Pharmacotherapy; 21: 1140-4.
- **Clavero S, Perez P, Rincon A, et al (2004):** Qualitative and quantitative analysis of the effect of splicing mutation in propionic acidemia underlying non-severe phenotypes. Hum Genet; 115: 239-47.
- **Cole-king A and Harding KG (2001):** Psychological factors and delayed healing in chronic wounds. Psychosom Med; 63: 216-20.
- **Collins SP, Lindsell CJ and Storrow AB (2006):** Prevalence of negative chest radiography results in the emergency department patient with decompensated heart failure. Ann Emerg Med; 47: 13-8.
- **Cooper AB, Gabor JY and Hanly PJ (2001):** sleep in the critically ill patients. Semin Respir Crit care Med; 22: 153-63.
- **Cordoba J, Lopez-Hellin J and planas M (2004):** Normal protein diet for episodic hepatic encephalopathy: results of randomized studies. J Hepatol; 41: 38-43.
- **Coull BM, Williams LS, Goldstein LB, et al (**2002): Anticoagulants and antiplatletes agents in acute ischemic stroke: Report of the Joint Stroke Guideline Development Committee of the American Academy of neurology and the American Stroke

Association(a division of American Heart Association). Neurology; 59: 13-22.

- **Coursin DB, Jacobi J, Fraser GL et al (2002):** Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult. Crit Care Med; 30: 119-41.
- **Cremer OL, Moons KGM, Bouman EAC, et al (2001):** Long term propofol infusion and cardiac failure in adult head-injured patients. Lancet; 357: 117-8.
- **Crippen DW (1990):** The rule of sedation in the ICU patient with pain and agitation. Crit Care Clin; 6: 169-92.
- **Cummins RO (1997):** Acute stroke, in textbook of Advanced Cardiac Life Support . Dallas, American Heart Association; 10: 1-28.
- **Dalakas MC (2004):** Intravenous immunoglobulin in auto immune neuromuscular diseases. JAMA; 291: 2367-75.
- **Dattani D and Wong G (2001):** Intensive care unit sedation: Agents used to sedate agitated ICU patients ,crit care med;44:34-43.
- **DeJonghe B, Cook D, Appere-De-Veechi, et al (2000):** Using and understanding sedation scoring system: a systematic review. Intensive care Med; 26: 275-85.
- **Detke MJ, Lu Y, Goldestien DJ, et al (2002):** Duloxextine 60mg once daily for major depressive disorder: A randomized

double-blind placebo-controlled trial. Journal of Clinical Psychiatry; 63: 308-15.

- **Devlin JW, Boleski G, Mlynarek M, et al (1999):** Motor activity assessment scale: A valid and reliable sedation scale for the use with mechanically ventilated patients in an adult surgical intensive care unit. Crit care Med; 27: 1271-75.
- **Donofrio PD (2005):** Chronic inflammatory demyelinating polyradiculopathy. New views and guidelines.J peripher Ner syst; 10: 217-9.
- **Dubois MJ, Bergeron N , Dumont M, et al (2001):** Intensive Care Delirium Screening Checklist: evaluation of a new screening tool. Intensive Care Med; 27: 859-64.
- **Ely EW, Gautam S, Margolin R, et al (2001):** The impact of delirium in the intensive care unit on hospital length of stay. Intensive Care Med; 27: 1892-1900.
- **Ely EW, Stephens RK, Jackson JC, et al (2004):** Current opinion regarding the importance, diagnosis and management of delirium in the intensive care unit: a survey of 912 healthcare professionals. Crit Care Med; 32: 106-12.
- **Erdmann PG, Van Meeteren NL, Kalmijin S et al (2005):** Functional health status of patients with chronic inflammatory neuropathies. J peripher Nerv Syst; 10: 181-9.
- **Ferenci P, Lockwood A and Mullen K (2002):** Hepatic encephalopathy - Definition, nomenclature,diagnosis and

quantification: Final report of the working party at the 11th world congress of Gastroentnrology, Vienna,1998. Hepatology; 35: 716-21.

- **Fiebach JB, Schellinger PD, Gass A, et al (2004):** Stroke magnetic resonance imaging is accurate in hyper acute intracerebral hemorrhage: a multicenter study on the validity of stroke imaging. Stroke; 35: 502-6.
- **Fliess JL, Levin B and Cho Piak M (2003):** Statistical methods for rates and proportions. New York, 3rd Ed;22: 12-16.
- **Foreman MD, Inouye Sk, Mion Lc et al (2001):** Nurses' recognition of delirium and its symptoms. Comparison of nurse and researcher ratings. Arch Intern Med; 161: 2467-73.
- **Fraser CL and Arieff AL (1997):** Nervous system manifestations of renal failure. IN: Schrier RW, Gottschalk CW, eds. Diseases of the kidney; 25: 26-46.
- **Fraser GL, Prato BS, Riker RR, et al (2000):** Frequency , Severity, and treatment of of agitation in young versus elderly patients in the ICU. Pharmacotherapy; 20: 40-6.
- **Furlan A, Higashida R, Gent M, et al (1999): The** PROACT Invistigators. Intra arterial prourokinase for acute ischemic stroke: The PROACT II Study-A randomized controlled trial. JAMA; 282: 2003-2011.

- **Gertler R, Clieghton Brown H, Mitchell DH, et al (2001):** Dexmedetomidine: A novel sedative-analgesic agent. BUMC Proc; 14: 13-21.
- **Goldberg JF and Truman CJ (2003):** Antidepressant-induced mania: an overview of current controversies. Bipolar Disorder; 5: 407-20.
- **Gumnick JF and Nemeroff CB (2000):** Problems with currently available antidepressants. Journal of Clinical Psychiatry; 61: 5-15.
- **Granja C, Teixeira-Pinto A, Costa-Pereira A (2002):** Quality of life after intensive care-evaluation with EQ-5D. Intensive Care Med; 25:746-52.
- **Gunn AJ and Gunn TR (1998):** The pharmacology of neuronal rescuewith cerebral hypothermia. Dev; 53: 19-35.
- **Hall RI, Sandham D, Cardinal P, et al (2001):** Propofol vs midazolam for ICU sedation: A Canadian multicenter randomized trial. Chest; 119: 1151-9.
- **Hart RP, Best AM, Sessler CN, et al (1997):** Abbreviated cognitive test for delirium. J Psychosom Res; 43: 417-23.
- **Harvey M (1996):** Managing agitation in critically ill patients. Am J Crit Care; 5: 7-15.
- **Haskel RM, Frankel HL, Rotondo MF, et al (1997):** Agitation. AACN CLIN Issues; 3: 335-50.

- **Hassan E, Fontaine DK and Nearman HS (1998):** Therapeutic considerations in the management of agitated or delirious critically ill patients. Pharmacotherapy; 18: 113-29.
- **Heffner JE (1997):** A wake-up call in the intensive care unit. N Eng J Med; 342: 1520-2.
- **Herr DL, Kelly K, Hall JB, et al (2000):** Safety and efficacy of propofol with EDTA when used for sedation of surgical intensive care unit patients. Intensive Care MED; 26: 452-62.
- **Herridge MS (2002):** Long term outcomes after critical illness. Curr Opin Crit; 8: 331-6.
- **Higgins TL, Murray M, Kett DH, et al (2000):** Trace element homeostasis during continous sedation with propofol containing EDTA versus other sedatives in critically ill patients. Intensive Care Med; 26: 413-21.
- **Hobson-Webb LD and Donofrio PD (2005):** Inflammatory neuropathies. Curr Rheumato; 7: 348-55.
- **Hopkins RO, Weaver LK, Pope D, Orme Jf Jr, Bigler ED, and Larson-Lohr V (1999):** Neuropsychological sequelae and impaired health status in survivors of severe acute respiratory distress syndrome.Am J Respir Crit Care Med; 160:50-6.
- **Hung SC, Hung SH and Tarng DC (2001):** Thiamine deficiency and unexplained encephalopathy in hemodialysis and peritoneal dialysis patients. American Journal of kidney diseases; 38: 941-7.

- **Inouye SK, Foreman MD, Mion LC, et al (2001):** Nurses' recognition of delirium and its symptoms: comparison of nurse and researcher ratings. Arch Inter Med; 161: 2467-73.
- **Irwin RS and Rippe JM (2003):** Neurologic problems in the Intesive Care Unit. Intensive Care Medicine; 187: 965-1025.
- **Irwin RS and Rippe JM (2003):** Psychiatric Issues in the Intensive Care Unit.Intensive Care Medicine; 203:1178-99.
- **Jacobi J, Fraser GL, Coursin DB, et al (2002):** clinical practice guidelines for sustained use of sedatives and analgesics in critically ill adult. Crit Care Med; 30: 119-41.
- **Jackson JC and Ely EW (2001):** Confusion assessment methods (CAM). Int J Geriatr Psychiatry; 11: 431-8.
- **Jenkines DH (2000):** Substance abuse and withdrawal in the intensive care unit: Contemporary issues; 80: 1033-53.
- **Kaller RH et al (2000):** The treatment of acidosis in acute lung injury with tris-hydroxymethyl aminomethane (THAM). Am J Respir Crit Care; 161:141-53.
- **Keller MB (2003):** Key considerations in choosing antidepressant. Postgraduate Medicine; 10:10-18.
- **Kessler RC, Berglund PB, Demler O, et al (2003):** the epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). JAMA; 289: 3095-105.

- **Kidwell CS, CHalela JA, Saver JL, et al (2004):** Comparison of MRI and CT for detection of acute intracerebral hemorrhage. JAMA; 292: 1823-30.
- **Kokontis L and Gutmann L (2000):** current treatment of neuromuscular diseases. Arch neurol; 57: 939-43.
- **Kress JP, Pohlman AS, O'Connor MF, et al (2000):** Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. N Eng J Med; 342: 1471-77.
- **Laffey JG and Kavanagh BP (1999):** Carbon dioxide and the critically ill –too little of a good thing; 354: 1283-6.
- **Laureti S et al (2000):** Low dose (1) ACTH test in the evaluation of adrenal dysfunction in pre-clinical Additions disease. Clin Endocrinol; 53: 107-15.
- **Leger JM and Behin A (2005):** Multifocal motor neuropathy; 18: 567-73.
- **Leonard JV, Walter JH and McKiernan PJ (2001):** The management of organic acidemias: the rule of transplantation. J Inherit Metab; 24: 309-11.
- **Maisel AS, Krishnaswamy P, Nowak RM, et al (2002):** Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. N Eng J Med; 347: 161-7.
- **Mann JJ (2005):** The medical management of depression. N Eng J Med; 353: 1819-34.

- **Marcantonio ER, Flacker JM, Wright RJ, et al (2001):** Reducing delirium after hip fracture: a randomized trial. J AM Geriatr ; 49: 516-22.
- **Marcantonio ER, Simon SE, Bergmann MA, et al (2003):** Delirium symptoms in post-acute care: prevalent, persistent and associated with poor functional recovery. J AM Geriatr Soc; 51: 4-9.
- **Margolin R, Ely EW, Francis J et al (2001):** Evaluation of mental status in the ICU. Validation of the CAM-ICU. Crit Care Med; 29: 1720-79.
- **Martinez JM and Marangell LB (2004):** Mood disorder. Conn's current therapy; 22: 1161-9.
- **Mas A, Rodes J and Sunyer L (2003):** Comparison of rifaximin and lactilol in the treatment of acute hepatic encephalopathy: results of randomized, double-blind, double-dummy, controlled clinical trial. J hepatol; 38: 51-8.
- **Mayer SA, Burn NC, Begtrup K, et al (2005):** Recombinant activated factor VII for acute intra cerebal hemorrhage. N Eng J Med; 352: 777-85.
- **McDonald S, Green SE and Hetrick S (2004):** Preoperative education for hip or knee replacement (Review). The Cochrane Database of systematic review; 20: 33-5.

- **McNicoll L, Pasani M, Zhang Y, et al (2002):** Adverse hospital outcomes in critically ill older patients: the effect of delirium [abstract]. The Geronotologist; 42: 212.
- **McNicoll L, Pisani MA, Zhang Y,et al (2003):** Delirium in the intensive care unit: Occurance and clinical course in older persons. J Am Geriatr Soc; 51: 1-9.
- **Mder TJ and Mandel A (2002):** A new clinical scoring system fails to differentiate hemorrhagic from ischemic stroke when used in the acute care setting. J Emerg Med; 16: 9-13.
- **Meade MO and Herridge MS (2001):** An evidence approach to acute respiratory distress syndrome. Respiratory care; 46: 1368-76.
- **Meagher DJ, Hanlon DO, Mahony EO, et al (2005):** Relationship between symptoms and motoric subtype of delirium. J Neuropsychiatry Clin Neurosci; 12: 51-6.
- **Mendelow AD, Gregson BA, Fernandes HM, et al (2005):** Early surgery versus initial conservative treatment in patients with spontaneous supratentorial intracerebral hemorrhage in the International Surgical Trial in the Intracerebral Hemorrhage(STICH): a randomized trial. Lancet; 365: 387-97.
- **Miyazaki T, Ohura T, Kobayashi M, et al (2001):** Fatal propionic academiain mice lacking propionyl-CoA carboxylase and its rescue by postnatal, liver-specific supplementation via a transgene. J Biol Chem; 279: 35995-9.

- **Moonis M and fisher M (2001):** Imaging of acute stroke. Cerebrovascular dis; 11: 143.
- **Mueller C, Laule-Kilian K, Frana B, et al (2006):** Use of B-type natriuretic peptide in the management of acute dyspnea in patients with pulmonary disease. AM Heart J; 151: 471-7.
- **Murray ML, Wong IC and de Vries CS (2004):** Treating major depression in children and adolescents: research is needed into safer and more effective drugs. BMJ; 328: 524-5.
- **Nasraway SA (2001):** Use of sedative medications in the intensive care unit. Semin Respir Crit Care Med; 22: 165-74..
- **Newswanger DL and Warren CR (2004):** Guillain-Barre syndrome. AM Fam Physician; 69: 2405-10.
- **Nunes B, Pais J, Garcia R, Duarte Z, Granja C and Silva MC (2003):** Cardiac arrest, long term cognitive imaging analysis, Resuscitation; 57:287-97.
- **Odaka M, Tatsumoto M, Hoshiyama E, et al (2005):** Side effect of combined therapy of methylepredinsolone and intravenous immunoglobulin in treatment of Guillain-Barre syndrome. Eur Neurol; 53: 194-6.
- **O'Keeffe S and Lavan J (2005):** The prognostic significance of delirium in older hospital patients. J Am Geriatr Soc; 45: 174-8.
- **Ostermann ME, Keenan SB, Seiferling RA, et al (2000):** Sedation in the intensive care uint :a systematic review. JAMA; 283: 1451-9.

- **Pandey CK, Raza M, Tripathi M, et al (2005):** The comparative evaluation of gabapentin and carbamazepine for pain management in Guillain-Barre syndrome patients in intensive care units. Anesth analg; 101: 220-5.
- **Parsons MW, Barber PA, Desmond PM, et al (2002):** Acute hyperglycemia adversely affects stroke outcome: a magnetic resonance imaging and spectroscopy study. Ann Neurol; 52: 20-8.
- **Pisani M, Inouye SK, McNicoll L, et al (2003):** Screening for pre-existing cognitive impairment in older intensive care unit patients: Use of proxy assessments. J Am Geriatr Soc; 51: 689-93.
- **Qureshi AI, Mohammed YM, Yahia AM, et al (2005):** A prospective multicenter study to evaluate the feasibility and safety of aggressive antihypertensive treatment in patients with acute intracerebral hemorrhage. J Intesive Care Med; 20: 34-42.
- **Qureshi AI, Tuhrim S, Broderick JP, et al (2001):** Spontaneous intracerebral hemorrhage. N Eng J Med; 344: 1450-60.
- **Ragland G (1996):** Hypoglycemia. In: Tintinalli J, et al, eds. Emergency Medicine: A Comprehensive Study Guide: 939-46.
- **Ridker PM, Cook NR, Leel-M, et al (2005):** Randomized study of low dose aspirin in the primary prevention of cardiovascular disease in women. Engl Med; 352: 1293-304.

- **Riker RP, Picard JT and Frasre GL (1999):** Prospective evaluation of –sedation-agitation scale for adult critically ill patients. Crit Care Med; 27: 1325-9.
- **Ringel MD (2001):** Management of hypothyroidism and hyperthyroidism in the intensive care unit. Crit Care Clin; 17: 59-74.
- **Rivers EP et al (2001):** Adrenal insufficiency in high-risk surgical ICU pa-tients; 119: 889-96.
- **Robins SJ, Collins D, Wittes JT, et al (2001):** Relation of gemfibrozil treatment and lipid level with major coronary events: VA-HIT: a randomized controlled trial. JAMA; 285: 1585-91.
- **Rose BD and Post TW (2001):** Clinical Physiology of Acid-Base and Electrolyte Disorders, 5th ed; 45:99-104.
- **Rosen H, Rosengren L, Herlitz J, et al (1998):** Increased serum levels of S-100 protein are associated with hypoxic brain damage after cardiac arrest. Stroke; 29: 473.
- **Rothschild JM, Bates DW and Leape LL (2000):** Preventable medical injuries in older patients. Arch Intern Med; 160: 2717-28.
- **Sandiumenge Camps A, Sanchez-Izquierdo Riera JA, Vasquez DT, et al (2000):** Midazolam and 2% propofol in long-term sedation of traumatized, critically ill patients: Efficacy and comparison. Crit Care Med; 28: 3612-9.

- **Schneider AT, Kissela B, Wood D, et al (2004):** Ischemic stroke subtypes: a population- based study on whites. Stroke; 35: 1552-6.
- **Schoerkhuber W, Kittler H, Strez F, et al (1999):** Time course of neuron specific enolase. A predictor of neurological outcomes after cardiac arrest. Stroke; 30: 1598.
- **Schwarz S, Georgiadis D, Aschoff A, et al (2002):** Effect of body position on intracranial pressure and cerebral perfusion in patients with large hemispheric stroke. Stroke; 33: 497-501.
- **Scott A (2004):** Managing anxiety in ICU patients: the rule of preoperative information provision. Nurs Crit care; 9: 72-9.
- **Seneviratne U (2000):** Guillain-Barre` syndrome. Postgard Med J; 76: 774-82.
- **Sessler CN, Grap MJ, Brophy GM, et al (2001):** Multidisciplinary management of sedation and analgesia in critical care. Semin Respir Crit Care Med; 22: 211-25.
- **Seta T, Nagayama H, Katsura K, et al (2005):** Factors influencing outcome in Guillain-Barre syndrome:comparisionof plasma adsorption against other treatments. Cin Neurol Neurosurg; 107: 491-6.
- **Shafer A (1998):** complications of sedation with midazolam in the intensive care unit and a comparison with other sedative regimens. Crit Care Med; 26: 947-56.

- **Shapiro BA, Warren J, Egol AB, et al (1995):** practice parameters for intravenous analgesia and sedation for adult patients in the intensive care unit: An executive summery. Crit Care Med; 23: 1596-1600.
- **Shi SF, Munjas Ba, Wan TT, et al (2003):** The effects of preparatory sensory information on ICU patients. J Med System; 27: 191-204.
- **Shintani A, Ely EW and Truman B (2004):** Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. Crit Care Med; 291: 1753-62.
- **Shuldham CM (2001):** Preoperative education for patients having coronary artery bypass surgery. Patient Educ Couns; 43: 129-37.
- **Shuldham CM, Fleming S and Goodman H (2002):** The impact of preoperative education on recovery following coronary artery bypass surgery. Eur Heart J; 23: 666-74.
- **Skirrow P (2002):** Delusional memories of ICU, Intensive care after care; 30:27-35.
- **Skorbik YK, Bergeron N, Dumont M, et al (2004):** Olanzapine vs haloperidol: treating delirium in critical care setting. Intensive care Med; 30: 444-9.
- **Spagnoli LG, Mauriello A, Sangiorge G, et al (2004):** Extracranial thrombatically active coronary plaque as risk factor for ischemic stroke. JAMA; 292: 1845-52.

- **Stephens RK, Ely EW, Jackson JC et al (2004):** Current opinions regarding the importance, diagnosis, and managemet of delirium in the intensive care unit. Crit Care Med; 32: 106-12.
- **Sukantarat KT and Brett S (2003):** The neuropsychological consequences of intensive care. In surviving Intensive Care; 39:51-61.
- **Thomas SA, Friedmann E, Wimbush F, et al (1997):** Psychological factors and survival in cardiac arrhythmia supprssion trial (CAST): a reexamination. Am J Crit Care; 6: 116-26.
- **Thompson KA and Goodale DB (2000):** The recent development of propofol (DIPRIVAN). Intensive Care Med; 26: 400-4.
- **Thomson AD, Cook CC and Touquet R (2002):** The Royal collage of physicians report on Alcohol: Guidelines for managing Wernickes encephalopathy in the accident and emergency department. Alcohol and Alcoholism; 37: 513-21.
- **Truman B, Ely EW, Shintani A et al (2004):** Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. JAMA; 291: 1755-59.
- **Vallverdu I, Calaf N, Subirana M, et al (1999):** Clinical characteristics, Respiratory Functional parameters, and outcome of a two-hour T-piece trial of patients weaning for mechanical ventilation. Am J Respir Crit Care Med; 158: 1855-62.

- **Van Bel F, Shadid M and Moison RM (1998):** Effects of allopurinol on postasphyxial free radical for cerebral hemodynamics and electrical brain activity. Pediatrics; 101: 185-97.
- **Van den Berghe G, Schoonheydt K, Becx P, et al (2005):** Insulin therapy protects central and peripheral nervous system of intensive care patients. Neurology; 64: 1348-53.
- **Wilmer A ,Van den Berghe G, , Hermans G, et al ( 2006):** Intensive insulin therapy in medical ICU. N Engl J; 354: 449-61.
- **Van Koningsveld R and Van Doorn PA (2005):** Steroids in Guillain-Barre syndrome:Is there a therapeutic window ?. Neurolagia; 20: 53-7.
- **Vasa FR and Molitch ME (2001):** Endocrine problems in the chronically Criti-cally ill patient. Clin Chest Med; 1: 193-208.
- **Vickrey BG, Rector TS, Wickstorm SL, et al (2002):** Occurrence of secondary ischemic events among persons with atherosclerotic vascular disease. Stroke; 33: 901-6.
- **Volpato S, Maraldi C, Ble` A, et al (2004):** Prescription on antithrombotic therapy in older patients hospitalized for transient ischemic attack and ischemic stroke: the GIFA study. Stroke; 35: 913-7.
- **Walder B, Elia N, Henzi I, et al (2001):** A lack of evidence of superiority of propofol versus midazolam for sedation in

mechanically ventilated critically ill patient: a qualitative and quantitative systematic review. Anasth Analg; 92: 975-83.

- **Walk D (1997):** Guillain-Barre syndrome. Surgery Neurol; 47: 305-7.
- **Weinart CR, Chaln L and Gross C (2001):** Sedating critically ill patients: factors affecting nurses' delivery of sedative therapy. AM J Crit Care; 10: 156-67.
- **Wijdicks EF (2001):** The diagnosis of brian death. N Eng J Med; 344: 1215.
- **Wijdicks EF, Henderson RD and McClelland RL (2003):** Emergency intubation for respiratory faliare in Guillain-Baree syndrome. Arch Neurol; 60: 947-8.
- **Winer JB (2002):** Treatment of Guillain-Barre syndrome. Q J Med; 95: 717-21.
- **Wise MG and Cassem NH (1997):** Behavioral disturbances. In: Critical Care; 20: 17-29.
- **Wong FY and Arthur DG (2000):** Hong Kong's Patients' experience of intensive care after surgery: nurses' and patients' views. Intensive Crit Care Nurse; 16: 290-303.
- **Yorifuji Y, Kawai M, Muroi J, et al (2002):** Unexpectedly high prevalence of the mild form of propionic academia in Japan: presence of a common mutation and possible clinical implication . Hum Genet; 111: 161-5.

- **Young C, Knudsen N, Hilton A, et al (2000):** Sedation in the intensive care unit. Crit Care Med; 28: 854-66.
- **Young GP, Roper AH and Bolton CF (2003):** Metabolic encephalopathies . Coma and impaired consciousness: a clinical perspective; 13: 333-8.
- **Zandbergen EGJ, de Hann RJ, Stoutenbeek CP, et al (1998):** Systematic review of early predictors of poor outcomes in anoxic-ischemic coma. Lancet; 352: 1808.
- **Zwiefler RM (2003):** Management of acute stroke. South Med J; 96: 380-5.

# Summary

Agitation is a medical emergency that threatens the well being of the ICU patient and staff. Delirium, or confusion, frequently heralds agitation, and prompt treatment may avert potentially serious consequences. A systematic approach to the evaluation of delirium will disclose its cause(s), in many instances permitting specific treatment. When a cause cannot be discovered or corrected, treatment with a neuroleptic agent such as haloperidol should be instituted. In some instances agitation is so sudden, explosive, or intense that both mechanical restraints and the infusion of rapidly acting sedating agents are required. Intravenous haloperidol has been used successfully to control intense agitation, but benzodiazepines used alone or in combination with haloperidol may offer certain advantages. The use of nondepolarizing muscle relaxants is generally withheld until these treatments have failed

The recognition and treatment of anxiety are important components of the management of the ICU patient. Timely and effective intervention enhances patient comfort and compliance and may have a salutary effect on outcome.

Intense emotions are evoked routinely in intensive care units. In the ICU, depression occurs as a psychological reaction to an acute medical illness or as a manifestation of a primary affective disorder detected at the time of medical evaluation. The term depression is often used to describe clinical signs and symptoms (e.g., transient feelings of discouragement, disappointment, sadness, grief) of a disorder with neurovegetative symptoms (i.e., major depressive disorder) that may involve psychotic features (e.g., hallucinations, delusions).

One may wonder why it is important to attend to a patient's mood in the ICU when vital organs (e.g., the heart, lungs, liver, kidneys, brain) are not working and survival is not assured. Moreover, many physicians believe that depression is appropriate in the ICU because severe illness devastates and disrupts a person's life. However, it is always important to treat depression. In fact, there is compelling evidence that untreated depression decreases survival and increases morbidity and mortality from cardiac conditions.

Metabolic encephalopathy is one of the most frequently seen neurologic disorders in the ICU. It is also one of the most diverse in its clinical presentations and requires a systematic approach to define the etiology and to institute effective treatment. The features that distinguish most metabolic encephalopathies from structural lesions are a nonfocal neurologic examination, increased motor activity, intact ocular and pupillary reflexes, and laboratory abnormalities that support the clinical picture. Additional tests such as an EEG, head CT, or toxicology screen are useful in ruling out other possible causes.

One should keep in mind that many patients in the ICU have an underlying chronic encephalopathy due to longstanding illness. Therefore, they are more susceptible to minor metabolic disturbances induced by small doses of drugs, slight shifts of fluid balance, or worsening organ failure. Early recognition and correction of such factors improve the patient's prognosis for a full neurologic recovery.

The effects of oxygen deprivation depend on many factors; the degree and duration of hypoxia are the most important. In cases of cardiac arrest, brain damage is proportional to the amount of time without perfusion. The patient's age, underlying medical conditions, infection, and other metabolic imbalances also play a role in the body's ability to withstand oxygen deprivation. Treatment strategies for the acute phase focus on supportive care. Elevation of the head of the bed,

maintaining a relatively hypovolemic state, and avoidance of hypotension may be of benefit. A vigorous search should be made for concurrent metabolic abnormalities. Administration of steroids, osmotic agents, neuroprotective agents, and prophylactic anticonvulsants are ineffective measures and may worsen the prognosis. Prognosis is best determined by the early return of brainstem and cranial nerve function. Absence of brainstem functions 72 hours after the event is associated with irreversible coma.

Stroke is the clinical term for acute loss of circulation to an area of the brain, resulting in ischemia and a corresponding loss of neurologic function. Classified as either hemorrhagic or ischemic, strokes typically manifest with the sudden onset of focal neurologic deficits, such as weakness, sensory deficit, or difficulties with language. Ischemic strokes have a heterogeneous group of causes, including thrombosis, embolism, and hypoperfusion, whereas hemorrhagic strokes can be either intraparenchymal or subarachnoid.

Although there are many neuromuscular disorders producing acute weakness, the most commonly encountered is GBS. Of increasing importance are the ICU-acquired disorders of nerve and muscle. Less commonly encountered disorders are toxic/ infectious neuropathies, porphyria, and metabolic myopathies. Careful evaluation in determining whether the weakness started before or after admission to the ICU is important in making the correct diagnosis and providing the appropriate treatment and prognosis. HIG and plasmapheresis may hasten recovery in patients with GBS, whereas the avoidance of corticosteroids and NMBAs (neuromuscular blocking agents) may prevent acute myopathy of intensive care. Recognition of these disorders early in the illness is the key in providing optimal care and treatment of these entities.

# الملخص

ان الهذيان والاضطراب العصبي كثيرا ما يكون مؤشرا للهياج العصبي وهو من الطوارئ الطبية التي تهدد مرضى الرعاية المركزة والطاقم الطبي المعالج بحيث يكون في العلاج الفوري لها تجنبا لكثير من العواقب الوخيمة المحتملة. والطريقة المنظمة في تقييم حالات الهذيان تساهم في الكشف عن اسبابه وفي مراحل عديدة تمكن من تطبيق العلاج الفعال، وحين يكون من غير الممكن ادراك الأسباب أو تصحيحها فمن الأفضل البدء باستخدام الأدوية العصبية المثبطة مثل الهالوبريدول.كما يكون استخدام القيود والتشريب بالمواد المهدئة سريعة المفعول ضروري في بعض حالات الهياج العصبي التي تظهر بصورة مفاجئة وشديدة وحادة والتي تستجيب بصورة مرضية للهالوبريدول المعد للحقن بالوريد، ولكن البنزوديازبينز قد يقدم نتائج افضل اذا مااستخدم منفردا او مع الهالوبريدول.أما مرخيات العضلات المستقطبة فمن الافضل تأجيل استخدامها حتى يثبت فشل وسائل العلاج السابقة.

ان الادراك المبكر وعلاج حالات القلق النفسي من المكونات الاساسية في المنظومة العلاجية لمرضى الرعاية المركزة. فالتدخل المطلوب في الوقت المناسب يعزز من ثقة المريض والتزامه بالعلاج و يحمل أثر جيد ومفيد على الوضع الصحى فيما بعد.

عادة ما يثير التواجد بالرعاية المركزة الكثير من الانفعالات العنيفة ويظهر الإكتئاب كرد فعل نفسي لبعض الاضطرابات العضوية الحادة أو كعرض من أعراض الاضطرابات المزاجية الأولية والتي تظهر عند التقييم الطبي المبدأي.ان مصطلح اكتئاب يسخدم غالبا في وصف الاعراض والاشارات الطبية المضطربة (مثل: الإحساس المؤقت بالوهن، الإحباط، الحزن والاسى) المصاحبة لبعض أعراض الاضطرابات العصبية

المتفاقمة ( الاضطراب الاكتئابي الأكبر) والتي قد تحمل بعض مظاهر الجنون(مثل:الهلوسات والضلالات).

قد يتساءل البعض عن سبب العناية بالحالة المزاجية لمريض الرعاية المركزة خاصة مع تدهور وظائف الأعضاء الحيوية مثل القلب والرئتان والكبد والكلى والمخ وتضاؤل فرص البقاء حيا. ويعتقد الكثير من الأطباء ان الاكتئاب و غيره من الاضطرابات المزاجية ملازم لمرضى الرعاية المركزة بسبب الأمراض العضوية الشديدة و التي تؤثر سلبيا على حياتهم . ومع ذلك من المهم دائما علاج الاكتئاب، ففي الحقيقة هناك الكثير من الأدلة القوية التي تفيد بأن عدم علاج الاكتئاب يقلل من فرص الشفاء ويزيد من معدلات الامراض والوفيات من امراض القلب.

المرض الدماغي الأيضي واحدا من أكثر الاضطرابات العصبية ظهورا في الرعاية المركزة والتي تتباين وتتعدد في طريقة ظهورها وتحتاج الى طريقة منظمة لمعرفة الاسباب والبدء بالعلاج الفعال. ان السمات المميزة للامراض الدماغية الأيضية عن غيرها من الاضطرابات العصبية الناتجة عن خلل تركيبي بالجهاز العصبي هي الفحص العصبي اللا مركزي، زيادة النشاط الحركي ، وسلامة كلا من الفعل المنعكس اللاارادى البصري والبؤبؤي والنتائج المعملية غير السليمة التي تدعم الصورة المرضية. بالاضافة لبعض الاختبارات الأخرى مثل رسم المخ الكهربائي والأشعة المقطعية ومسح السموم التي تفيد في استبعاد الأسباب الأخرى المحتملة.

يجب الأخذ بعين الاعتبار ان كثير من مرضى الرعاية المركزة يعانون ضمنيا من مرض دماغي مزمن نتيجة لطول فترة المرض العضوي ، وبهذا يصبحوا اكثر عرضى للاصابة بالاضطرابات الأيضية الصغرى والتي تنتج عن جرعات صغيرة من الأدوية ، تغير طفيف في الاتزان المائي والفشل العضوي المتدهورولذا فان الادراك المبكر لهذه العوامل وتقويمها يحسن من حالة المريض من أجل الشفاء التام.

ان الآثار الناتجة عن نقص الأوكسجين تعتمد على عدة عوامل من أهمها درجة نقص الاوكسجين ومدته.ففي حالات السكتة القلبية يتناسب الضرر الدماغي طرديا مع المدة الزمنية التي انقطع فيها الامداد بالاوكسجين. كما ان عمر المريض والظروف الصحية المصاحبة و الامراض المعدية وبعض الاضطرابات الأيضية الاخرى تلعب دورا مهما في قدرة الجسم على تحمل ومواجهة نقص الاوكسجين. كما ان استراتيجيات العلاج في حالات نقص الاوكسجين الحادة تركز على وسائل الرعاية والدعم مثل رفع الرأس عن السرير وتجنب هبوط الضغط الدموي قد تكون ذو فائدة. وهذه الاضطرابات الأيضية المتزامنة لابد وان تخضع لكثير من الأبحاث القوية والاختبارات الجادة. ان استخدام بعض الأدوية مثل الاستيرويد والمواد الازموزية والمهدئات ومضادات الصرع الوقائية غير مجدي بل على العكس قد يتسبب في تدهور الوضع الصحي للمريض. التقييم الامثل للوضع الصحي للمريض يتحدد بالاستعادة المبكرة لوظائف جذع المخ والاعصاب الدماغية، حيث ان غياب وظائف جذع المخ لاكثر من 72 ساعة يصاحبه غيبوبة نهائية.

السكتة الدماغية هو مصطلح طبي يصف النقص الحاد بالدورة الدموية المغذية لمنطقة محددة من المخ والتي تؤدي الانقطاع الدما وفقد الوظائف العصبية للمنطقة المصابة. تصنف السكتة الدماغية الي سكتة دماغية نزيفية وسكتة دماغية نتيجة لانقطاع الدم ، وتظهر السكتة الدماغية عادة بوقوع خلل عصبي مركزي مفاجئ مثل ضعف حركي، خلل حسي أو صعوبات في النطق واللغة. ان للسكتة الدماغية الناتجة عن انقطاع الدم مجموعة متباينة من الاسباب منها التجلط الدموي، السدادات الدموية وهبوط الدورة الدموية. أما السكتة الدماغية النزيفية فقد تكون نزيف مابين طبقات النسيج الحشوي أو نزيف ماتحت العنكبوتية.

على الرغم من ان هناك الكثير من الاضطرابات العصبية والعضلية التي تؤدي الى ضعف حاد بالنشاط الحركي إلا أن اكثرها شيوعا هي متلازمة جوالين باري يليها

**الاضطرابات المكتسبة للاعصاب والعضلات وهي في تزايد مستمر ويليها وهي اقلها حدوثا الامراض العصبية السامة والمعدية والبروفيريا والاضطرابات العضلية الأيضية. ان التقييم الدقيق للحالة المرضية لتحديد ما اذا حدثت قبل أم بعد الدخول للرعاية المركزة مهم للوصول للتشخيص الصحيح وتحديد وسائل العلاج الملائمة والوضع الصحي الراهن. ان استخدام البروتينات المناعية والفصل البلازمي الكهربائي يعجل بالشفاء لدى مرضى متلازمة جوالين باري ، في حين ان تجنب استخدام الكورتيزون و الأدوية المرخية للعضلات قد يحول دون وقوع الامراض العضلية الحادة. ان ادراك مثل هذه الاضطرابات في المراحل الأولى من المرض هي الطريق المؤدي لرعاية افضل وعلاج امثل لمثل هذه الظروف والحالات.**