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Gag Reflex

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Synonyms

Pharyngeal reflex

Definition

The gag reflex is a reflex contraction of the back of the throat, elicited by touching the posterior pharyngeal wall, tonsillar area, or the base of the tongue. Stimulation results in a visible contraction of the pharyngeal wall. The gag reflex is a protective response that prevents oral contents from entering the throat except as part of normal swallowing and helps prevent choking. The afferent limb of the reflex is supplied by the glossopharyngeal nerve (cranial nerve IX), which inputs to the nucleus solitarius and the spinal trigeminal nucleus. The efferent limb is supplied by the vagus nerve (cranial nerve X) from the nucleus ambiguus. All of these are located in the medulla. The lower cranial nerves are involved in pharyngeal and laryngeal function as well as in movements of the neck and tongue. Damage to them can result in problems with speech and swallowing. These nerves are commonly affected by conditions that damage the medulla or cause bilateral damage to corticobulbar connections. This can create motor problems that affect tongue and pharynx movement as well as speech. Individual or combined lesions of the glossopharyngeal and vagus nerves may result in an impaired gag reflex.

Characteristics

Stimulation of the gag reflex produces a brisk and brief elevation of the soft palate and a bilateral contraction of the pharyngeal muscles evoked by touching the posterior pharyngeal wall. In an isolated glossopharyngeal nerve (sensory) lesion, there will be no response when the affected side is touched. In isolated vagal nerve damage, the soft palate will elevate and pull toward the intact side, regardless of the side of the pharynx that is touched. If both cranial nerve (CN) IX and CN X are damaged on one side, stimulation of the normal side elicits only a unilateral response, with deviation of the soft palate to that side. Touching the damaged side produces no response at all. Sensitivities to the gag reflex vary among individuals. The gag reflex may be under such strong voluntary control that stimulation causes very little or no response. In contrast, in very sensitive individuals a simple gag may progress to retching and vomiting.

Absence of the gag reflex can be a symptom of severe medical conditions that result in damage to the glossopharyngeal nerve, the vagus nerve, or brain. Yet, up to one third of healthy people do not have a gag reflex. Moreover, with increasing age the gag reflex weakens without evident impairment. Individuals may learn to suppress the gag reflex, for example, sword swallowers. Others may learn to trigger the reflex, as observed in patients suffering from bulimia nervosa, who intentionally induce vomiting. To differentiate between involvement of the peripheral or brainstem portion of a cranial nerve pathway, it is important to consider whether there is additionally the involvement of the corticospinal or spinothalamic tracts of the cranial nerves that course through the brainstem and/or evidence of damage to cerebellar function. It is unusual for brain stem lesions to involve one or two cranial nerves in isolation, without also affecting the contiguous long-tracts or cerebellar system structures. Supranuclear motor pathways to the palate, and pharyngealand laryngeal musculature are bilateral. Therefore, unilateral lesions, even large strokes, rarely produce a persistent problem with lower cranial nerve function. Bilateral acute or subacute loss of hemispheric connections to the medullary nuclei causes difficulty with swallowing, phonating and, initially, a depressed gag reflex. In time, the gag reflex may become uncontrollably hyperactive, as do many other skeletal and autonomic reflexes when they are no longer under supranuclear control.

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Clinical Relevance

Evaluation of the gag reflex is utilized in the clinical assessment of brain injury, the risk of dysphagia, and is a component of the brain death examination to ascertain absent or present brain stem function.

Neurologic Examination: Rostrocaudal deterioration is a predictable sequence of neurological deterioration which occurs from a mass lesion in the head. A comatose patient with an untreated mass lesion will progress from consciousness to impaired consciousness, to a reversible state of coma, and finally to an irreversible state of coma in a predictable fashion. Serial examinations of pupillary response, cranial nerves, and motor function permit assessment of the level of injury, the extent of injury, and the rapidity of deterioration. An untreated unilateral mass lesion produces caudal progression of injury and culminates in herniation. Irreversible injury is characterized by involvement of the brainstem. The absence of gag reflex indicates brainstem injury, although it must be remembered that one third of healthy individuals lack a normal gag response. Therefore, the cough reflex, mediated by the vagus nerve (CN X), should also be assessed. The cough reflex is rarely absent in healthy individuals and does not appear to be affected by aging. Dubinsky found in patients with known or suspected intracranial hemorrhages that patients with a post-transfer GCS score ≤ 5 and an absent gag reflex had a 100% incidence of death or severe, permanent neurological dysfunction compared to a 25% incidence in those arriving with GCS scores ≤ 5 and an intact gag reflex [1].

Neurogenic Dysphagia: In the adult population, the most common etiology of dysphagia is stroke, but closed head injury, anoxic encephalopathy, and CNS depression due to intoxication can also result in loss of the protective cough and swallow reflexes. These swallowing impairments due to central nervous system injury are categorized as neurogenic dysphagia. Two thirds of patients suffering severe brain injury demonstrate functional deficits involving swallowing. Aspiration occurs in approximately 40% of stroke patients with dysphagia. Dysphagic patients who aspirate are at an increased risk of acquiring pneumonia. Pneumonia is four times greater in stroke patients who aspirate, as compared to those who do not.

The patient with severe traumatic brain injury (TBI) demonstrates abnormal muscle tone, reflexes, and sensory deficits that result in prolonged oral transit, delayed swallowing reflex, and reduced pharyngeal peristalsis. Normal swallowing is comprised of the following phases: oral phase, pharyngeal phase, and an esophageal phase which require the coordination of multiple paired muscles, cranial nerves, and levels of the central nervous system. Impairment of normal protective mechanisms predisposes to swallowing dysfunction and aspiration. The most common brain injury lesions associated with swallowing dysfunction and aspiration occur following multicentric hemispheric or brainstem injury. The risk for aspiration is further increased with endotracheal intubations or tracheostomies that are often required in the care of the brain injured patient and both are known to interfere with normal swallowing. Furthermore, over 20% of patients demonstrate ongoing dysphagia following extubation. Post-extubation dysphagia appears most pronounced in those patients requiring prolonged intubation but it can even follow relatively brief periods of endotracheal intubation.

Aspiration is defined as the misdirection of oropharyngeal or gastric contents into the larynx and lower respiratory tract. The gag reflex and the cough reflex are important defenses against oropharyngeal aspiration, with abnormalities of both increasing the risk of aspiration pneumonia. A clinical assessment evaluates the structure and function of the swallow. It enables the prediction of impaired pharyngeal, laryngeal, and esophageal swallow physiology. The findings from the clinical evaluation help to determine appropriate management, specific treatment strategies, and the need for further testing. The clinical parameters of impaired swallowing include cough, change in voice after swallowing, and an impaired gag reflex. The absence of a gag reflex alone does not predict aspiration. The most frequent impairments detected by videofluoroscopy (VFS) are oral phase dysfunction, delayed or absent gag reflex, and aspiration. Many patients with TBI and dysphagia demonstrate impairment in the pharyngeal phase of swallowing. In addition, many of these patients demonstrate concomitant impairment of the laryngeal cough reflex mediated by CN X. In patients with stroke, aspiration occurs in 40% of patients, of which half the events are silent. Terre found that 65% of patients with TBI had an impaired gag reflex but significant correlation with aspiration was only observed in those who aspirated prior to swallowing [2]. This illustrates the importance of an intact cough reflex in concert with an intact gag reflex to prevent aspiration. It appears that the greater the derangement in the cough reflex, the greater the risk of pneumonia.

Available evidence suggests that a full clinical assessment has approximately 80% sensitivity and 70% specificity for detecting aspiration. Further evaluation after the clinical assessment may be necessary. VFS assessment is the most commonly used test to further determine the nature and extent of a swallowing disorder. Radiopaque material, usually barium, is administered to the patient

and radiographic images are obtained. Disorders in movement patterns of the structures that may result in aspiration or inefficient swallowing are identified. Abnormal gag reflex and impaired voluntary cough appear to predict radiographically verified aspiration in patients suffering stroke. The risk of aspiration based on the findings of clinical assessment can be stratified: low risk (cough and gag normal), moderate risk (either cough or gag reflex abnormal), and high risk (cough and gag reflex both abnormal). Following a stroke, dysphagia will be present in most patients with an absent gag reflex. However, the converse is not true and only one third of patients with dysphagia will have an absent gag reflex. Comparison of an absent gag reflex to bedside swallow assessment demonstrates a high specificity but low sensitivity for aspiration when the gag reflex is intact.

Sole use of clinical assessment requires caution. Martino reported in a systematic literature review of patients suffering stroke that the reported incidence of dysphagia was lowest when cursory screening techniques (37–45%) were used, higher using clinical testing (51–55%), and highest using instrumental testing (64–78%). Moreover, the review confirms that there is an increased risk for pneumonia in stroke patients with dysphagia (RR, 3.17) and greatest in stroke patients with aspiration (RR, 11.56) [3]. Given the high incidence of aspiration in stroke patients it must be kept in mind that only one third of patients demonstrate overt aspiration while the remaining two thirds aspirate silently and can only be identified with VFS. In patients suffering TBI, Terre found that 65% of patients had impaired gag reflex, 44% had impaired cough during oral feeding, and 6% had changes in voice during clinical examination. Videofluoroscopy revealed some type of disorder in 90% of cases: 65% during the oral phase and 73% in the pharyngeal phase indicating that aspiration is often silent in this group of patients [2]. So while impairment of the gag reflex is often present in brain injury, the absence of a gag reflex cannot solely be relied upon to identify patients at risk for swallowing dysfunction and aspiration. The clinical assessment of swallowing dysfunction is relatively accurate but will fail to detect a significant number of patients with aspiration, particularly if they have concomitant impairment of the cough reflex. In patients who have an equivocal or suspicious clinical swallowing assessment then a VFS should be obtained.

Brain Death Examination: Brain death is the irreversible loss of all brain function. The brainstem is responsible for regulating breathing, heart rate, and reflexes such as gagging or coughing. Without a functioning brainstem, life cannot be sustained. Therefore, the diagnosis of brain death requires confirmation of absent brainstem function. The neurological determination of death is primarily made by clinical examination. Brain injury, stroke, cerebral hypoxia, and intracranial hemorrhage may lead to brain death. To establish a diagnosis of brain death, the clinician must first identify the underlying causes and determine that they are irreversible. All confounding factors such as hypothermia, hypoxia, intoxication by legal or illegal drugs, shock/hypotension, and severe electrolyte disturbances must be excluded prior to examination. Brainstem reflexes are generally lost in a rostral caudal direction. The cranial nerve nuclei are found in the midbrain, pons, and medulla. The absence of intact brainstem reflexes reflects the loss of function in the nuclei and the corresponding area of the brain stem. Cranial nerve mediated reflexes include the pupillary response to light – CN II, III; eye movement (oculocephalic and oculovestibular reflexes) – CN III, IV, VIII; the corneal reflex – CN V, VII; and the gag or cough reflex – CN IX, X. In practice, an apnea test follows cranial nerve examination and evaluates the respiratory center within the medulla. A retrospective review of brain death declarations in a tertiary medical center found that the clinical tests most likely to be documented were tests of pupillary response (86%), gag reflexes (78%), motor response (66%), and corneal reflexes (57%) [4]. The accuracy of the clinical diagnosis of brain death appears highly reliable. Flowers found that the clinical evaluation of brain death (coma, absent brain stem reflexes, and apnea) performed by experienced neurosurgeons or neurologists correlated nearly 100% with the absence of cerebral blood flow by radionuclide angiography [5].

In summary, the gag reflex is relevant to the initial assessment of brain injury, swallowing dysfunction, the risk of aspiration, and brain death determination. Yet, absence of the gag reflex on examination cannot be interpreted in isolation but rather mandates further assessment of other components of brain and brain stem function.

References

1. Dubinsky I, Penello D (2002) Can specific patient variables be used to predict outcome of intracranial hemorrhage? Am J Emerg Med 20:26–29
2. Terre R, Mearin F (2007) Prospective evaluation of oro-pharyngeal dysphagia after severe traumatic brain injury. Brain Inj 21:1411–1417
3. Martino R et al (2005) Dysphagia after stroke: incidence, diagnosis, and pulmonary complications. Stroke 36:2756–2763
4. Wang MY et al (2002) Brain death documentation: analysis and issues. Neurosurgery 51:731–735
5. Flowers WM Jr, Patel BR (2000) Accuracy of clinical evaluation in the determination of brain death. South Med J 93:203–206

Gamma Trace

► Cystatin C

Gas Gangrene

► Soft Tissue Infections, Life-Threatening

GAS in Gynecology

► Group A Streptococcal Toxic Shock in Gynecology

Gastric Residual Cutoff Value

► Gastric Residuals

Gastric Residual Volumes

► Gastric Residuals

Gastric Residuals

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Synonyms

Gastric residual cutoff value; Gastric residual volumes; GRVs

Definition

Utilization of gastric residual volumes (GRVs) as a monitor for risk of aspiration pneumonia represents a nursing procedure in the intensive care unit (ICU) to assess tolerance of delivery of enteral nutrition (EN). GRVs are obtained during enteral feeding by having the nurse aspirate (at periodic intervals) from the feeding tube and report the total volume of formula and fluid obtained. The use of GRVs as a monitor for risk of aspiration is based on the premise that delayed gastric emptying will lead to accumulation of formula in the stomach, which in turn, poses greater risk for aspiration and pneumonia [1]. Usually an arbitrary level or volume is selected as a cutoff value, above which automatic cessation of feeding is ordered to prevent the progression to vomiting and aspiration. Though the origins of GRVs are difficult to trace, they first appeared in nursing textbooks approximately 20 years ago, were quickly adapted for use in the ICU, and have subsequently become standard of care [2].

Unfortunately, there is little supporting evidence through clinical trials to support the use of GRVs, and the basic premise supporting their utilization is seriously flawed [2]. The practice of performing GRVs or using GRVs as a monitor for risk of aspiration makes several assumptions: (1) that the practice of GRVs is well standardized; (2) that GRVs reliably and accurately measure gastric contents; (3) that GRVs distinguish between normal and abnormal gastric emptying; (4) that GRVs are easy to interpret; (5) that there is a tight correlation between elevated GRVs and aspiration; and (6) that high GRVs will subsequently lead to pneumonia and deleterious clinical outcome [2].

There is little data to support any one of these assumptions. Thus, GRVs ultimately turn out to be an inaccurate and unreliable measure of gastric emptying, risk of aspiration, and likelihood for progression to pneumonia.

Ironically, while GRVs were designed to help protect critically ill patients from aspiration pneumonia while receiving EN, their use leads to frequent inappropriate cessation of EN, and the reduced delivery may actually increase risk for pneumonia [2, 3]. The benefits of early EN in the critically ill patient relate to maintenance of gut integrity, modulation of systemic immunity, and attenuation of oxidative stress. An early sufficient volume of EN delivered to the patient may be expected to reduce infectious morbidity, hospital length of stay, duration of mechanical ventilation, and multiple organ failure. Misinterpretation, inappropriately low cutoff values, and overreliance on the practice of GRVs have been shown to lead to frequent cessation of EN and reduced volume of

delivery. The reduced delivery of EN ultimately puts the patient at increased risk of pneumonia [2, 3].

Pre-existing Condition

No aspect of the practice of GRVs has been standardized. There is wide variation in the definition or arbitrary cutoff value above which EN is held or discontinued [1, 2]. In the literature, the cutoff value ranges from 50 to 500 mL, with variation from one institution to the next and sometimes from one unit to the next within a single hospital center [1, 2]. The size of the aspiration syringe and the caliber of the feeding tube affect the ability and accuracy by which GRVs are obtained. A minimum caliber of 12-French is required to obtain reasonable accuracy for GRVs, as tubes below this caliber will simply collapse on aspiration and give falsely low GRVs. Larger tubes above 12-French yield greater GRVs. The duration and manner (from the application of manual negative pressure with a syringe to application of low wall suction) of aspiration differentially affects GRV [2]. Percutaneous endoscopic gastrostomy tubes positioned high on the anterior gastric/abdominal wall will yield lower GRVs than a nasogastric tube with the tip in the gastric pool. Using an absolute value for GRV to indicate cessation of feeds is the most conventional practice, but a GRV value derived as a percentage of bolus infusion volume has also been utilized. Again, convention dictates that GRVs are checked every 4 h, and that there is automatic cessation of EN for the first value above a certain cutoff level. The duration of the cessation period prior to rechecking GRVs and reinitiating feeds has not been standardized. Virtually every aspect of the practice of GRVs is arbitrary, with little or no basis from controlled studies [2].

When interpreting GRVs, it is important to realize that a large volume of physiologic endogenous fluid passes through the gastrointestinal (GI) tract each day. A total of 4,000–5,000 mL of salivary and gastric secretions pass through the stomach daily. When combined with usual volumes of infusion of enteral formula (ranging from 25 to 125 mL/h), then volumes up to 464 mL/h may be expected in a normal stomach [2]. Therefore, choosing any volume as the cutoff value for GRV less than 464 mL would be expected under normal physiologic conditions, and certainly could not be expected to differentiate a patient with delayed gastric emptying from one with normal gastric physiology. Position of the tip of the feeding tube within the stomach, and position of the patient in bed would be expected to affect the GRV obtained at the bedside [2]. When a patient lies in the supine position, gastric contents should pool in the fundus. Conversely, when the patient is positioned in the right lateral decubitus position, gastric contents should pool in the antrum. Performing an abdominal radiograph to ascertain the tube position and then placing the patient in such a way to take advantage of that position of the tube within the stomach would be expected to yield more reliable GRVs. Unfortunately, there is variability in these factors that contribute to the inaccuracy of the GRV obtained. Studies in critically ill patients and normal volunteers have shown that the tip of the tube can migrate from one position in the stomach to another within an 8-h period [1]. When the patient lies in the supine position, the stomach may actually cascade, or break, over the spine into two separate pools [2]. These factors make it unlikely that GRVs can reliably and accurately measure gastric contents.

A number of factors in the ICU can lead to delayed gastric emptying in the critically ill patient. Such factors include hyperglycemia, sepsis, use of opioid narcotics, ischemia, and hypoxemia [2]. Unfortunately, GRVs failed to distinguish between normal and abnormal gastric emptying. In a prospective trial in critically ill patients examining GRVs over an 8-h period following initiation of EN, use of GRVs were compared to findings on physical exam and abdominal radiographs performed at the beginning and end of the testing period [1]. Physical findings to suggest ileus and gastroparesis (such as abdominal distention, hypoactive bowel sounds, hypertympani) correlated significantly with radiographic evidence of ileus (air-filled stomach, air/fluid levels, dilated loops of small bowel) [1]. However, there was no significant correlation between residual volumes and either radiographic evidence of intolerance or findings on physical exam [1].

GRVs are very difficult to interpret given the numerous physiologic variables which can occur in the ICU patient. While the average daily production of salivary and gastric secretions is estimated to be within 4,000–5,000 mL/day, a number of factors may interfere with this volume output [2]. The fact that patients are not chewing and eating their meals may reduce salivary secretions, and use of proton pump inhibitors may reduce the volume of gastric secretion. Introducing water flushes following infusion of medication and to maintain patency of the feeding tube is used with great frequency, and are often poorly documented in the nursing records of intake and output. While the intake of formula volume may be easy to track in the ICU, volume of endogenous fluids may be impossible to predict or interpret.

The correlation between elevated GRVs, aspiration, and pneumonia is the most difficult to appreciate.

Aspiration pneumonia is the most feared complication of EN in the ICU and is the main argument for continued use of GRVs. Delayed gastric emptying is only one factor that increases risk for aspiration, among a myriad of other factors which include supine position, vomiting, endotracheal tube, nasogastric tube, altered mental status, sedation, limited nursing care, and transport out of the ICU. Using the presence of pepsin in tracheal secretions as a surrogate marker for aspiration of gastric contents, Metheny has shown that a higher incidence of aspiration episodes does correlate with increased risk of pneumonia [4]. Unfortunately, these studies have shown that because of the inaccuracies and poor reliability of GRVs, no significant correlation exists between GRVs and aspiration, or GRVs and pneumonia [2, 4].

The premise that high GRVs invariably lead to pneumonia and deleterious clinical outcomes has been shown not to be true. Clinicians in the past have believed that lowering the cutoff value for GRVs for automatic cessation of EN protects their patients against aspiration and pneumonia. The same clinicians believe, if the patient is stable and doing well, that they can raise the cutoff value for GRVs with the false understanding that risk for aspiration will increase concomitantly. A number of prospective randomized trials have shown that raising the cutoff value for GRV simply results in increased delivery of EN, with no increase in risk of aspiration or pneumonia [2, 5]. In fact, in some of these studies, the incidence of GI complications, infectious morbidity, and hospital length of stay were improved with a higher residual volume compared to those patients randomized to a lower value [2, 5]. Further studies now have evaluated discontinuing GRVs, and have shown that cessation of the practice reduces tube clogging and increases delivery of EN (without a concomitant increase in aspiration, vomiting, or pneumonia) [2, 5].

Application

It is unlikely that nurses or clinicians will cease utilization of GRVs in the ICU setting. The best strategy is to alter interpretation of GRVs and have protocols in place directing management as a result of that interpretation.

It is appropriate that clinicians continue to check GRVs every 4 h following initiation of EN, being careful to return aspirated contents (up to 500 mL) back to the patient. In the absence of other signs of intolerance, it is inappropriate to stop delivery of EN for any GRV less than 400–500 mL. For the first GRV >400 mL, it is prudent to continue EN at its current rate, turn the patient over into the right lateral decubitus position (to put the antrum in the dependent position to promote gastric emptying), and initiate prokinetic therapy with metoclopramide 10 mg IV every 6 h. If the patient is on opioid narcotics, the clinician might consider an infusion of naloxone 8 mg in 10 mL of saline per the feeding tube every 6 h. If a second GRV 4 h later is >400 mL, then it may be appropriate to withhold EN while the patient is being reassessed. GRV should be rechecked every 2 h at that point, with the EN restarted once the GRV drops <400 mL. If there are no other signs of intolerance, the EN may be restarted at the same rate as before. If there are other signs of intolerance (such as abdominal distention, hypoactive bowel sounds, failure to pass stool or gas), then it may be prudent to reduce the rate by 25 mL/h or to a baseline of 25 mL/h. Checking GRVs is probably more important upon initiation of EN. Once EN has been infused successfully for 48–72 h, clinicians should be encouraged to stop checking GRVs and simply follow physical findings or other clinical signs of tolerance [2].

In summary, early and adequate delivery of EN has been linked to improved patient outcomes. EN therapy in the critically ill patient is difficult, and excessive emphasis on GRVs tends to impede its delivery. The current use of GRVs is based on a number of flawed assumptions with little scientific basis [2]. The interpretation of GRV should never be done in a vacuum, without paying attention to clinical signs and symptoms, and physical findings of intolerance and intestinal ileus. Having protocols in place improves the interpretation and response to elevated GRVs, reduces inappropriate cessation, and promotes a greater percentage of goal calories of EN delivered. Once tolerance of EN is established, it may be appropriate to cease performing GRVs to better allocate nursing time and healthcare resources.

References

1. McClave SA et al (1992) Use of residual volume as a marker for enteral feeding intolerance: prospective blinded comparison with physical examination and radiographic findings. JPEN J Parenter Enteral Nutr 16(2):99–105
2. Parrish RP, McClave SA (2008) Checking gastric residual volumes: a practice in search of science? Pract Gastroenterol October:33–47
3. Taylor SJ et al (1999) Prospective, randomized, controlled trial to determine the effect of early enhanced enteral nutrition on clinical outcome in mechanically ventilated patients suffering head injury. Crit Care Med 27(11):2525–2531
4. Metheny NA et al (2006) Tracheobronchial aspiration of gastric contents in critically ill tube-fed patients: frequency, outcomes, and risk factors. Crit Care Med 34:1007–1015
5. Montejo JC, Minambres E, Bordeje L et al (2009) Gastric residual volume during enteral nutrition in ICU patients. The REGANE study. Intens Care Med 2009 Mar (Online)

Gastroenteritis

► HIV-Related Diarrhea

Gastrointestinal Bleeding

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Synonyms

Gastrointestinal hemorrhage; hematemesis; hematochezia; melena

Definition

Gastrointestinal bleeding (GIB) may be divided into upper and lower gastrointestinal bleeding (UGIB and LGIB, respectively), defined by bleeding originating proximal or distal to the ligament of Treitz. UGIB is more common, with an annual incidence of 50–150 per 100,000 population, and accounts for a larger proportion of admissions in adults. The annual incidence of LGIB is approximately 20–27 per 100,000. Both upper and lower GIB are more common in men and older adults. The overall mortality of GIB is approximately 10%. While most cases of GIB are self-limited with the majority of patients having only one episode of bleeding, there are a number of independent markers that increase morbidity and mortality. These include age greater than 60 years, hemodynamic instability, melena or hematochezia, esophageal varices, recurrent bleeding, requiring more than five units of packed red blood cells, endoscopic stigmata of recent hemorrhage, and bloody nasogastric aspirate [1].

Differential Diagnosis

The most common cause of UGIB is peptic ulcer disease (PUD), which accounts for 50–60% of cases (Table 1). Esophageal and gastric varices are responsible for approximately 10–25% of UGIB overall and 60% of episodes in cirrhotic patients. Varices are the most common cause of persistent and severe UGIB and more often have bright red hematemesis on presentation. Patients with portal hypertension-related bleeding, which includes varices and portal hypertensive gastropathy, have a mortality rate of over 50% compared to the much lower mortality rate of 4% with bleeding due to PUD. While older adults are more likely to present with bleeds due to PUD, esophagitis, and gastritis, younger adults account for a greater percentage of cases due to Mallory–Weiss tears, varices, and gastropathy [2].

Gastrointestinal Bleeding. Table 1 Major causes of upper gastrointestinal bleeding

Peptic ulcer disease
Gastric ulcer
Duodenal ulcer
Varices
Esophageal
Gastric
Gastritis
Esophagitis
Duodenitis
Mallory–Weiss tear
Angiodysplasia
Malignancy
Stomal ulcer
Esophageal ulcer
Dieulafoy lesion

The most common cause of LGIB is colonic diverticulosis, which manifests as painless hematochezia. Other lower tract etiologies of bleeding include angiodysplasia, colitis, and post-polypectomy (Table 2). Lower tract bleeding has a re-bleeding rate of 10–20% and requires surgery 10–15% of the time. The majority of LGIB resolves spontaneously and has an overall mortality rate of 4%. Identifying the source of lower tract bleeding may be challenging if the bleeding is intermittent or located in the proximal small bowel.

Some patients with a chief complaint of hematemesis or blood in the stool may in fact not be bleeding from a gastrointestinal source. Their symptoms may be caused by swallowed blood from the nasopharynx or oropharynx. Red-colored food products in the vomitus may also look like "blood". The ingestion of beets may give the stool the appearance of hematochezia, while iron or bismuth ingestion may result in the appearance of melena. When analyzed, these stools will be heme negative on fecal occult testing.

Gastrointestinal Bleeding. Table 2 Major causes of lower gastrointestinal bleeding

Diverticular disease
Angiodysplasia
Colitis
Ischemia
Infectious
Inflammatory bowel disease
Radiation
Post-polypectomy bleeding
Malignancy
Anorectal causes
Hemorrhoids
Rectal varices
Fissures
Small bowel etiologies
Angiodysplasia
Meckel diverticulum
Jejunoileal diverticula
Enteritis
Aortoduodenal fistula
Upper gastrointestinal bleeding

Disease

Clinical Features

Although many patients will specifically describe the presence of blood in their emesis or stool, clinicians should also suspect GIB in patients who present with more subtle signs and symptoms, such as confusion, syncope, dizziness, angina, hypotension, or tachycardia. The initial evaluation of GIB involves obtaining a thorough yet focused medical history and performing a physical examination, while paying special attention to the presence or absence of hemodynamic compromise. Elucidating the details of the bleeding (i.e., duration, quantity, and frequency of bleeding) and associated symptoms of hypovolemia (lightheadedness, dizziness) and anemia (chest pain, dyspnea, fatigue) can help guide the patient's management.

The symptoms of GIB are often described as "bright red" or "coffee ground" vomit (hematemesis), "bright red" or "maroon-colored" blood in the stool (hematochezia), or "black" or "tarry" stools (melena). About half of patients with an upper source of bleeding present with hematemesis, whereas hematochezia often suggests either a lower source of bleeding or a brisk upper source of hemorrhage (14%). Patients with hematochezia from upper-tract bleeding are more likely to be transfused, require surgery, and have a higher mortality rate. Similarly, melena can be caused by an upper or lower source of hemorrhage but is associated with a lower mortality rate than hematochezia. For the majority (90%) of patients with melena, the bleeding source is proximal to the Ligament of Treitz, so the long transit time of the stool allows the blood to degrade and form the characteristic black color [2].

A past medical history of coagulopathy, prior past GIB, liver disease, hemorrhoids, prior radiation for prostate or pelvic cancer, inflammatory bowel disease, and recent colonoscopy with polypectomy may be helpful. Use of medications which have been shown to contribute to GIB should be obtained, including aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, anticoagulants, and anti-platelet medications. The presence of a family history of colon cancer or a social history of alcohol and tobacco use may be useful in risk stratification of patients.

Abnormal vital signs such as hypotension and tachycardia may indicate significant hemorrhage, although normal vital signs do not exclude a life-threatening event. The physical examination in the patient with GIB should include an assessment of general appearance, mental status, conjunctival pallor (suggesting anemia), skin color and temperature, adequacy of capillary refill, petechiae or ecchymoses (suggesting coagulopathy), and any stigmata of cirrhosis, such as jaundice, caput medusa, ascites, hepatomegaly, and palmar erythema. Examination of the nasopharynx and oropharynx may identify a swallowed source of blood. Examining the abdomen for tenderness, masses, and peritoneal signs is important. Rectal examination may reveal anal fissures, hemorrhoids, or rectal masses; stool should be evaluated for color and occult blood.

Laboratory Testing

Laboratory tests that are important in the evaluation of GIB include a type and crossmatch, hemoglobin and hematocrit, platelet count, blood urea nitrogen (BUN) and creatinine, and coagulation profile. Do not be falsely reassured by a normal initial hemoglobin, since it may take more than 24 h for bleeding to cause a change in the hemoglobin level. However, a low hemoglobin ($<$10 g/dL) has been shown to be associated with higher re-bleeding and mortality rates. An elevated BUN level is associated with upper tract bleeding, and the BUN to creatinine ratio may be used to distinguish UGIB from LGIB. In the

absence of renal failure, a BUN to creatinine ratio greater than 36 has a sensitivity of 90–95% in predicting UGIB [3]. Finally, because significant hemorrhage may result in cardiac ischemia, an electrocardiogram and cardiac biomarkers are recommended in patients at risk for acute coronary syndrome. GIB patients diagnosed with concurrent myocardial infarction may present with shortness of breath, dizziness, or abdominal pain rather than the typical chest pain.

Nasogastric Aspiration

Nasogastric (NG) aspiration detects active hemorrhage and may be useful in the evaluation of some patients with GIB. Once considered important in the initial management of patients, there is now controversy surrounding its clinical utility, especially in light of the significant patient discomfort associated with its use. In patients with hematemesis, nasogastric aspiration with lavage may be utilized to quantify hemorrhage, when clinically indicated. In those without a clear source of bleeding, a bloody aspirate identifies an upper source of the bleed and may help guide further management. In patients without hematemesis, NG aspiration has a low sensitivity (42%) and accuracy (66%) for identifying UGIB [4]. While bright red blood from the NG aspirate suggests an active hemorrhage, dark coffee grounds suggest a recent bleed or a slow rate of bleeding. On the other hand, a negative aspirate does not necessarily exclude an UGIB as it has been shown to miss up to 50% of duodenal bleeding. In addition, a negative aspirate may imply that the source of hemorrhage is distal to the Ligament of Treitz or that the bleeding has stopped entirely.

Emergency Department Management

Patients with significant GIB require expeditious assessment and aggressive resuscitation. A definitive airway may be needed in patients with intractable vomiting and/or mental status change who are unable to protect their airway or at risk for aspiration. Supplemental oxygen and cardiac monitoring are recommended as significant bleeding may lead to hypoxia and end-organ ischemia, as evidenced by demand ischemia due to decreased oxygen delivery to cardiac tissue. Two large-bore peripheral intravenous catheters are recommended for rapid resuscitation with crystalloid fluids. Close monitoring and continuous reassessment of volume status and hemodynamic stability should be used to guide the resuscitation.

Patients with persistent bleeding and hemodynamic instability despite crystalloid resuscitation require transfusion of blood products. To determine the amount of blood to transfuse, the clinician should consider the patient's age, co-morbidities, baseline hemoglobin/hematocrit, and presence of signs of tissue hypoperfusion (e.g., cardiac, renal, cerebral). While there are no definite parameters for transfusion in GIB, it has been suggested that patients with UGIB due to varices do not benefit from aggressive transfusion because it may increase portal pressure and worsen bleeding. Patients who are transfused more than 5 units of packed red blood cells are more likely to need operative intervention and have a higher mortality rate [1].

Medical Therapies

A number of medical therapies have been shown to improve patient outcomes in GIB. Somatostatin and octreotide, its longer-acting derivative, have been shown to lower the risk for persistent bleeding and re-bleeding in UGIB due to both variceal and non-variceal causes. In a large systematic review of the efficacy of somatostatin analogs in patients with acute esophageal variceal bleeding, somatostatins decreased the rate of bleeding and the need for transfusion but did not significantly reduce mortality [5]. The recommended dose for octreotide is a 50 μ intravenous bolus followed by a continuous infusion of 50 μ/h. In patients with UGIB due to PUD, proton pump inhibitors have been shown to decrease the risk of re-bleeding and need for operative intervention and blood transfusion, but with conflicting evidence for a reduction in mortality. While vasopressin has been used most often for GIB due to varices, it is associated with significant re-bleeding and a high complication rate, which includes dysrhythmias, hypertension, myocardial and peripheral ischemia, and decreased cardiac output. H2-receptor antagonist use for UGIB has been shown to be only weakly beneficial for gastric ulcer bleeding and not beneficial for duodenal ulcers.

Consultation and Disposition

All patients with significant upper or lower GIB should be hospitalized. Patients with severe or life-threatening GIB require urgent consultation with gastroenterology. The decision to perform emergent endoscopy will often be based clinically on the severity of the hemorrhage and the patient's hemodynamic stability. Intensive-care unit admission and early involvement of intensivists may be warranted for patients with hemodynamic instability, shock, mental status change, and evidence of end-organ damage. Patients with cardiac ischemia or infarction may need cardiology consultation. Various studies have identified a subset of low-risk patients who may be discharged

home with UGIB, but all of the study participants underwent short observation and endoscopy prior to discharge. These patients were younger than 60 years of age with no significant co-morbidities, no signs of shock, no history of liver pathology or varices, no significant anemia, no frequent hematemesis or melena, and had follow-up care [6]. As risk stratification for patients with LGIB has not been well studied, most of these patients are hospitalized for further care.

Endoscopy

For the majority of UGIB, endoscopy can identify the source of bleeding. Moreover, endoscopic therapies, such as sclerotherapy and band ligation, are valuable in the treatment of acute variceal hemorrhage. Patients who undergo early endoscopy, within 12–24 h of bleeding, have lower re-bleeding rates and shorter hospital stays compared to those who undergo delayed endoscopy. Endoscopy may also be used to risk stratify patients and change disposition decisions. While balloon tamponade with a Sengstaken–Blakemore tube is rarely utilized due to its high complication rate, it may be life-saving in the exsanguinating patient with variceal bleeding when endoscopy is not readily available.

In patients with LGIB, use of colonoscopy to identify and treat the source of bleeding obviates the need for a subtotal colectomy. When a brisk upper tract bleed is suspected in a patient presenting with hematochezia, endoscopy may be performed prior to colonoscopy. Typically, colonoscopy is performed in hemodynamically stable patients with self-limited bleeding or those with a high likelihood of having a localized lesion. Colonoscopy is less useful than radiographic imaging in patients with brisk bleeding.

Radiographic Imaging

Nuclear scintigraphy, or technetium-labeled red cell scanning, is a non-invasive method used to identify an obscure LGIB source. Less specific but more sensitive than angiography in detecting bleeding, nuclear scans require active bleeding at a rate of 0.1 mL/min. This technique is often utilized when the source of bleeding is difficult to visualize by endoscopy or when the bleeding recurs. The nuclear scans are then used to guide further treatment (i.e., angiography or surgical intervention).

Angiography is also used to detect an obscure lower bleeding source, but is most useful when the bleeding rate is at least 0.5 to 1 mL/min. Compared to nuclear scanning, angiography is also both a diagnostic and therapeutic intervention, but it has several disadvantages, including contrast-related reactions (e.g., anaphylactoid reaction, contrast-induced nephropathy), arterial thrombosis or dissection at the puncture site, and bowel infarction. Angiography is usually reserved for a severe, continuous lower source of bleeding, especially in cases of brisk bleeding for which colonoscopy is impractical. Since there is no evidence-based practice guideline for evaluating and managing LGIB, institutional availability and consultant expertise often influence management.

Conclusion

Gastrointestinal bleeding is a common reason for patients to seek emergency care and a frequent cause of hospitalization. Advanced age, concurrent underlying medical conditions, hemodynamic instability, significant hematemesis or melena, and marked anemia are all important risk factors for high morbidity and mortality. Patients with GIB require prompt diagnosis and risk stratification, aggressive resuscitation, and timely gastroenterology consultation.

Cross Reference

▶ HIV-Related Diseases of the Stomach, Intestines, and Colon

References

1. Hussain H, Lapin S, Cappell MS (2000) Clinical scoring systems for determining the prognosis of gastrointestinal bleeding. Gastroenterol Clin North Am 29(2):445–64
2. Cappell M, Friedel D (2008) Initial management of acute upper gastrointestinal bleeding: from initial evaluation up to gastrointestinal endoscopy. Med Clin N Am 92:491–509
3. Ernst AA, Haynes ML, Nick TG et al (1999) Usefulness of the blood urea nitrogen/creatinine ratio in gastrointestinal bleeding. Am J Emerg Med 17:70
4. Witting MD, Magder L, Heins AE et al (2004) Usefulness and validity of diagnostic nasogastric aspiration in patients without hematemesis. Ann Emerg Med 43:525–532
5. Gotzsche PC (2002) Somatostatin or octreotide for acute bleeding oesophageal varices [update in Cochrane Database Syst Rev (1): CD000193; PMID: 11869569] Cochrane Database Syst Rev CD000193, 2000
6. Rockall TA, Logan RF, Devlin HB et al (1996) Selection of patients for early discharge or outpatient care after acute upper gastrointestinal haemorrhage. National Audit of Acute Upper Gastrointestinal Haemorrhage. Lancet 347:1138

Gastro-intestinal Bleeding

▶ Gastro-intestinal Bleeding in ICU Patients

Gastro-intestinal Bleeding in ICU Patients

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Synonyms

Gastro-intestinal bleeding; Gastro-intestinal hemorrhage

Definition

Gastro-intestinal bleeding can be classified according to the location of bleeding in the digestive tract. Upper gastro-intestinal bleeding occurs in the tract from mouth to jejunum. Lower gastro-intestinal bleeding occurs in the tract from the ileocecal region to the rectum. The jejunal-ileal tract is not easily accessible for routine diagnostic procedures, nor for interventional endoscopy. Bleeds from this part of the digestive tract can be classified as mid gastro-intestinal bleeding, mostly after exclusion of bleeding locations in the upper and lower digestive tract. Clinical symptoms consist of macroscopically visible bleeding, such as bloody aspirate from the gastric tube, hematemesis or melena, hypotension, and anemia.

The clinical importance of a bleeding complication depends on several aspects, such as the overt loss of blood, the occurrence of a fall in blood pressure and an increase in pulse rate, a decrease in hemoglobin level necessitating the transfusion of blood products, pro-hemostatics or any intervention, and the long-term consequences of hemorrhagic shock such as acute renal failure and (transfusion-related) acute lung injury [1]. Landefeld's Bleeding Severity Index takes these aspects adequately into account [2]. This method of classification of bleeding complications is based on criteria for the amount, rate, and clinical consequences of bleeding and has been shown to be highly reproducible. Clinically important major bleeding is defined as overt bleeding that is fatal, life-threatening, potentially life-threatening, or acute or subacute and leads to severe or moderate blood loss or to intervention to stop the bleed. Minor bleeding includes other overt bleeding from an internal site, such as gastrointestinal bleeding, hemoptysis, and gross hematuria.

The incidence of gastro-intestinal bleeding varies between 0.6% and 3.5% [1, 3]. Gastro-intestinal bleeding significantly contributes to morbidity, length of stay in the ICU, and mortality [3]. The majority of gastro-intestinal bleedings in the population of the critically ill originate from stress ulcers in the upper gastro-intestinal tract.

Treatment

Prophylaxis

Traditionally, stress ulcer related bleeding has been regarded as a substantial source of morbidity and mortality in critically ill patients. Therefore, much attention has been given in the last 2 decades to prohylactic measures, such as cytoprotection (sucralfate), neutralization of gastric acids (antacids), and reduction of gastric acid (histamine-2 receptor antagonists, proton pump inhibitors). A meta-analysis reported that various prophylactic therapies reduced the incidence of overt or clinically important bleeding compared to no prophylaxis. Mortality, however, was not affected. In the pathophysiology of stress related mucosal disease, gastric acid secretion, mucosal ischemia (as a result of splanchnic hypoperfusion), and reflux of upper intestinal contents into the stomach are of great importance. Risk factors for the development of stress related mucosal disease include respiratory failure, coagulopathy, hypotension, sepsis, hepatic failure, renal failure, surgery, burns, and major trauma [4].

It is believed that the incidence of stress ulcer related bleeding has decreased considerably independently from the use of prophylaxis. Factors responsible for this phenomenon may include improved tissue oxygenation following more aggressive shock management, improved infection control using selective decontamination of the digestive tract, early enteral feeding, and the optimal use of steroids to suppress the generalized state of inflammation in the critically ill [1].

Treatment

When clinically important gastro-intestinal bleeding occurs, therapy should be aimed at the termination of bleeding. In case of hypotension, patients should be admitted in the ICU and therapy should be aimed at resuscitation of shock. In general, transfusion of blood products, prohemostatics, neutralization of anticoagulants, and suppression of gastric acid secretion will be the primary treatment of bleeding. It needs to be stressed that in case of heparin use, protamine sulphate should be given to neutralize the heparin effect and that in case of use of platelet aggregation inhibition, platelets should be given.

To investigate the focus of blood loss, endoscopy needs to be performed by the gastro-enterologist and – if necessary – interventions can be performed to stop the bleeding, such as sclerotherapy, cauterization, ligation, or

clipping. This may be difficult and when unsatisfactorily done, interventional radiology may bring the solution by means of selective catheterization and coiling of the vasculature of the digestive tract. When all options fail and massive blood loss persists, eptacog alpha (activated) can be considered as rescue therapy. Abdominal surgery can be necessary if all other therapies have failed.

Evaluation/Assessment

Effectiveness

Tolerance

Pharmacoeconomics

It was calculated that an episode of clinically important bleeding can result in a mean of 7 additional hematology tests, 11 blood product transfusions, and 24 days of treatment, resulting in an overall cost of clinically important bleeding of $12,000 [3].

After-care

Critically ill patients with gastro-intestinal bleeding will frequently require extended treatment for 4–8 days in the ICU due to their comorbidities and the existence of multiple organ dysfunction, which may be preexistent or due to hemorrhagic shock [3]. Treatment to reduce gastric acid production should be continued for several weeks. If necessary, control endoscopy can be performed.

Prognosis

Gastro-intestinal bleeding has a substantial affect on morbidity and mortality associated with a relative risk of death of 1–4. Their ultimate prognosis is largely dependent on the underlying disease responsible for the occurrence of bleeding.

References

1. Zandstra DF, Stoutenbeek ChP (1994) The virtual absence of stress-ulceration related bleeding in ICU patients receiving prolonged mechanical ventilation without any prophylaxis. A prospective cohort study. Intensive Care Med 20:335–340
2. Landefeld CS, Anderson PA, Goodnough LT, Moir TW, Hom DL, Rosenblatt MW, Goldman L (1989) The bleeding severity index: validation and comparison to other methods for classifying bleeding complications of medical therapy. J Clin Epidemiol 42:711–718
3. Cook DJ, Griffith LE, Walter SD, Guyatt GH, Meade MO, Heyland DK, Kirby A, Tryba M, for the Canadian Critical Care Trials Group (2001) The attributable mortality and length of intensive care unit stay of clinically important gastrointestinal bleeding in critically ill patients. Crit Care 5:368–375
4. Stollman N, Metz DC (2005) Pathophysiology and prophylaxis of stress ulcer in intensive care unit patients. J Crit Care 20:35–45

Gastrointestinal Endoscopy

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Synonyms

Colonoscopy; Endoscopic Retrograde Cholangio-pancreatography (ERCP); Endoscopic Ultrasound (EUS); Enteroscopy; Esophago-gastro-duodenoscopy (EGD); Gastroscopy; Oesophago-gastro-duodenoscopy (OGD); Panendoscopy; Proctoscopy; Sigmoidoscopy; Videoendoscopy

Definition

Gastrointestinal (GI) endoscopy is the visual inspection of the luminal surface of the upper and/or lower GI tract with a flexible fiber-optic camera apparatus. Since the initial introduction of the technology over 40 years ago, GI endoscopy has flourished and what began as a purely diagnostic modality has now become an effective diagnostic and therapeutic facility for the management of all forms of GI disease. Disorders of the esophagus, stomach, duodenum, and proximal jejunum; colon; rectum; and anal canal are particularly suited to endoscopic diagnosis, investigation, surveillance and in many cases, definitive therapy. GI endoscopy is now an ubiquitous skill that should be an element of the basic skill-set of all general surgeons, GI specialists, and gastroenterologists.

Technology

The advent of fiber-optic technology facilitated the development of flexible endoscopes, thereby extending the range of GI endoscopy beyond the limits imposed by unwieldy and often hazardous rigid endoscopic devices. The use of rigid esophagoscopes and sigmoidoscopes remains an essential skill, but the practise is appropriately reserved for those expert in its application in the management of proximal aero-digestive tract and ano-rectal disease.

Modern endoscopes utilize high-quality optical devices coupled with digital image-processing technology to render high-fidelity images of the GI lumen. Images are now routinely displayed on large visual-display monitors, allowing image capture, video recording, and electronic image manipulation. Endoscopes can be adapted to suit a variety of functions, with narrow caliber endoscopes

available for pediatric use, longer devices for enteroscopy or small-bowel examination, multiple channel devices for therapeutic intervention, and side-viewing devices for complex pancreato-biliary or EUS applications. Modern devices are now quite robust instruments, suited to the rapid turnover, multiuse needs demanded of endoscopic services by modern hospital practise. Typically, endoscopy units have automated washing machines that clean and autoclave endoscopes within 30 min.

Technique and Indications

OGD

Patient preparation usually involves a period of fasting for 4–6 h prior to endoscopy to ensure the stomach is empty; however, under emergency circumstances, gastric lavage can be helpful. If there is concern that the patient may be unable to protect his/her airway, OGD should be performed under general anesthesia with endo-tracheal (ET) intubation with a cuffed tube. In the case of OGD for unstable upper GI hemorrhage, ET intubation is advisable. ET intubation does not make access to the posterior oropharynx more difficult. The other option especially in elderly patients is to perform awake unsedated OGD. This will gernally allow the patient to protect his/her own ariway. The option for advanced airway intervention (endo-tracheal intubation) should always be available for emerency endoscopy. In addition, for patients who are bleeding, transfer to the operating room should be considered.

In the elective setting, it is recommended that upper GI endoscopy be performed using awake sedation. This is usually effected using intravenous administration of short-acting benzodiazepines, which yield satisfactory levels of sedation and amnesia but which can rapidly be reversed. Other intravenous hypnotic agents such as propofol are used regularly, however, these require greater expertise and titration of dosage and are therefore best used in the presence of an anesthetist. Local anesthetic, usually Lignocaine, may also be applied topically to the posterior oropharyngeal mucosa in an aerosolized spray to allow easier esophageal intubation by suppressing the gag reflex. The only disadvantage is the necessity to avoid oral intake postprocedure until the anesthesia has subsided.

The patient is placed in the left lateral decubitus position; however, OGD can safely be performed in the intubated patient in the supine position. A plastic mouth-guard is inserted to protect both the patient's dentition and the endoscope. The endoscope is advanced under direct vision over the tongue into the posterior oropharynx. The endoscopist's fingers can be used to guide the endoscope, however this results in significant discomfort for the patient if local anesthesia has not been used and there is potential for injury to the guiding fingers should the mouth-guard be dislodged! Gentle forward pressure will allow the endoscope to traverse the cricopharyngeus and intubate the proximal esophagus. It is important that the upper esophagus be examined thoroughly as pathology in this location can easily be missed at flexible endoscopy. Air insufflation will distend the esophageal lumen allowing examination of the mucosa, esophageal peristalsis, and the normal anatomy of the esophagus throughout its length. The location of the esophago-gastric junction (OGJ/EGJ/GEJ) should be noted and recorded as the distance in centimeters from the incisor teeth.

The stomach should be fully insufflated with air and examined throughout for obvious mucosal or anatomical abnormality, or abnormal extrinsic compression/indentation secondary to upper abdominal or retroperitoneal pathology. The endoscope is advanced towards the gastric antrum, noting the incisura separating the body from the antrum. At the incisura, the endoscope is fully retroflexed, to allow inspection of the cardia, OGJ, fundus, and lesser curvature. This "j-view" is an essential maneuver and OGD is not complete without it. The endoscope is then straightened and the antrum traversed. The pylorus may be open or closed. Gentle forward pressure and insufflation of air will usually allow entry to the duodenal bulb, also referred to as D1. Entry to the second-part of the duodenum (D2) can be difficult and requires a composite maneuver during which a safe, clear view of the lumen may be lost. The endoscope shaft is rotated clockwise, while the tip is also rotated clockwise. Further rotation of the tip will angulate the endoscope downwards and backwards into the descending duodenum and forward pressure applied now will allow more distal intubation. Alternatively, withdrawal and straightening of the endoscope may advance the intubation further as the redundant length of endoscope in the stomach is shortened. At this point, the duodenal mucosa is carefully inspected. The Ampulla of Vater and, if present, accessory papilla may be visualized; however, this is difficult with standard "end-viewing" endoscopes and usually requires the "side-viewing" devices used for ERCP. Having successfully intubated D2, the endoscope is slowly withdrawn and the mucosa carefully inspected throughout the duodenum, stomach, and esophagus.

OGD is indicated for the investigation of dysphagia, upper GI hemorrhage, gastro-esophageal reflux, dyspepsia, regurgitation or emesis, abdominal pain, weight loss or suspected GI malignancy, and GI tract perforation. Tissue biopsy for histological assessment may be effected

by simple cutting forceps biopsy. More extensive biopsy or definitive mucosal resection can be performed with submucosal injection of saline or blue dye and subsequent wire-snaring with coagulation electrocautery for hemostasis. Laser ablation of mucosal lesions can be performed via the endoscope and may come to play a major role in the management of premalignant conditions in the future. Acute GI hemorrhage is managed particularly well endoscopically. The entire spectrum of hemorrhagic lesions, ranging from superficial ulcers to frankly bleeding esophageal varices are now routinely managed endoscopically. Local injection of adrenaline solution, Argon laser coagulation, endoscopic clipping, and band ligation are standard therapies employed for the management of GI hemorrhage, rendering emergency surgical intervention a rare necessity. Finally, deployment of endo-luminal stent-prostheses has been greatly facilitated by advances in endoscopic technology and now plays a major role in the management of esophageal and duodenal disease.

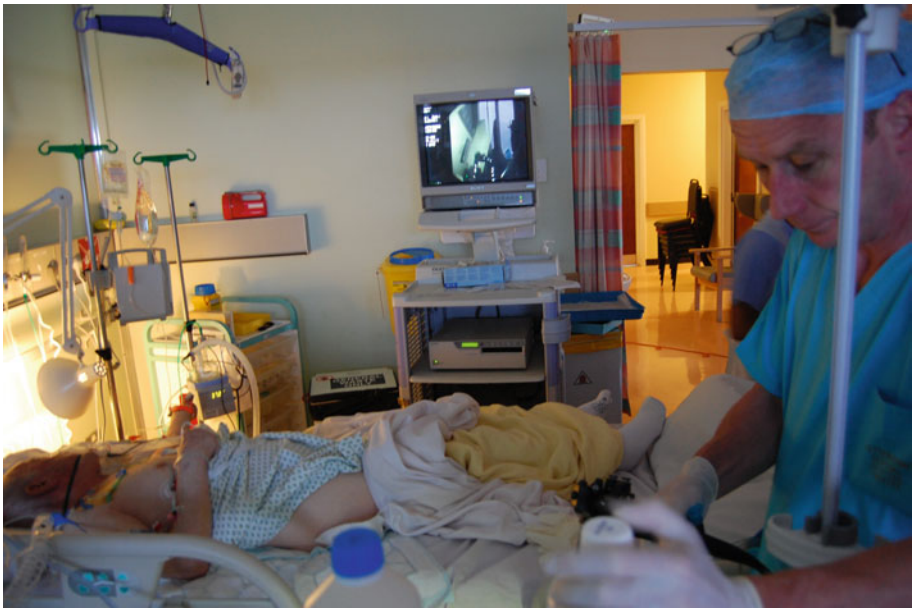
OGD is a safe procedure. Complications depend on the underlying disease process and performance of therapeutic intervention. Hemorrhage and perforation are rare but incidence can approach 0.1% following therapeutic intervention [1]. The main indications for ICU OGD are shown in Table 1.

Gastrointestinal Endoscopy. Table 1 Common indications for bedside ICU OGD

Diagnosis and therapy of upper GI bleeding
Diagnosis and therapy of esphageal perforation
Naso-jejunal tube placement
Insertion of PEG

Tips and Pitfalls

OGD, although a simple procedure under emergency situations when performed in ICU, requires a dedicated team approach ideally with an on-call endoscopy team. The scope should be presterilized to avoid delays. An emergency pack should be available with the scope to include an injecting needle, biospy forceps, band ligation apparatus, Argon laser, or clip applicators. A large, two-channel endoscope with continuous irrigation will improve suction ability and facilitate identification of bleeding vessels. The staff should wear eye protection to avoid blood splattering and contamination (Figs. 1 and 2). Biopsies in the ICU should only be done with clear awareness of coagulation status as there are risks of hemorrhage. One should be aware of the potential interation between COX-II antagonists and clopidigrel. Intra-abdominal pressure needs to be carefully monitored as patients can develop signifcant intra-abdominal hypertension leading



Gastrointestinal Endoscopy. Figure 1 Endoscopy in paediatric ICU, note flatscreen viewing stack

Gastrointestinal Endoscopy. Figure 2 Endoscopy stack housing endoscope, light-source, image processor & insufflator

to abdominal compartment syndrome. At the end of the endoscopy, as much gas as possible should be sucked out. Finally ICU endoscopy should never be performed using the high-flow settings on the endoscopy insufflator.

ERCP

ERCP is an extension of standard OGD and its use has yielded enormous benefits in the management of pancreato-biliary disease. ERCP utilizes "side-viewing" endoscopes in order to visualize the duodenal papilla, and these endoscopes typically have two or more operating channels to facilitate intervention. The Ampulla of Vater is cannulated using a fine guide-wire and cannula, allowing subsequent dye-opacification of the biliary and pancreatic ductal systems which are examined fluoroscopically. Demonstration of pancreato-biliary ductal anatomy is the primary goal of diagnostic ERCP, but biopsy of pancreatic and biliary neoplasms is also possible. Therapeutic manipulations include stenting of benign and malignant biliary tract obstruction, evacuation of bile-duct stones, and management of biliary leak following cholecystectomy.

The technique of ERCP is more specialized than routine OGD and ERCP is therefore retained for those with specialist interest. The principal complications are hemorrhage, cholangitis, post-ERCP pancreatitis, and perforation with an overall incidence of approximately 10%. In ICU patients, it is essential to have checked the coagulation profile as sphincterotmy in the coagulapathic ICU patient will result in hemorrhage. Recently, the Dutch Pancreatic group has identified that early ERCP in gallstone pancreatitis will reduce complications in patients with evidence of cholestasis, which may be particularly relevant in the ICU setting [2].

EUS

EUS is a developing modality that couples an ultrasound probe with an endoscope. The addition of focused, intraluminal ultrasonography, allows detailed examination of the upper GI tract, rectum, and anal canal. The local anatomical relationships of normal and abnormal tissue can be assessed in detail, allowing highly accurate staging of GI tract malignancies. Malignant morphology, tumor size, extent of invasion, vascular or nodal involvement, and even metastatic disease can be assessed prior to treatment with previously unattainable accuracy. Image-guided biopsy is also possible and has revolutionized the management of esophageal, gastric, pancreatic, and biliary disease. Debate regarding the facility of EUS in the management of ano-rectal disease persists, with an emerging body of data suggesting that Magnetic Resonance Imaging (MRI) is a superior modality.

EUS remains a highly-specialized modality as yet and availability is limited both by expertise and infrastructure. It is a relatively safe procedure with a complication profile similar to OGD. If biopsy is performed, complication rates approach approximately 1% overall.

Colonoscopy

The indications for colonsocpy are shown in Table 2. Normally the colon must be cleansed thoroughly to allow endoscopic examination. This is rarely possible in ICU patients. Several techniques are used, the most widely practised being the use of osmotic laxatives 24 h prior to examination, coupled with a fluid-only intake. Consideration must be given to the patient's baseline condition, as vigorous colonic lavage may not be suitable for those with significant cardiac or renal disease. The initial position is left lateral decubitus, but the patient may be turned to supine or right lateral to facilitate passage of the

Gastrointestinal Endoscopy. Table 2 Common indications for colonoscopy in ICU

Diagnosis of colitis (particularly ulcerative colitis and ischemic colitis)
Diagnosis and therapy of lower GI hemorrhage
Deflation for pseudobstruction
Stenting left colonic onstructing tumours
Therapy of sigmoid volvulus

endoscope. The tip of the endoscope is passed into the rectum and a combination of gentle forward pressure, insufflation, suction, withdrawal, and shaft rotation will allow advancement of the endoscope. The endoscope should not be advanced unless there is a clear view of the lumen. At several locations, advancement is hindered due to anatomical relationships. Negotiation of the recto-sigmoid portion can be difficult and may require turning of the patient's position. Application of pressure by the assistant, directly onto the endoscope, or in the left or right paracolic gutters can greatly assist passage. Beyond the sigmoid, forward pressure may not yield further intubation as a large sigmoid loop can form. Retroflexion of the endoscope tip combined with withdrawal and rotation of the shaft will reduce the redundant loop and facilitate further intubation. Splenic and hepatic flexures can also present difficulties. Once passed, hooking the tip of the endoscope upon mucosal folds and a composite withdrawal/rotation/suction maneuver may yield significant forward advancement. This maneuver is particularly useful in the right colon, allowing complete intubation of the caecum. Blind insertion is always unsafe and is absolutely to be avoided in diseased segments of bowel. Ocasionally, the "slide-by" technique, where gentle forward pressure is applied to allow the endoscope glide along and past an acute angulation despite loss of a clear luminal view, can be employed, but this is a maneuver for the expert endoscopist and is not to be recommended in most cases.

Once the caecum has been fully intubated, the position must be confirmed. The anatomical landmarks are the triradiate mucosal fold (convergence of the taenia coli), the ileo-caecal valve, and the appendiceal orifice. If clinical suspicion of ileal disease exists, the terminal ileum may be intubated. To assist with confirmation of location, the endoscopist may indent the right iliac fossa or perform transillumination, where the endoscope light source is shone through the anterior abdominal wall to confirm its position in the right iliac fossa. The endoscope is now carefully withdrawn, allowing complete inspection of the mucosa. The luminal appearance will depend upon the anatomical location: right colon – circular profile with prominent haustrations; hepatic flexure – the bluish outline of the liver will be visible through the colon wall; transverse colon – triangular profile with prominent haustrations; descending colon – circular profile with few haustrations; sigmoid colon – tortuous with eccentric mucosal folds; rectum – wider lumen, prominent blood vessels, and mucosal shelves representing the Valves of Houston. The endoscope may be fully retroflexed and rotated at this point to allow complete inspection of the rectum.

Colonoscopy is indicated for investigation of all forms of colonic disease. Even in acute inflammatory conditions, limited colonoscopy may safely be performed to obtain diagnostic biopsy. Endoscopic biopsy is usually effected using insulated biting forceps and coagulation electrocautery for hemostasis. Wire snaring and electrocautery is used universally for the management of colonic polyps and there is an emerging role for endoscopic mucosal resection in the setting of complex polyp disease. Endoluminal stent prostheses are being used increasingly in the management of colorectal malignancy, combining endoscopy with fluoroscopy for safe deployment. Finally, colonoscopy may be both diagnostic and therapeutic in cases of colonic volvulus or pseudo-obstruction.

Colonoscopy in experienced hands is a safe procedure. Principal complications are hemorrhage and perforation, occurring with an overall incidence of 1% and 0.1% respectively [3].

Emerging Technologies

Endoscopic technology has developed steadily over the past 20 years. Its facility in the field of diagnosis is well recognized and advances now focus upon interventional applications. As mentioned, Endoscopic Mucosal Resection (EMR) is gaining increased popularity in the western world, having been used extensively in Japan for some years. Similarly, laser thermal coagulation and photodynamic therapy appear promising for the future management of premalignant conditions of the mucosa. Gastroesophageal reflux disease has been treated endoscopically with some success and several modalities are now available, including submucosal biopolymer injection (Stretta Procedure) and endoscopic suturing techniques. There are as yet, no long-term outcome data available, however. In terms of pancreato-biliary disease, the technology now exists to enable endoscopic visualization of the bile duct lumen, with a host of therapeutic interventions available from sphincterotomy to duct clearance. As with ERCP, it is likely that this will become more widely available in time. It is likely also, that endo-luminal

Gastrointestinal Endoscopy. Table 3 Possible endoscopies in ICU

Upper GI hemorrhage	Lower GI hemorrhage
Colonic decompression	Gastric lavage
Biliary decompression/Stenting	Stenting/Suturing anastomotic dehiscence
Feeding tube insertion (Nasal & PEG)	EUS-guided biopsy
EUS-guided pericardial drainage	EUS-guided pseudocyst drainage

stent prostheses will continue to develop, allowing their use in heretofore inaccessible or "unstentable" anatomical locations. Natural Orifice Transluminal Endoscopic Surgery (NOTES) is a new technology that allows intraperitoneal surgery, cholecystectomy for example, to be performed via a trans-gastric, trans-vaginal or trans-colonic route, using specially adapted endoscopic equipment. The facility of the technology has been demonstrated in numerous animal models and early human trials are now under way. Small bowel enteroscopy is rarely, if ever, used in ICU.

Endoscopy in the Critical Care Setting

Modern endoscopy equipment and the emerging ubiquity of endoscopic expertise has rendered endoscopy particularly useful in the management of the critically ill patient. Both diagnostic and therapeutic endoscopy can be performed safely at the ICU bedside. There are significant advantages to such bedside management of unstable or septic patients. Logistic limitations are greatly reduced with newer, portable endoscopic stacks which can effectively be used in most hospital settings. The list of indications for bedside endoscopy is growing and much as airway endoscopy is already an important skill for the intensive care specialist, it is likely that gastrointestinal endoscopy will also become an element of the intensivist's skillset. Relative and absolute indications for ICU bedside endoscopy are listed in Tables 1, 2, and 3.

References

1. Eisen GM et al (2002) Complications of upper GI endoscopy. Gastrointest Endosc Jun 55(7):784–793
2. van Santvoort HC et al (2009 July) Early endoscopic retrograde cholangiopancreatography in predicted severe acute biliary pancreatitis: a prospective multicenter study. Ann Surg 250(1):68–75
3. Pignone M et al (2002) Screening for colorectal cancers in adults at average risk: a summary of the incidence for the US preventive services task force. Ann Int Med 137(2):132–141

Gastrointestinal Hemorrhage

► Gastrointestinal Bleeding

Gastro-intestinal Hemorrhage

► Gastro-intestinal Bleeding in ICU Patients

Gastroscopy

► Gastrointestinal Endoscopy

Gelfoam

An absorbable sponge derived from purified porcine skin gelatin. Can be employed as a topical or embolic hemostatic. Frequently used when performing super-selective angiography.

Gender

► Sex Steroids: Role in ICU Outcome

Geriatric Trauma

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Synonyms

Trauma in extremes of age; Trauma in our elders

Definition

The "elderly" patient is not easy to define as chronologic age does not accurately define one's physiologic age or

ability to recover from injury. A widely accepted definition for geriatrics is those patients 65 years and older. However, the health and medical characteristics of each patient over 60 years of age are a blend of the effects from biologic aging, the presence of medical comorbid conditions, and sequelae of their treatments. Each individual is unique and no two people are exactly alike as each "ages" at different rates, as does each organ system within a patient. Thus the ability to predict outcomes from injury is complex and requires assessment of the type and severity of injury, age, physical and mental fitness, pre-injury functional state, and comorbid medical conditions. As a rule, the older patient with more severe medical conditions and injury does poorer than younger, more fit individuals with the same wounds.

Statistics and Epidemiology

In 1980, 26.5 million people in the USA (11.3% of the population) were older than 65 years of age. 2004 witnessed the arrival of the "Boomer" generation to this demographic and some 72 million people will be older than 65 years by 2030 (20% of the total population).

Currently, trauma is the fourth leading cause of death in patients between the ages of 55 and 64 years and the ninth leading cause of death in patients over the age of 65 [1]. Trauma centers are seeing an increasing number of injured elderly patients as people live longer, are more active and exposed to increased risk for injury. Aging involves changes in organ function, muscle and bone strength, and the ability to withstand physical trauma. Although younger individuals are more likely to be injured, the mortality after injury, even some minor injuries, is higher in people in their seventh decade and beyond.

Characteristics

Physiology of Aging

The normal biologic changes in physiology associated with aging are well-known. In general, as people age beyond the seventh decade, their biologic and physiologic reserve to tolerate injury is reduced. These age-related changes affect all organ systems and a fundamental understanding of these is essential. Each person ages differently and each organ system within a person ages at different measurable rates. For example, a patient with normal renal and liver function can have profound cardiac dysfunction while another patient may have end stage renal disease and require dialysis with a normal cardiac profile.

The brain undergoes atrophy reducing its gross size and putting dural bridging veins under increased tension resulting in susceptibility to rupture and bleeding with impact. The smaller brain within the skull also increases the space into which blood can collect, which may mask symptoms of mass effect and rising intracranial pressure. Cerebellar atrophy can affect balance and gait, and blunted auditory, visual and pain sensation increase the risk of injury exposure. Although intelligence is largely unaffected with aging, cognitive function declines. Dementia is a growing public health concern causing impairments in cognition, function, and behavior. Thus, poor judgment in risky situations often results in injury [2].

The cardiovascular system undergoes a variety of expected changes with aging. Myocytes are progressively lost with a compensatory augmentation of myocyte volume in the ventricles. These changes are associated with a stiffening of the heart also seen in the great vessels that result in impaired diastolic filling and increased afterload, respectively. Coupling these factors with a decreased sensitivity to beta-adrenergic stimulus, the maximum achievable heart rate decreases and the ability to increase cardiac output when physiologically demanded is impaired [2]. The prevalence of coronary artery disease and atherosclerosis in this population further compromises the amount of cardiac reserve and ability to increase oxygen delivery.

The respiratory system goes through changes including the chest wall becoming more rigid and weakening of the muscles of respiration. An increase in ventilation-perfusion mismatch widens the alveolar-arterial oxygenation gradient. Additional changes in the lungs themselves include significant growth of the alveolar ducts, which decreases the available surface area for gas exchange and the lungs will have decreased elastic recoil. The elderly patient relies more on the diaphragm and abdominal muscles for breathing, both waning in strength over time [2]. Thus, pulmonary reserve is limited, the chest wall is "brittle," and less force is required to break ribs and contuse lungs.

The renal system experiences cortical tissue loss from glomerulosclerosis, which is accelerated by atherosclerosis, hypertension, and diabetes. Glomerular filtration rate (GFR) decreases, which increases risk for ischemic and nephrotoxic insults resulting in acute renal failure. The kidney is also less able to reabsorb and secrete solutes owing to tubular senescence [2]. The team providing care is cautioned to weigh risks and benefits vigilantly when prescribing nephrotoxic agents such as iodinated contrast solutions, certain antibiotics, diuretics, and

vasoactive medications. Drugs dosage is often based on serum creatinine, a less reliable measure in the elderly than creatinine clearance that can be calculated as:

$$\mathrm{Cl_{Cr}(mL/\,min)} = (140 - \mathrm{age}) \times \mathrm{weight(kg)}/[\mathrm{serum\ creatinine(mg/dL)} \times 72]$$

to accurately assess renal function and appropriate dosages [2].

An increase in activity appears to be associated with slowing of the aging process. Changes within musculoskeletal systems are significant [3]. Overall, a decrease in muscle mass, strength, and responsiveness progresses throughout adult life, however, increased activity appears to be associated with slowing these. Decreasing bone density increases the likelihood and severity of fractures. Arthritis is highly prevalent, compromises patient mobility, and is a source of chronic pain. Progressive changes (stiffening, shortening, and lordosis) in the spinal column alter pulmonary mechanics. Spinal cord stenosis secondary to osteoarthritis predisposes patients to cord syndromes. These changes adversely affect the older patient's ability to avoid injury and linked to changes in the central nervous system predispose patients to the common mechanisms of injury (falls, motor vehicle crash, and getting struck by automobiles).

Comorbid Conditions

While the normal physiological changes associated with aging affect the patient's response to injury, the presence of preexisting comorbid conditions greatly affect outcome. Several studies have shown that the presence of comorbid conditions adversely affect outcome independent of age and injury severity [3].

Patients who are free of comorbid conditions fare better than those who have chronic medical conditions, regardless of chronological age. Older patients have an increased incidence and more types of preexisting diseases. Most are managed medically, which adds medications (prescription and over the counter drugs) and their side affects to the clinical situation [4].

Carefully evaluating the older trauma patient to ascertain what comorbid conditions may be present is critical to adjust resuscitation and ongoing care. Table 1 summarizes the more commonly discovered conditions and how to quantify them [3]. Table 2 summarizes the prevalence of disabilities, limitations, and chronic disease by age [5]. More than 80% of elders take at least one medication ever day. Table 3 lists common medications that can affect resuscitation strategy.

Geriatric Trauma. Table 1 Premorbid illness criteria [3]

Cardiac disease – History of cardiac surgery – Any cardiac medication – MI < 12 months before admission – MI > 12 months before admission
Diabetes mellitus – Insulin dependent – Non-insulin dependent
Liver disease – Bilirubin > 2 mg/dL (on admission) – Cirrhosis
Malignancy – Any documented history
Pulmonary disease (asthma, COPD, others) – Bronchodilator therapy – No bronchodilator therapy
Obesity – Female > 200 lbs – Male > 250 lbs
Renal disease – Serum Cr > 2 mg/dL (on admission)
Neurologic (cerebrovascular accident) – Any documented history
Hypertension – Any antihypertensive medication – Any documented history

Geriatric Trauma. Table 2 Prevalence by age

Disability/limitations			
	Age 18+	Age 65–74	Age 75+
Trouble hearing	16.8	31.9	50.4
Vision limitations	9.5	13.6	21.7
Absence of all natural teeth	8.0	22.8	29.4
Chronic disease			
	Age 18+	Age 65–74	Age 75+
Hypertension	22.9	52.9	53.8
Heart disease	10.9	26.2	36.6
Any cancer	7.1	17.2	25.7
Diabetes	7.7	18.6	18.3

Institute of Medicine Consensus Report, 2008

Geriatric Trauma. Table 3 Common medications affecting resuscitation/diagnostic strategy

Drug	Potential effect on approach
Insulin	May cause mental status changes
Aspirin	TBI – platelets needed
Clopidogrel	TBI – platelets needed
Warfarin	TBI – FFP and vitamin K needed
Beta blocker	Blunts response to hypovolemia
Diuretics	Impaired renal function
Benzodiazepines	Changes in mental status – withdrawal
Chronic narcotics	Pain control – withdrawal
Steroids	Adrenal insufficiency

Mechanisms of Injury

The leading causes of nonfatal injury in the USA for patients over 65 years are: (1) falls (2) struck by an object (pedestrian – automobile impact) (3) motor vehicle crash, and (4) violence [1].

Falls remain the most common cause of injury in the elderly population [1]. The changes of the nervous and musculoskeletal systems contribute to this prevalence. Altered balance, strength, and agility impair stability leading to falls. Other causes relate to comorbid medical conditions (e.g., syncope, cardiac dysrhythmias, and transient ischemic attacks) or side effects of medications [5]. Younger elders fall from heights (ladders, roofs, or down stairs), while those in the 80s more commonly fall from a standing position. Soft tissue lacerations, brain injury, and long bone fractures are the most common injuries after fall from standing.

Motor vehicle crashes are the third leading cause of nonfatal injury and the second leading cause of death after unintentional injury [4]. As the proportion of elders in our population increases, the numbers of older drivers will also increase. Driving patterns in the elderly differ; crashes more commonly occur during the day, in fair weather and close to where the patient lives. Alcohol consumption is less prevalent. The same physiologic changes associated with aging (vision, hearing loss, impaired cognition, slower reflex time, and decreased muscle strength) contribute to the higher rate of crash in this age group. Similar to the changing circumstances that change how one falls, after 80 years, patients are more commonly passengers rather than drivers in these later years and sustain different injury patterns.

The mortality for a pedestrian struck in this age group is very high [4]. The physiologic changes of aging, mentioned above, coupled with the altered gait, decreased speed of walking, and decreased agility and strength make it more difficult to avoid dangerous situations.

Violence is an unfortunate reality in managing the elderly trauma patient. Older patients are more susceptible to unintentional injury, criminals, or abuse. Suicide is common and the problem of domestic violence is increasing in our society. Multiple visits to the emergency department, unexplained bruising or fractures at various stages of healing, or chronic signs of poor general hygiene should raise suspicion for abuse [3].

Thermal injury is another common mechanism of injury. Burns account for approximately 8% of injury-related deaths in the elderly and are currently the seventh leading cause of injury-related death. Impaired mobility and blunted sensory responses increase risk due to fire or prolonged heat exposure. More extensive damage and injury is sustained with equivalent levels of exposure when compared to younger patients as the elderly have thinner and more fragile skin.

Trauma Evaluation

The initial approach to evaluating the elderly trauma patient follows the same protocols used for any other trauma patient. However, certain nuances are applied. While resuscitating, attempts are made to contact the patient's family members or physician to provide information about health status, level of function, past medical history, and existence of advance directives.

The ABCDEs of the ATLS course should be followed with the understanding that the physiology of aging may warrant modification of the resuscitative process as it unfolds, such as earlier hemodynamic monitoring and heightened suspicion for occult injury, blunted cardiovascular response, and potential for early deterioration.

Securing the airway and assuring adequate oxygenation and ventilation early in the resuscitation is paramount. Careful evaluation of the chest to identify injuries ensures optimal oxygenation and ventilation. Pneumothorax or hemothorax should prompt immediate therapy. The presence of crepitance suggests rib fracture or flail segments. Pain control is central to ongoing management and requires exquisite balance between narcotic and sedative use and the adverse effects of somnolence, blunting the respiratory drive and disorientation.

Volume resuscitation in the elderly trauma patient can be challenging to assure optimal organ perfusion. Patients are often taking beta blockers that blunt the usual sympathetic response to hypovolemia and preexisting peripheral vascular disease alters signs of low intravascular volume. Though volume should not be withheld, it should be administered judiciously. Early placement of invasive

monitoring with central venous catheters, arterial lines, and pulmonary artery catheters may be necessary and guide therapy. The use of noninvasive monitoring such as ultrasound can characterize cardiac function and volume status (vena caval fullness) as further monitors of cardiac output and guide volume repletion.

Assessing patients for brain injury is difficult as physical examination is often misleading. Significant blood accumulation can occur in and around the brain with little alteration in mental status. A very high index of suspicion and early CT scanning of the brain are critical. Any history of a change in the patient's baseline mental function is helpful to avoid treating chronic problems as acute ones and vice versa. CT scan of the head and cervical spine should be obtained early with any suspicion of head injury, even a minor one. Identifying the use of anticoagulation medication is critical to direct reversal therapy as needed (platelets for aspirin or clopidogrel and plasma for Coumadin).

Complete physical examination is important and careful inspection for clues of medical illness or previous surgeries is very helpful. Posterior lacerations or hematomas can be the source of significant bleeding, old surgical scars may be faded and hard to see even in bright light, body wall hernias are not readily apparent, and signs of malnutrition can be evasive unless searched for diligently. The secondary survey proceeds with a head to toe examination while appropriate adjunctive and additional studies aimed at evaluating comorbid conditions, the presence of medications, etc., are obtained as necessary. Special attention to the patient's history regarding the circumstances of the event may suggest a chronic or occult medical condition, medication reaction or misuse (single vehicle car crash in the middle of the day, clustering of falls), or an unsafe environment (fall down stairs by tripping on a loose rug).

An age-related approach to patient care is presented in Table 4 [4].

Geriatric Trauma. Table 4 Age-related approach to patient care

Treatment axioms, 55 through 69 years 1. Assume some mild decrease in physiologic reserve. 2. Suspect the presence of some common disease of middle age (diabetes, arteriosclerosis, hypertension, previous surgery/transfusion). 3. Suspect use of prescription or OTC medication. 4. Assume the patient is competent to provide an accurate medical history. 5. Look for subtle signs of organ dysfunction, especially cardiovascular and respiratory systems; ABG measurements and EKG are crucial. 6. With history of LOC or abnormalities in cognitive function or personality, assume serious brain injury until proven otherwise; CT scan is invaluable; MRI may be a useful adjunct. 7. Proceed with standard diagnostic and management schemes, unless contraindicated by information collected during history taking.
Treatment axioms, 70 through 80 years 1. Accept presence of age-related and acquired disease-induced physiologic alterations of organ systems. 2. Accept the presence of acquired diseases and medications to correct or control them; assume a higher incidence of previous surgery and transfusion. 3. Decide whether the patient is competent to give a reliable medical history; review the history as soon as possible with the patient's relative or personal physician. 4. Aggressively monitor the patient and control the physiologic characteristics to optimize cardiac performance and oxygen metabolism. 5. Assume that any alteration in mental status or cognitive or sensory function indicates presence of a brain injury; brain imaging is mandatory. 6. Proceed with standard diagnostic and management schemes, including early, aggressive operative management. 7. Be aware of poor outcome, especially with severe injury to the central nervous system or marked physiologic deterioration secondary to injury; check for advance directives.
Treatment axioms, 80 years or older 1. Proceed as in items 1 through 5 for patients 70 through 80 years of age. 2. Assume a poor outcome with moderately severe injury, especially in the central nervous system or for any injury causing physiologic dysfunction. 3. After aggressive initial resuscitation and diagnostic maneuvers, examine item 2 and discuss appropriateness of care with the patient (if competent) and family members. 4. Attempt to be humane; recognize the legal and ethical controversies involved; consider early consultation of ethics experts and social services to help family and medical team with difficult decisions.

Outcome

Age, physiologic reserve, comorbid conditions (number and type), injury complex (pattern of injury and severity), and physiologic insult (shock, GCS, paralysis, etc.) all have an effect on outcome. No single measure or scoring system predicts mortality but in general, increasing age, comorbid conditions, and injury severity foretells of increases in length of stay, complications, and mortality.

Special Considerations

Unfortunately, patients presenting to trauma centers rarely have documented advance directives in hand upon arrival. It is appropriate to embark on aggressive

resuscitative efforts until family members or surrogate decision makers can be contacted. Conversations with the patient's primary care physician are helpful as are medication lists obtained from pharmacies. If the patient is a nursing-home or a life-care resident, transfer of records can reconcile medications and provide medical history and recent information about functional level.

Ethical and end-of-life situations are common. Because patients have poorer outcomes, conversations with the patient and family members are crucial to ensure an appropriate level of definitive care is rendered. As information about the patient, their directives, and injury complex is obtained, a more informed plan can be made, consultants secured, and support for the family, if necessary, obtained. Often, the conversation must focus on the issues of futility and ability of the patient to return to their expectation of a meaningful life. These end-of-life situations are approached and valued differently by persons of other cultures, religions, and countries and require sensitivity and time for communication and acceptance [5].

References

1. Richmond TS, Kauder DR, Strumpf N, Meredith T (2002) Characteristics and outcomes of serious traumatic injury in older adults. J Am Geriatr Soc 50:215–222
2. Aalami OO, Fang TD, Song HM et al (2003) Physiological features of aging persons. Arch Surg 138:1068–1076
3. Milzman DP, Boulanger BR, Rodriguez A et al (1992) Pre-existing disease in trauma patients: a predictor of fate independent of age and ISS. J Trauma 32(2):236–244
4. Schwab CW, Kauder DR (1992) Trauma in the geriatric patient. Arch Surg 127:701–706
5. Duthie EH, Katz PR, Malone ML (2007) Practice of geriatrics. W.B. Saunders, Philadelphia

GGT

► Tubular Enzymuria

Gibraltar Fever

► Brucellosis

Gift-of-Life Management

► Organ Donation: Management of the Potential Donor

Gilchrist's Disease

► Blastomycosis

Glasgow Coma Scale

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Synonyms

Brain injury prognosis; Injury severity indices; Neurological scale

Definition

The Glasgow ► Coma Scale (GCS) is the most widely used clinical instrument to evaluate the level of consciousness [1]. It is a neurological scale that aims to give a reliable, objective way of recording the conscious state of a patient for initial as well as subsequent neurological assessment [2]. A patient is assessed against three criteria of the scale based on response to stimuli by eye opening, verbal response, and motor response. These responses are graded by a standardized score. This standardization allows for assessments of different examiners, at different times, to be reproducible.

The GCS was introduced by Teasdale and Jenett in 1974, as a descriptive tool of the functional status of the central nervous system after head injury [2]. The GCS has subsequently become the standard as a clinical measure of the severity of head injury. It has been borrowed extensively for assessment of neurological status resulting from other medical conditions such as intracranial hemorrhage, hypoxia, neurodegenerative disease, metabolic disorders (e.g., hepatic or renal failure, hypoglycemia, diabetic ketoacidosis), infectious meningitis, as well as in cardiac arrest [1]. Further, it has been modified accordingly into a Pediatric Glasgow Coma Scale.

Classification

The three components of the GCS reflect the different levels of CNS function and integration [2]: with eye opening corresponding to the brain stem, verbal response corresponding to integration between the cortex and the brain stem, and motor response corresponding to integration between the cortex and the spinal cord.

A GCS score is obtained by scoring the best eye response (E), the best verbal response (V), and the best motor response (M), as described in Table 1. Points for each response are added for the total score. The GCS score ranges between 3 and 15, the lower score of 3 corresponds to no response; thus, a brain-dead patient could have a GCS = 3. When reporting a GCS score, each response scored should be reported separately (e.g., E2-V3-M4) along with the total score (e.g., GCS 9).

Categorization

Coma: No eye opening, no ability to follow commands, no word verbalizations (GCS 3–8).

The Advanced Trauma Life Support (ATLS) identifies three categories of head injury based on GCS scoring:

Severe Head Injury – GCS score of 8 or less

Moderate Head Injury – GCS score of 9–12

Mild Head Injury – GCS score of 13–15

Glasgow Coma Scale. Table 1 Scoring of the Glasgow Coma Scale

Response		Score (points)
Best eye opening	Spontaneous – eyes open with blinking at baseline	4
	To verbal stimuli, command, or speech	3
	To pain only (not applied to face)	2
	No response	1
Best verbal	Oriented	5
	Confused conversation, but able to answer questions	4
	Inappropriate words	3
	Incomprehensible speech	2
	No response	1
Best motor	Obeys commands for movement	6
	Purposeful movement to painful stimulus	5
	Withdraws in response to pain	4
	Flexion in response to pain (decorticate posturing)	3
	Extension in response to pain (decerebrate posturing)	2
	No response	1

Adapted from the Centers for Disease Control and Prevention: emergency preparedness and response: Glasgow Coma Scale

Application

The GCS is useful as an index of depth of impaired consciousness, as well as for predicting neurologic recovery. It is used widely by Emergency Department, Medical and Surgical Intensive Care Units, as well as by prehospital providers and emergency medical systems (EMS) [1, 3]. With good interobserver reliability, the GCS has been linked to accurate prediction of neurologic recovery from a number of conditions, including ► traumatic brain injury, cardiac arrest, subarachnoid hemorrhage, and bacterial meningitis [1].

In patients who remain comatose after resuscitation from cardiac arrest, a GCS score of less than 5 points, on day 3 following cardiac arrest, has a predictive value of poor outcome in 100% [4]. These results, however, must be duplicated on multiple examinations to achieve the highest predictive value.

The simplicity of the GCS and its rapidity of administration have made it popular among EMS providers for triage and to guide therapies, and have become a component of algorithms for out-of-hospital triage to trauma centers. Upon arrival, and as part as the ATLS initial assessment of the injured patient, the GCS is included in the primary survey, and often reassessed during the secondary survey.

In intensive care units, the GCS is included as a calculating factor for various outcome predicting scores (TRISS, Acute Physiology and Chronic Health Evaluation – APACHE II). In fact, the GCS has proven to be the most powerful predictive component of the APACHE II score [4].

As a limitation, the presence of unmeasureable components of the GCS compromises its usefulness. The most common unmeasureable feature of the GCS is the verbal score, most often due to the presence of endotracheal intubation. Various solutions have been adopted for this matter, including only reporting a motor and an eye-opening score; commonly referred to as GCS-T. A strong correlation between eye and motor components with the verbal component of the GCS has been reported. In fact, of the three scores, the motor score has been reported as the most predictive of neurologic outcome [5].

Cross-Reference to Disease

► Altered Mental Status

► Coma

► Traumatic Brain Injury

References

1. Hamel MB, Goldman L, Teno J, Lynn J, Davis RB, Harrell FE Jr, Connors AF Jr, Califf R, Kussin P, Bellamy P et al (1995) Identification of comatose patients at high risk for death or severe disability. SUPPORT investigators. Understand prognoses and preferences for outcomes and risks of treatments. JAMA 21(273):1842–1848

2. Teasdale G, Jennett B (1974) Assessment of coma and impaired consciousness. Lancet 2:81–84
3. Edgren E, Hedstrand U, Kelsey S, Sutton-Tyrrell K, Safar P (1994) Assessment of neurological prognosis in comatose survivors of cardiac arrest. BRCT I study group. Lancet 30(343):1055–1059
4. Bastos PG, Sun X, Wagner DP, Wu AW, Knaus WA (1993) Glasgow Coma Scale score in the evaluation of outcome in the intensive care unit: findings from the acute physiology and chronic health evaluation III study. Crit Care Med 21:1459–1465
5. Healey C, Osler TM, Rogers FB, Healey MA, Glance LG, Kilgo PD, Shackford SR, Meredith JW (2003) Improving the Glasgow Coma Scale score: motor score alone is a better predictor. J Trauma 54:671–678

GLN

► Glutamine

Global End-Diastolic Volume (GEDV)

The sum of the end-diastolic volumes of all heart chambers.

Glomerular Filtration

► Renal Blood Flow Regulation

Glomerular Filtration Rate

► Creatinine and Creatinine Clearance in Children

Glomerulonephritis

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Synonyms

Bright's disease

Definition

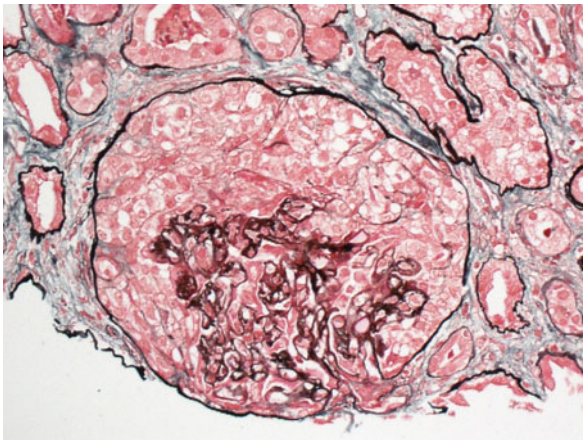
The term "glomerulonephritis" refers to a diverse group of diseases characterized by inflammation affecting the renal glomeruli. Glomerulonephritis is classified according to both pathological characteristics and etiology. The many different types produce a spectrum of clinical presentations, and the major types and their causes are described below with an emphasis on presentations and conditions most relevant to the Intensive Care Unit (ICU).

Clinical Presentations

Glomerulonephritis is a relatively uncommon cause of renal failure in the ICU, where most acute kidney injury is caused by ischemic or nephrotoxic insults. Recognition of glomerulonephritis in the ICU patient is important, however, since the timely diagnosis and initiation of specific therapy are critical in preventing progression to irreversible renal failure. The finding of an active urinary sediment, defined by the presence of dysmorphic ("glomerular") red blood cells, red cell casts, and proteinuria, is most consistent with a proliferative form of glomerulonephritis.

Rapidly Progressive Glomerulonephritis

The most common glomerulonephritis "syndrome" associated with the need for admission to ICU is rapidly progressive glomerulonephritis (RPGN). RPGN is characterized by a rapid deterioration of renal function over days, weeks, or several months. Patients with RPGN typically have glomerular hematuria, red cell casts, and proteinuria. In the presence of large numbers of urinary red blood cells (>500,000/ml), erythrocyte morphology should be interpreted with caution, since they often appear "non-glomerular" despite a glomerular origin. Macroscopic hematuria (sometimes called "coca cola–colored urine") is not uncommon in these patients and usually indicates severe disease. The pathological correlate of RPGN is widespread "crescent" formation (Fig. 1). The important causes of RPGN are pauci-immune crescentic nephritis associated with anti-neutrophil cytoplasmic antibodies (ANCA), anti-glomerular basement membrane (anti-GBM) disease, and immune complex forms of glomerulonephritis, which include severe forms of lupus nephritis (Class IV), IgA nephropathy, post-infectious glomerulonephritis, and cryoglobulinemic glomerulonephritis. ANCA-associated pauci-immune glomerulonephritis occurs as one of several clinical syndromes including microscopic polyangiitis, Wegener's granulomatosis, Churg–Strauss syndrome, and renal-limited vasculitis. Each of these has distinctive features but overlap is common.



Glomerulonephritis. Figure 1 High-powered view of silver-stained section of a renal biopsy showing a single glomerular tuft almost surrounded by a highly cellular crescent or cap

Uncomplicated RPGN typically does not require admission to the ICU. It is not unusual, however, for patients with RPGN to develop other complications of their illness or its treatment that necessitate ICU support. Pulmonary hemorrhage is a relatively common and life-threatening complication of both anti-GBM disease and ANCA-associated vasculitis. The term "Goodpasture syndrome" refers to the simultaneous occurrence of glomerulonephritis and pulmonary hemorrhage that is caused by anti-GBM antibodies. Patients with pulmonary hemorrhage may need respiratory support and require ICU management.

Infectious complications of treatment with potent immunosuppressive agents also lead to ICU admission for patients with RPGN. These patients are at risk of severe sepsis caused by common gram-positive and gram-negative infections of the respiratory and urinary tract. Patients with central venous catheters are at particular risk of staphylococcal septicemia. In addition to the general immunosuppressive effect of corticosteroids and cytotoxics, patients treated with plasma exchange frequently develop hypogammaglobulinemia, which contributes to their risk of severe infection. This group is also at risk of opportunistic infections such as *Pneumocystis carinii* pneumonia, invasive cytomegalovirus infections, and fungal infections.

Nephritic Syndrome

The "nephritic syndrome" is characterized by the acute onset of hypertension, hematuria (microscopic or macroscopic), proteinuria, edema, oliguria, and sometimes renal impairment. While the clinical features of the nephritic syndrome and RPGN overlap, in the typical nephritic syndrome, renal impairment is milder and glomerular inflammation is more self-limiting. The prototypical nephritic syndrome is due to post-streptococcal glomerulonephritis, which occurs 1–2 weeks after a group A streptococcal throat infection or 3–6 weeks after a group A streptococcal skin infection. Post-infectious glomerulonephritis also follows infection with other organisms such as *Staphylococci* and is associated with various forms of endocarditis.

Post-streptococcal glomerulonephritis is predominantly a condition of children but people of all ages may be affected. Patients with nephritic syndrome are usually cared for on the general medical or renal ward, but serious complications requiring ICU admission occur occasionally. Most, but not all, cases of acute nephritic syndrome due to post-streptococcal glomerulonephritis are self-limiting, and the mainstay of treatment is, therefore, supportive care. In children with the nephritic syndrome, the most common reason for ICU support is the development of hypertensive encephalopathy, which may be associated with the "reversible posterior leukoencephalopathy syndrome." In elderly patients, post-streptococcal glomerulonephritis may present with acute pulmonary edema. This has a poor prognosis and often requires ICU support too. Older patients with post-streptococcal glomerulonephritis are more likely to require dialysis acutely and are less likely to make a complete recovery.

Nephrotic Syndrome

"Nephrotic syndrome" is defined by the presence of severe proteinuria (>3.5 g/24-h), hypoalbuminemia, generalized edema, and hyperlipidemia. The clinical consequences of the nephrotic syndrome are mainly due to the urinary protein loss, leading to systemic hypoproteinemia and hypoalbuminemia. Patients presenting with the nephrotic syndrome often have a preserved glomerular filtration rate, but loss of renal function can occur over time. Important causes of the nephrotic syndrome include diabetes, minimal change disease, focal and segmental glomerulosclerosis, membranous nephropathy, amyloidosis, and lupus nephritis.

Patients with the nephrotic syndrome are usually managed on the general or renal ward, or as outpatients. The most serious complications of the nephrotic syndrome that require ICU support are thrombotic events and infections. The predisposition to thrombotic events is caused by the loss of anticoagulant proteins in the urine, especially anti-thrombin III. There is an increased risk of both venous thromboembolism and arterial thrombosis. Renal vein thrombosis is a particular risk, especially in

patients with membranous nephropathy. The role of prophylactic anticoagulation in patients with severe nephrotic syndrome remains controversial, but many units institute prophylactic anticoagulation when the serum albumin falls below 15–20 g/L. Bacterial infection was an important cause of death in patients with nephrotic syndrome in the pre-antibiotic era and remains a threat. The risk of pneumococcal infection, especially pneumococcal peritonitis, is markedly increased.

Asymptomatic Urinary Abnormalities

The finding of glomerular hematuria or marked proteinuria in an ICU patient with a critical non-renal illness suggests glomerular disease. This may reflect a preexisting lesion, for example, IgA nephropathy or thin basement membrane nephropathy. However, glomerulonephritis also develops secondary to a variety of bacterial and viral infections. In this situation, the histology is usually membranoproliferative (also called mesangiocapillary) glomerulonephritis. While the microscopic hematuria or proteinuria may be incidental, progressive worsening or deterioration of renal function warrants a more aggressive approach to formal diagnosis with serological tests and possibly a renal biopsy.

Treatment

Treatment for patients in the ICU who have glomerulonephritis must be individualized according to the diagnosis and clinical symptoms. Immunosuppression has an important role in most forms of crescentic or necrotizing glomerulonephritis. In contrast, immunosuppression is not indicated and is potentially harmful in infection-associated proliferative glomerulonephritis.

Immunosuppression

Without treatment, RPGN inevitably progresses to irreversible end-stage kidney failure with the need for permanent renal replacement therapy. The mainstay of immunosuppression for the treatment of RPGN is the combination of corticosteroids and cyclophosphamide. Treatment with corticosteroids alone or in combination with azathioprine is ineffective. Treatment based on cyclophosphamide and corticosteroids is best established for the treatment of ANCA- and anti-GBM associated-RPGN, although other cases of RPGN are managed similarly. Patients with anti-GBM disease who are dialysis-dependent have a poor renal prognosis and, in general, should not be treated with immunosuppression [1]. Corticosteroids are often initiated as methylprednisolone pulses (0.5–1.0 g per day for 3 days), followed by oral prednisolone (1 mg/kg/day), the dose of which is tapered over several months. Cyclophosphamide is most commonly given orally (2 mg/kg/day) as induction therapy for 3–6 months. Some units induce remission with cyclophosphamide as monthly or 3-weekly intravenous pulses (0.5–1.0 g/m^2) for 3–6 months, especially in patients with lupus nephritis. After the induction of remission (3–6 months), patients are commonly switched to maintenance therapy in order to prevent relapse. This most commonly consists of azathioprine (2 mk/kg/day) and low-dose prednisolone (5–7.5 mg day).

While treatment with cyclophosphamide and prednisolone is effective, this treatment is also associated with significant morbidity and mortality. Leukopenia is an important side effect of cyclophosphamide, and close monitoring of the white cell count is essential. Serious infections can occur with treatment, and *Pneumocystis carinii* pneumonia prophylaxis with trimethoprim-sulphamethoxazole is recommended. Cyclophosphamide also increases the risks of infertility and malignancy, especially cancer of the bladder. Side effects of prednisolone include diabetes, osteoporosis, and peptic ulcer disease. Vitamin D and calcium supplementation, and proton pump inhibitor prophylaxis are recommended.

A promising newer therapy for relapsing or refractory RPGN caused by ANCA-associated vasculitis is rituximab, which is a chimeric mouse/human antibody that depletes B lymphocytes. In a recent series, rituximab resulted in complete remission in 75% of cases of refractory ANCA-associated vasculitis [2]. In this series, relapses occurred in 57% of patients but re-treatment appeared effective and safe.

Alternative immunosuppressive therapies that have been used in the treatment of patients with RPGN include mycophenolate mofetil, cyclosporine, and methotrexate. The role of these treatments in RPGN at present, however, remains limited.

Plasma Exchange

Plasma exchange achieves rapid removal of pathogenic autoantibodies and has been shown to be of benefit in specific situations in RPGN. The indications for plasma exchange in the management of RPGN include:

- Anti-GBM disease complicated by pulmonary hemorrhage or RPGN. Plasma exchange of 3–4 l is commonly performed daily to second daily for 2–3 weeks until the anti-GBM level is undetectable. The replacement fluid is usually 4% albumin, but if there is pulmonary hemorrhage or a recent renal biopsy, part

of the replacement fluid should be given as fresh frozen plasma at the end of the exchange, in order to avoid depletion of clotting factors. Patients with anti-GBM disease who require dialysis at the time of presentation and have crescents in 100% of glomeruli should generally not be treated with plasma exchange and immunosuppression, because the likelihood of achieving useful recovery of renal function in this situation is very small compared with the risks of this aggressive form of therapy [1].

- Plasma exchange has been shown to be beneficial in patients with ANCA-associated RPGN who have a serum creatinine greater than 500 μmol/L or require dialysis at presentation [3, 4]. Unlike anti-GBM disease, with ANCA-associated RPGN, meaningful recovery of renal function in dialysis-dependent patients may occur. In patients with ANCA vasculitis and less severe renal failure, plasma exchange is generally not indicated, although the level of severity at which plasma exchange confers a benefit is not evident [4]. Plasma exchange is also recommended for patients with ANCA-associated pulmonary hemorrhage and for patients with RPGN and serology simultaneously positive for both ANCA and antiGBM antibodies. The most common plasma exchange regimen for ANCA-associated RPGN is treatment with seven sessions of plasma exchange (3–4 l) over 2 weeks [3].

Renal Replacement Therapy

In general, the indications for renal replacement therapy and its means of delivery do not differ in patients with glomerulonephritis from other causes of renal failure. Where possible, the integrity of the cephalic veins of the forearms and arms should be preserved as important future vascular access sites in patients at risk of needing future long-term renal replacement therapy. For central venous access, the femoral and internal jugular veins are preferred over the subclavian veins, because of the risk of future development of subclavian venous stenosis, which can limit long-term hemodialysis options.

General and Supportive Care

Nutritional support is important in the care of this group of patients, and proactive measures are required to avoid the development of malnutrition. Careful control of blood pressure to avoid exacerbation of renal injury is important. Fluid balance involving regular bedside assessments as well as monitoring of central venous pressure and hemodynamics is important. Sepsis is a major threat to this patient group, and general infection control measures are essential. Symptoms or signs suggesting infection require rapid evaluation, and the empirical use of broad-spectrum antibiotics is required while awaiting a formal microbiological diagnosis. Exposure to nephrotoxins such as aminoglycosides, nonsteroidal anti-inflammatory drugs, and iodinated contrast should be avoided.

Evaluation and Assessment

General Investigations

Evidence of hematuria and proteinuria are usually found in patients with proliferative forms of glomerulonephritis. Distinguishing between glomerular and non-glomerular morphology of urine erythrocytes is important but interpretation depends on the observer's technical skill and is complicated by previous use of a bladder catheter. Nevertheless, the finding of urinary red cell casts is pathognomonic for RPGN. Although increased levels of serum creatinine and urea indicate reduced renal function, these are insensitive markers. For example, serum creatinine only rises above normal when more than 50% renal function is lost. The role of novel markers of kidney injury such as cystatin C and neutrophil gelatinase–associated lipocalin (NGAL) is still to be established. Inflammatory markers such as C reactive protein and ESR are commonly raised, although these are not specific. Infiltrates on chest X-ray may represent pulmonary hemorrhage or infection.

Serology

Serological tests have a central role in the diagnosis of various forms of glomerulonephritis. The serological test results most likely to influence management are a positive anti-GBM antibody or ANCA result. If RPGN is strongly suspected, these tests should be performed urgently.

The detection of anti-GBM antibodies by ELISA strongly suggests a diagnosis of anti-GBM disease or Goodpasture's syndrome. Antibody levels do not, however, correlate with disease severity, and 10% of patients have no antibodies. "False positives" are rare but occur sometimes with SLE.

ANCA testing is performed by both direct immunofluorescence and ELISA. Immunofluorescence is more sensitive, but ELISA is more specific. There are two ANCA fluorescence patterns. Diffuse cytoplasmic fluorescence (C-ANCA) is typically associated with antibodies directed against proteinase-3 (PR3), and is found in patients with Wegener's granulomatosis. Perinuclear fluorescence (P-ANCA) is present with myeloperoxidase

(MPO) specificity in most patients with microscopic polyangiitis. There is, however, substantial overlap in the clinical presentations of both these conditions.

Testing for antinuclear antibodies (ANA) is highly sensitive for the diagnosis of systemic lupus erythematosus (SLE), although false positive results are common. Positive serology for anti-dsDNA is, in contrast, highly specific for SLE and is commonly found in association with lupus nephritis. Other serological abnormalities that occur in SLE include antibodies against extractable nuclear antigens (ENA) and antiphospholipid antibodies (lupus anticoagulant and antibodies against cardiolipin and β2 glycoprotein).

Antibodies directed against streptococcal antigens are found in patients with post-streptococcal glomerulonephritis. Sensitivity of testing is improved by testing for antibodies against both antistreptolysin O (ASO) and deoxyribonuclease (DNAase) B.

Reduced serum complement levels are commonly observed in patients with immune complex–mediated glomerulonephritis. In most cases, both C3 and C4 levels are reduced. Causes of this pattern include lupus nephritis, cryoglobulinemia, endocarditis, and type 1 idiopathic MPGN. Isolated reduction of C3 with a normal C4 level is consistent with activation of the alternate pathway. This pattern is observed in post-streptococcal glomerulonephritis and type 2 MPGN (also called "dense deposit disease"). Other causes of low serum complement include fat embolism, hemolytic uremic syndrome, severe sepsis, advanced liver disease, and hereditary complement deficiencies.

Renal Biopsy

A renal biopsy is required for definitive diagnosis, classification, and assessment of the severity of glomerulonephritis. The decision if, and when, to perform a renal biopsy is based on the balance of the expected benefit of the information gained versus the risk of complications, with bleeding being the major consideration. Renal biopsy is usually performed percutaneously with real-time ultrasound assistance. If possible, two cores of tissue should be obtained for examination by light microscopy, immunofluorescence, and electron microscopy. Urgent immunofluorescence of fresh tissue is especially valuable for the rapid diagnosis of anti-GBM disease. Some units use immunohistochemistry rather than immunofluorescence although this technique is less sensitive for the diagnosis of anti-GBM disease. Renal biopsy is usually performed under local anesthesia, but a general anesthetic is recommended for children. Alternative techniques are open biopsy, laparoscopic biopsy, and trans-jugular biopsy, but it is not clear that any of these reduces the bleeding risk. Clotting parameters must always be checked and should be normalized before the procedure. Antiplatelet agents should be withheld for 7–10 days if possible. Desmopressin (DDAVP) at a dose of 0.3 mcg/kg can be administered pre-biopsy to reduce the bleeding risk associated with uremic platelet dysfunction. Severe hypertension should be controlled before the biopsy is performed. Transient macroscopic hematuria occurs in 3–18% of patients and is usually self-limiting. Severe uncontrolled bleeding can often be managed by urgent renal arteriography with embolization of the culprit vessel. The risk of nephrectomy post-renal biopsy varies between nephrology units and is about 0.3%, and the mortality rate approximates 0.1%. Potential relative or absolute contraindications to renal biopsy include bleeding diatheses, uncontrolled hypertension, small kidneys (<9 cm), a solitary kidney, and an uncooperative patient.

After-care

Patients with glomerulonephritis require regular follow-up by a renal physician. When they are admitted to the ICU, close co-operation with the renal team is critical. Patients with glomerulonephritis are at risk of progressing to end-stage kidney disease requiring long-term renal replacement therapy. Damage to cephalic forearm and arm veins with intravenous cannulae should be avoided as much as possible, because these represent important options for future hemodialysis access. For central venous access, the internal jugular and femoral veins are preferred over the subclavian veins because of the risk of subclavian stenosis, which can become a major problem for hemodialysis patients. Long-term management of glomerulonephritis may require ongoing immunosuppression, which requires regular review to assess its effectiveness and toxicity. Complications of therapy that require monitoring and treatment include steroid-induced diabetes and osteoporosis. Many patients with glomerulonephritis have associated hypertension, which needs to be expertly controlled to minimize secondary renal injury and cardiovascular risk. Patients in their reproductive years treated with cyclophosphamide frequently become infertile and require specialist assessment and possibly sperm, ovary, or embryo harvesting, before the treatment is commenced.

Prognosis

The prognosis varies markedly for different forms of glomerulonephritis. In the era prior to the development of

effective immunosuppression, patients with RPGN rapidly progressed to end-stage renal failure or death. While the prognosis has improved markedly with current immunosuppression, morbidity and mortality remain substantial. For example, in a series of patients with ANCA-associated vasculitis treated with cyclophosphamide and prednsisolone and followed for 5 years, the mortality rate was 24% and the risk of end-stage kidney disease was 28% [5]. Adverse outcomes are due to ongoing disease activity or the complications of therapy. Post-streptococcal and other infection-associated glomerulonephritides usually resolve with treatment of the precipitating infection, although the prognosis is less favorable in the elderly. In patients who develop chronic kidney disease, predictors of progression include proteinuria, raised serum creatinine at presentation, poorly controlled hypertension, and the demonstration of interstitial fibrosis and tubular atrophy on renal biopsy. All patients with glomerulonephritis require ongoing follow-up by a nephrologist to monitor disease progression and treatment over time.

References

1. Levy JB, Turner AN, Rees AJ, Pusey CD (2001) Long-term outcome of anti-glomerular basement membrane antibody disease treated with plasma exchange and immunosuppression. Ann Intern Med 134:1033–1042
2. Jones RB, Ferraro AJ, Chaudhry AN et al (2009) A multicenter survey of rituximab therapy for refractory antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum 60:2156–2168
3. Jayne DR, Gaskin G, Rasmussen N et al (2007) Randomized trial of plasma exchange or high-dosage methylprednisolone as adjunctive therapy for severe renal vasculitis. J Am Soc Nephrol 18:2180–2188
4. Pusey CD, Rees AJ, Evans DJ, Peters DK, Lockwood CM (1991) Plasma exchange in focal necrotizing glomerulonephritis without anti-GBM antibodies. Kidney Int 40:757–763
5. Booth AD, Almond MK, Burns A et al (2003) Outcome of ANCA-associated renal vasculitis: a 5-year retrospective study. Am J Kidney Dis 41:776–784

Glucose Control

► Diabetes, Insulin Therapy/Glycemic Control

Glucose Modulation

► Diabetes, Insulin Therapy/Glycemic Control

Glutamine

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Synonyms

Alanyl-glutamine dipeptide; GLN

Trade Names

Dipeptiven; Nutrestore

Class and Category

Amino acid, food product, drug

Indications

Glutamine has a long history of intensive care unit (ICU) prescribing worldwide for medical, surgical, trauma, and burn patients based on evidence that it improves clinical outcome, and is a minimal-risk, low-cost intervention. The interest in glutamine supplementation is due to the fact that glutamine is released in large amounts from muscle tissue during catabolic states serving as a vital nutrient source for many cell types and a stress signal inducing key cellular protection pathways (i.e., heat shock protein expression). However, despite this massive release from muscle, plasma levels of glutamine decrease rapidly in critical illness due to limited muscle stores. Admission deficiency in plasma glutamine has been found to be predictive of mortality in the ICU. Glutamine plays a vital and versatile role in many key pathways required for survival from critical illness and injury.

Thus, given the available data every worldwide critical care and clinical nutrition society's guidelines give glutamine a grade "A" recommendation for all patients requiring parenteral nutrition in the ICU. This data is based on 4 level 1 and 13 level 2 randomized controlled trials showing significant reductions in mortality and infectious morbidity in ICU patients. Oral glutamine presently receives a grade "B" recommendation for use in trauma and burn patients to reduce infection and mortality in

these settings. Finally, recent clinical data reveals that glutamine appears to be the first, and at present, the only clinically available therapeutic agent able to induce the protective heat shock protein response to improve outcome in critically ill patients. Currently large clinical trials are studying the use of glutamine as a separately administered "pharmaconutrient" to reduce mortality in critical illness.

Dosage

The greatest clinical efficacy in currently available randomized trials was achieved when doses of 0.5 g/kg/day either orally, enterally, or intravenously were administered. Clinical trials have administered GLN at doses ranging from 10 g/day up to 1.0 g/kg/day. Meta-analysis data reveals the greatest reductions in mortality and infectious morbidity at dosages greater then 0.2–0.3 g/kg. Very few trials show clinical benefit at doses lower than this in an ICU population. Glutamine can be given orally, enterally, or intravenously. Dosing orally/enterally should be at a minimum of 0.5 g/kg/day, typically in divided doses either three or four times daily. Successfully studied enteral doses in trauma and burn injury include 0.5 g/kg/day given continuously or in divided doses every 4–6 h. In markets where intravenous glutamine dipeptide formulations (such as alanyl-glutamine or glycyl-glutamine) are available, the recommended dose is 0.35 g/kg/day (yields 0.2 g/kg glutamine) as a continuous infusion. However, doses as large as 1.0 g/kg/day have been studied in critically ill patients without adverse effect. Glutamine dipeptides are commonly added to complete parenteral nutrition solutions as glutamine is often the only amino acid not included in standard parenteral amino acid preparations. The approved doses in parenteral nutrition solutions in most markets are from 0.35 g/kg to 0.5 g/kg of alanyl-glutamine, which yields 0.2–0.35 g/kg of free L-glutamine.

Preparation/Composition

The most common form of glutamine given in the ICU intravenously is the alanyl-glutamine dipeptide. This form is readily soluble in water and is stable at room temperature for up to 24 months. It is typically available as a 20% solution. L-glutamine solutions are available in some countries. However, these solutions have limited solubility and are available in a maximal concentration of 2.5–3.0%. These solutions also have limited shelf life due to L-glutamine's limited solubility and stability in solution.

Enteral and oral preparations of glutamine are typically made with free L-glutamine and are commercially available worldwide.

Contraindications

In cirrhotic liver failure the significant nitrogen content of glutamine can lead to elevation in ammonia that must be monitored when glutamine is given in this setting. Previous concerns about glutamine administration in head injury have been decreased by data showing that even large intravenous doses of glutamine have not been found to lead to increases in brain glutamate levels.

Mechanisms of Action

There are numerous hypotheses pertaining to glutamine's mechanism of action in the ICU population, and its dramatic release from muscle. It acts as a fuel source for rapidly dividing cells, is a precursor for nucleic acid synthesis, and aids the kidney in acid–base homeostasis. Glutamine also serves as a cell-signaling molecule in catabolic states regulating the expression of genes, and functioning in intracellular signaling pathways, signal transduction, and cell repair/defense. It is likely that glutamine release from muscle serves as a "stress signal" signaling the transcription of genes important for immunity and cellular metabolism.

Induction of Heat Shock Proteins

A central theme in glutamine's beneficial effects involves the induction of heat shock proteins, particularly HSP-70. Through the use of knock-out cells and knock-out animals it has been shown that the capacity to express HSPs is required for glutamine's protection against injury. It has also been shown that administration of glutamine to critically ill patients can enhance their HSP expression, and this increased expression correlates with improved ICU outcome. The mechanism for glutamine-mediated induction of HSP-70 is via the hexosamine biosynthetic pathway (HBP), which is required for glutamine to function optimally. Glutamine utilizes the HBP to modify gene expression via the transcription factors Sp1 and HSF-1. It is likely that the HBP is part of an early cellular protective response; it responds quickly to stress by modifying proteins. Other experiments have shown that the glutamine-mediated induction of HSP-70 is via the hexosamine biosynthetic pathway (HBP). Intravenous glutamine administration has been shown to enhance HSP-70 expression in critically ill patients. This increased expression of HSP-70 was found to be correlated with reduced length of stay in the ICU and reduced ventilator

days. Thus, glutamine can be regarded as the first, and presently the only clinically relevant inducer of heat shock protein expression to improve outcome in critical illness.

Attenuation of Hyperinflammatory Response

In experimental models, glutamine supplementation leads to a decrease in the release of pro-inflammatory cytokines (specifically, IL-6 and TNF-α) following injury or surgery, which correlates with improved survival after infection. This reduced hyperinflammatory response is mediated through glutamine's attenuation of nuclear binding/activation of nuclear factor-kappa B (NF-κB).

Immune Function

The immune system is affected by glutamine intake. Lymphocytes and macrophages metabolize glutamine at a high rate. Cell surface activation markers CD25 [inerleukin (IL)-2 receptor α chain], CD45 RO (leukocyte common antigen), and CD71 (transferring receptor) are dependent on the presence of glutamine for their expression. Monocyte function is hindered when glutamine is deficient. Altered monocyte major histocompatibility complex class II is associated with postoperative infection and sepsis and has been linked to expression levels of human leukocyte antigen on DR locus (HLA-DR expression).

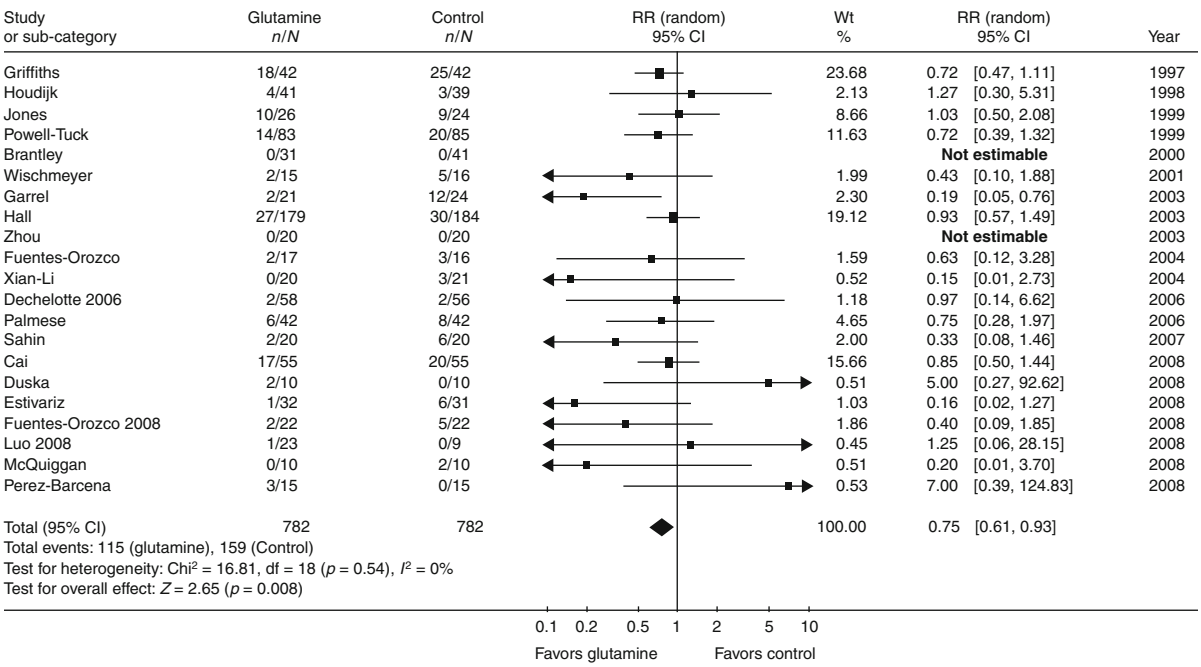
Cellular Metabolism, Mitochondrial Function, Insulin Resistance

Glutamine's relationship to cellular metabolism and mitochondrial function is through its preservation of ATP/ADP and NAD levels in the face of sepsis, shock, and I/R injury. This knowledge has been put to use clinically as glutamine has been tested as a resuscitation fluid in hemorrhagic shock to restore hepatic ATP levels. Experimental work also shows that it plays a role in prevention of apoptosis following injury, likely through the extracellular signal-regulated kinase (ERK) signaling pathway.

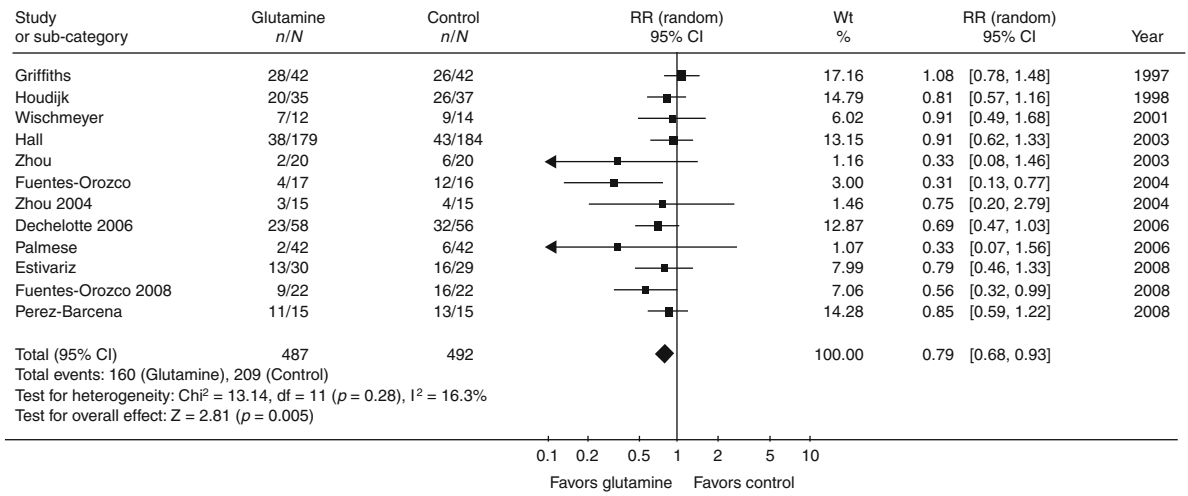
Another contributor to mortality in the ICU is hyperglycemia and insulin resistance. It has been observed that glutamine supplementation can improve parameters of hyperglycemia and reduce insulin requirements, particularly in trauma patients.

Meta-analysis of Glutamine Use in the ICU

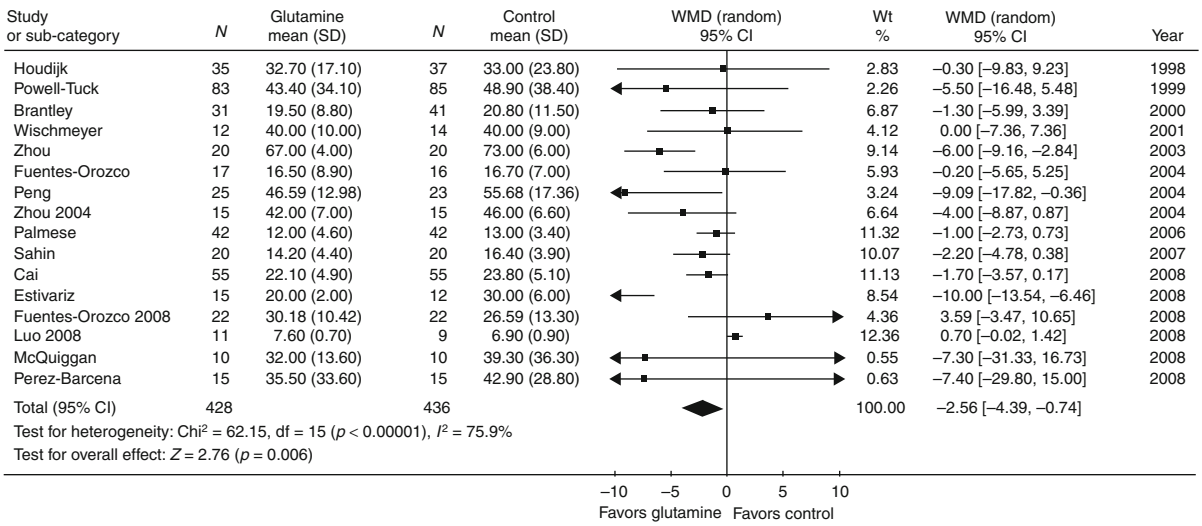
A meta-analysis of all published clinical trials of glutamine in the ICU setting has been conducted and has since been updated on January 31, 2009 (Fig. 1), with the most recent trials of glutamine therapy in critical illness. The new updated data/meta-analysis is available on http://www.criticalcarenutrition.com. This updated work reveals that glutamine given by either the enteral or parenteral route leads to significantly reduced mortality in



Glutamine. Figure 1 Effect of enteral and parenteral glutamine on overall mortality in critical illness



Glutamine. Figure 2 Effect of enteral and parenteral glutamine on infectious complications

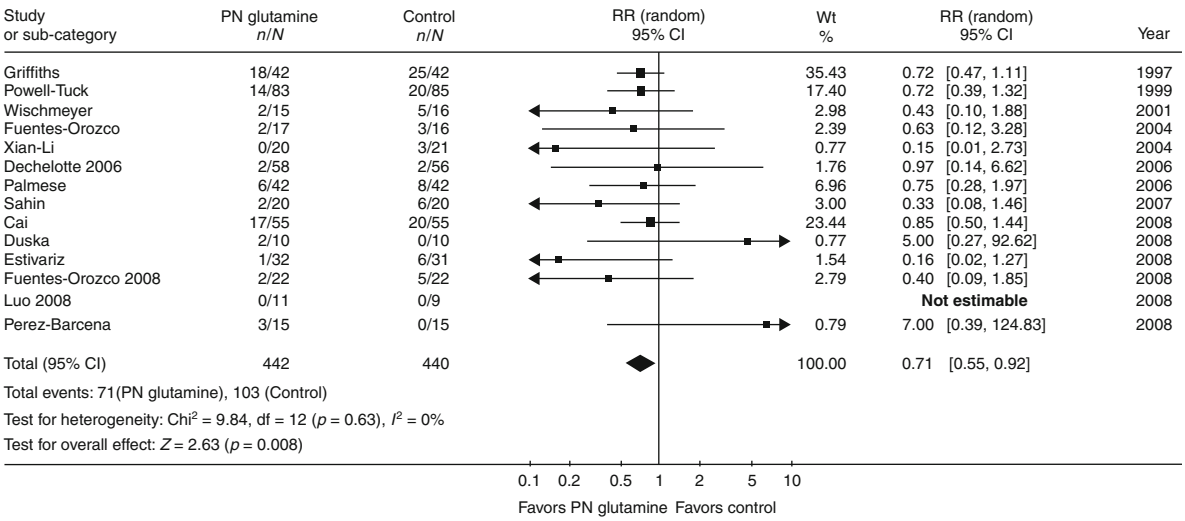


Glutamine. Figure 3 Effect of enteral and parenteral glutamine administration on length of stay

critical illness (RR 0.79, 95% CI 0.61–0.93, $p = 0.008$), and infectious morbidity was also significantly reduced [Fig. 2 (RR 0.79, 95% CI 0.68–0.93, $p = 0.005$)]. Glutamine also led to a 206-day reduction [Fig. 3 (95% CI −4.39, −0.74, $p = 0.006$)] in ICU length of stay. The subgroup of patients requiring parenteral nutrition was analyzed separately. In this group, glutamine led to a 29% reduction in the risk of death [Fig. 4 (RR 0.71, CI 0.55–0.92, $p = 0.008$)].

Summary

Glutamine-deficient patients in the ICU seem unable to generate an HSP response, which may put them at increased risk for a systemic inflammatory response and organ failure. Glutamine has a long history of safe prescribing worldwide and a number of clinical trials (and a meta-analysis) that show that it protects against infectious morbidity and mortality in the ICU. While there have been few trials that did not show a positive effect from glutamine supplementation, there were clear differences between the positive and negative trials. Trials showing positive effects of glutamine therapy gave larger doses, and more often delivered it via the parenteral route. Glutamine is now considered by many to be a "conditionally essential" nutrient in critical illness.



Glutamine. Figure 4 Effect of parenteral glutamine on mortality

References

1. Hamiel CR, Pinto S, Hau A, Wischmeyer PE (2009) Glutamine enhances heat shock protein 70 expression via increased hoxosamine biosynthetic pathway activity. Am J Physiol Cell Physiol 297(6): C1509–19
2. Novak F, Heyland DK, Avenell A, Drover JW, Su X (2002) Glutamine supplementation in serious illness: a systematic review of the evidence. Crit Care Med 30:2022–2029
3. Singleton KD, Wischmeyer PE (2007) Glutamine's protection against sepsis and lung injury is dependent on heat shock protein 70 expression. Am J Physiol Regul Integr Comp Physiol 292(5):R1839–45
4. Weitzel LB, Wischmeyer PE (2010) Glutamine in critical illness: the time has come, the time is now? Crit Care Clin 26(3):515–525
5. Wischmeyer PE (2008) Glutamine: role in critical illness and ongoing clinical trials. Curr Opin Gastroenterol 24(2):190–7, Review

Glutamine Metabolism

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Definition

Glutamine is the most abundant free amino acid in the human body. A large number of tissues and cells of the body utilize glutamine at high rates, and availability of glutamine is essential for their function. It plays a central role in several important functions of the human cell. These functions include:

- Essential metabolic precursor in nucleotide and glucose biosynthesis
- Constituent for proteins – usually 5–10% of the total amino acid content
- Energy substrate for immunocompetent cells and enterocytes
- Precursor for the important excitatory neurotransmitter glutamate in the brain
- A pathway for glutamate transport out of the brain
- Precursor for the antioxidant glutathione
- Interorgan transporter of nitrogen
- A substrate for renal ammoniagenesis and acid-base regulation
- Direct effects on gene expression

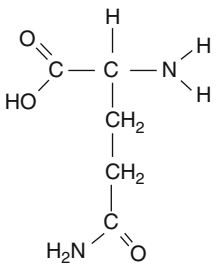
Characteristics

Biochemistry

Glutamine has a molecular weight of 146 Da and is built up from an alfa-ketoglutarate carbon skeleton and two amino groups as illustrated in Fig. 1. As alfa-ketoglutarate is a constituent of the Citric Acid Cycle, glutamine has a fast entry to the aerobic energy production of the mitochondria. Glutamate is built from the same carbon skeleton and hence closely related and easily transformed to glutamine and alfa-ketoglutarate. With removal or addition of amino groups, these three substances are

synthesized from each other as shown in Fig. 2. Hence, glutamine is produced from the combination of glutamate and NH_3 by glutamine synthetase.

Skeletal muscle is the major synthesizer of glutamine in the body, but smaller amounts are also synthesized in other tissues, such as liver, lungs, and astrocytes. The major source for this synthesis is glutamate exported from the liver. The estimated endogenous synthesis rate of glutamine is 50–80 g/day in healthy adults. Plasma glutamine concentration is 0.5–0.8 mmol/L, which is 20–40% of the total free amino acid content in plasma. Glutamine is also the most abundant intracellular free amino acid in many tissues. In skeletal muscles, the intracellular concentration is around 20 mmol/L, which is a lot higher than in other tissues due to its role as glutamine producer. In the basal state, skeletal muscles export all free amino acids, except glutamate. However, in the fed state, this tissue has an uptake of all free amino acids except glutamine, which is constantly exported. Skeletal muscle can even use essential amino acids to produce glutamine [1].



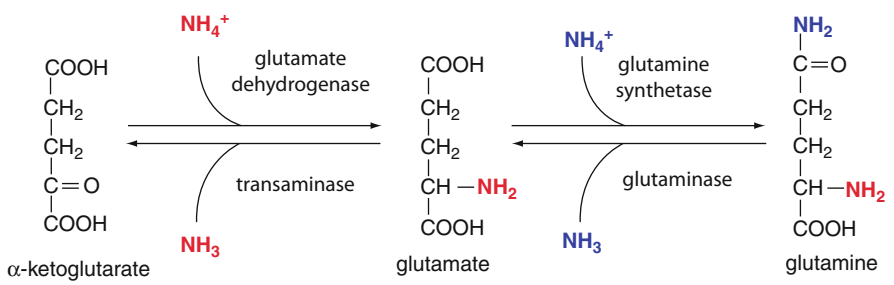
Glutamine Metabolism. Figure 1 Structure formula for glutamine

Energy Substrate

Glutamine is quantitatively the most important energy fuel for rapidly dividing cells such as enterocytes, fibroblasts, and immune cells. Glutamine can be transported into mitochondria via a transport system specific for glutamine and asparagine. There it is metabolized to glutamate by the action of glutaminase, an enzyme found at high concentration in cells which often utilize glutamine. The role of glutamine in energy production is particularly important in cells that can export free ammonia. Glutamine can provide the cell with almost as much energy as glucose, thus it is a valuable energy source.

Most cultured cells in the laboratory use glutamine as an energy substrate, and it is of high importance to cell survival and proliferation in vitro. It is difficult to grow cells in culture medium that does not contain an excess of glutamine. This is probably due to its combined role in energy production and nucleotide synthesis. Especially immunocompetent cells and enterocytes are sensitive to the concentration of glutamine and need it in order to divide in vitro.

Newsholme et al. have proposed the leading theory on the high utilization of glutamine in these cells [2]. They have a high rate of glutamine uptake, high levels of glutaminase, but a low rate of oxidation. This keeps a constant high flow and availability of glutamine in the cells, which at any given moment can be used to highly increase nucleotide and glutathione synthesis. The nucleotides are needed both for DNA as the cells divide and for RNA necessary for protein synthesis. As these are cells that in crucial situations need to multiply rapidly as a response to a challenge at any time, they need to keep the flow of glutamine constantly high also when they are quiescent and do not really need it.



Glutamine Metabolism. Figure 2 Glutamine is synthesized from α-ketoglutarate and glutamate by the action of glutamate dehydrogenase and glutamine synthetase respectively

Nitrogen Transportation, the Liver and the Kidney

The liver is the only organ in the body with the ability to metabolize ammonia into urea, which is nontoxic and can be transported to the kidneys for excretion. Free ammonia from the splanchnic region is hence taken care of when the blood is filtered through the liver. Ammonia from the rest of the body, however, needs to be transported to the liver. As high circulating levels of free ammonia in the general circulation are toxic to the central nervous system, glutamine is used as a nitrogen vehicle.

In astrocytes the ability to synthesize glutamine is normally used to return the glutamate removed from the synaptic cleft back to the neuron where it can be recycled to glutamate. During a state of hyperammonia, this becomes an important protective mechanism for the CNS as glutamine synthesis is a way for the astroglia to remove ammonia from the circulation.

Another destination for the nitrogen is the kidneys, where glutamine is the most important donor of NH_3. Glutaminase cleaves the NH_3 off from the glutamine, creating glutamate. The expression of this enzyme in the kidneys is regulated by pH. The NH_3 is secreted and combines with H^+ in the collecting tubule to form ammonia. The H^+ which is thus gotten rid of comes from renal synthesis of HCO_3. Hence, glutamine metabolism in the kidney is essential for acid-base buffering and maintenance of blood pH. The left over glutamate is converted and enters the gluconeogenesis. Glucose produced from the kidneys accounts for up to 25% of the whole body glucose production.

Glutamine and the Immune System

As discussed above, glutamine is utilized at high rates by several cells of the immune system, including lymphocytes, macrophages, and neutrophils, and crucial for their function. Depletion of glutamine leads to a G0/G1 phase arrest of these cells' proliferation. Glutamine supplementation has been shown to attenuate proinflammatory cytokine release in experimental endotoxemia and reduce the immunosuppression induced by surgery. The understanding of the mechanisms involves increases over time.

Glutamine availability has been reported to be necessary for many functions of immune cells, such as T-cell proliferation, B-lymphocyte differentiation, expression of key lymphocyte cell surface markers such as CD25, macrophage phagocytosis, antigen presentation and cytokine production (IL-1, IL-2 IL-6, TNF-α, IFN-γ) plus neutrophil superoxide production, and delaying or preventing apoptosis [3]. Whereas lack of glutamine reduces lymphokine-activated killer cell activity and impairs cellular stress response.

In septic patients, there is a considerable decrease in the number of functional phagocytes. As they play an important role in antigen presentation and T-cell activation, this can have serious effects for the patient. In vitro studies have shown that a lack of glutamine, equal to the low concentrations found in critically ill patients, downregulates several important surface and adhesion molecules in monocytes in a concentration-dependent manner. These finding was paralleled by a diminished capacity of antigen presentation to T-cells. Reduced glutamine concentrations also led to a decreased phagocytic capacity of the monocytes [2].

Apoptosis

Glutamine depletion has been shown to modulate apoptosis in a large number of cell types. In cell cultures of enterocytes, it has been found that glutamine inhibits apoptosis via the extrinsic, death receptor, pathway in a dose-dependent manner by preventing activation of or suppressing caspases and kinases involved in the signalling of the receptor [3]. In cultivated T-cells, glutamine has been found to significantly downregulate the expression of Fas and Fas ligand, upregulate the anti-apoptotic protein Bcl-2, and decrease activity of caspases, hence protecting them from apoptosis. Studies of neutrophils have also shown that glutamine provision decreases expression of pro-apoptotic proteins and increases expression of anti-apoptotic proteins also in these cells.

Glutathione and Heat Shock Proteins

Experimentally, glutamine availability protects the gastrointestinal mucosa and cardiomyocytes following ischemia/reperfusion. Some of the cell protective effects of glutamine may be mediated by heat shock proteins, which have been shown to be expressed at a lower rate in glutamine deficiency, but enhanced when glutamine is available. These proteins are essential to cellular survival under stressful situations. Both in vitro and in vivo studies show that glutamine is a potent enhancer of heat shock protein 72, Hsp72, which in turn downregulates cytokine expression. Also the expression of Hsp70 has been shown to be connected to glutamine concentrations as reduced levels of glutamine significantly impaired Hsp70 expression in cultured immune cells. Hence, glutamine-starving cells are unable to express normal amounts of Hsp70. One study indicates that this depends on a tremendously shortened half-life of Hsp70 mRNA (less than 20% of the

half-life in normal glutamine levels). In vivo studies have shown that glutamine-mediated Hsp70 induction in sepsis and shock is tissue dependent, liver shows almost no induction, whereas heart and lung get a significant increase following glutamine treatment.

Glutamine is also a precursor for glutathione, important as an antioxidant and protecting cells from apoptosis. In postoperative patients, glutamine has been shown to attenuate the depletion of glutathione in skeletal muscle induced by surgery [3]. It can also preserve hepatic glutathione levels after liver injury. In vitro cells damaged by reactive oxygen species has shown a restoration of mitochondrial structure and metabolism when incubated with glutamine. The cell death seen in hyperoxia is preceded by a degeneration of the mitochondria. Glutamine protected mitochondria and other cellular structures in cells exposed to hyperoxia. Although the mechanisms behind this are not fully understood, findings imply that glutathione and ATP production play important roles.

The cultured cells exposed to hyperoxia doubled their glutamine consumption compared to normal oxygen conditions. In addition, it was demonstrated that glutamine can protect the TCA cycle enzyme alfa-ketoglutarate dehydrogenase from inactivation under oxidative stress. Hence, glutamine can prevent a loss of ATP that is seen in cells with glutamine depletion exposed to hyperoxia. It has been suggested that this available ATP could then be used by the cell for homeostatic, protective, and repair mechanisms. These mechanisms could be important in ICU patients in need of respiratory aid and high concentrations of oxygen to retain O_2 saturation.

Another method for the cytoprotective effect of both Hsp and glutamine seems to be influencing ion transport across the cell membrane and maintaining the intracellular ion milieu, another ATP-demanding action.

Intestine

Several animal studies report that glutamine prevents bacterial translocations by maintaining integrity of the mucosal barrier of the intestines. This is done by increasing DNA and protein synthesis, villous height, and mucosal proliferation leading to a decrease in mucosal permeability. In vitro studies have shown that glutamine is involved as an activator in signal transductions pathways of growth factors in epithelial intestine cells regulating expression of genes involved in cell division and inflammation [3].

Insulin and Pancreatic Beta Cells

Pancreatic islet cells can metabolize glutamine at high rates. Recent studies have shown that glutamine influences (enhances) insulin secretion and gene expression in the beta cells. Some of the genes regulate code for ion channels, metabolic enzymes, and protein kinases and phosphatases involved in insulin secretion. It has also been shown to be involved in the metabolic mechanisms mediating insulin resistance in the glucose transport system in the way of attenuating insulin-desensitization in intensive care unit patients. Presumably, glutamine improves adipose tissue insulin sensitivity.

Metabolic Stress

Although glutamine is a nonessential amino acid, it has been shown that critically ill patients have a relative lack of glutamine, and that glutamine supplementation in parenteral nutrition to these patients improves both mortality and morbidity [4]. Metabolic stress, such as severe trauma or infection, major surgery, or multiple organ failure, causes an increased export of glutamine from skeletal muscle which in turn causes an intracellular depletion of glutamine in the muscle. Studies have observed that glutamine synthetase expression increases greatly, whereas glutaminase activity remained constant in skeletal muscle during sepsis. Despite the increase in glutaminase activity, the rate of release exceeds that of synthesis. One of the factors behind this is cortisol, which is known to upregulate glutamine synthesis in skeletal muscle.

ICU patients have a profound depletion that often goes down to 20% of the normal level already on the first day in the ICU and then remains unaltered during the entire ICU stay. In these patients, glutamine is considered a conditionally essential amino acid. When giving glutamine supplementation to critically ill patients, the subject of enteral versus parenteral administration has been widely discussed. To patients receiving parenteral nutrition, glutamine supplementation is considered the standard of care. However, when it comes to enteral nutrition, there is no conclusive evidence for the benefits of glutamine supplementation. One reason for this may be the high fraction of first path elimination through the splanchnic area. Most of the glutamine provided enterally is utilized by enterocytes and immunocompetent cells in the intestine. Then more is taken up as the blood passes through the liver and only a fraction of the originally given dose appear in the general circulation. In contrast parenteral administration provides a wide distribution to the whole body in relation to the blood flow to the different tissues and organs.

In the future, it has been suggested to use plasma glutamine concentration at admission to the intensive care unit as a prognostic marker and an indicator for the need of glutamine supplementation.

References

1. Roth E (2008) Nonnutritive effects of glutamine. J Nutr 138 (10):2025S–2031S
2. Newsholme P et al (2003) Glutamine and glutamate – their central role in cell metabolism and function. Cell Biochem Funct 21(1):1–9
3. Curi R et al (2007) Glutamine, gene expression, and cell function. Front Biosci 12:344–357
4. Wernerman J (2008) Clinical use of glutamine supplementation. J Nutr 138(10):2040S–2044S

γ-Glutamyl Transpeptidase

► Tubular Enzymuria

α-Glutathione S-Transferase

► Tubular Enzymuria

π-Glutathione S-Transferase

► Tubular Enzymuria

Goal-Directed Resuscitation

► Goal-Directed Therapy

Goal-Directed Therapy

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Synonyms

Goal-directed resuscitation; Hemodynamic optimization; Quantitative resuscitation

Definition

A management strategy for patients with inadequate oxygen delivery that applies an algorithmic approach to correct key hemodynamic variables at a proximal point of the treatment process.

Characteristics

► "The consumption of oxygen is the essence of life. Thus, one of the fundamental aspects of critical care medicine is to recognize and reestablish global tissue normoxia to maintain the natural order of cellular homeostasis in our patients."

Emanuel P. Rivers, M.D.
Journal of Critical Care
2008; (23): 604

Introduction

Early goal-directed therapy (EGDT) is a management strategy for patients with critical infections, applying an algorithmic approach to correct key hemodynamic variables at a proximal point of the treatment process. This can occur in the Emergency Department (ED) in the case of patients presenting from the community or on the wards, in the operating rooms, and in intensive care units (ICUs) in patients who develop their infections while hospitalized. To understand the rationale for and efficacy of EGDT, it is important to have a general understanding of infectious disease and the continuum of severity of disease.

It is unknown how many people develop an infection from a bacterium, virus, or fungus each year. The majority of these infections are asymptomatic but a significant percentage cause symptoms that make the person aware that their body is fighting an infection. A continuum exists between asymptomatic infection and life-threatening disease. Sepsis occurs when a person has a source of infection and the body mounts a protective response to that infection in an attempt to eliminate the infectious source. The body's protective response has been described as the systemic inflammatory response syndrome (SIRS) and can be identified by the presence of common signs of inflammation: core body temperature $<36°C$ (96.8°F) or $>38°C$ (100.4°F); heart rate >90 beats per minute (BPM); a respiratory rate >20 breaths per minute; a white blood cell (WBC) count $<4{,}000/\mu L$ or $>12{,}000/\mu L$ or with $>$ 10% immature cells. If the patient has two or more of these SIRS criteria in response to an infection, the patient has sepsis. If an infection and the body's response to that infection produce organ dysfunction, the patient has severe sepsis. If the illness progresses to the point of

ongoing hypotension, classified as a systolic blood pressure (SBP) <90 mmHg despite adequate volume resuscitation, the patient has septic shock. Different management strategies are needed as the severity of disease moves along this continuum, and EGDT has emerged as one of the cornerstones for the management of patients with severe sepsis and septic shock.

It has been estimated that 750,000 patients have severe sepsis or septic shock each year in the USA and the overall mortality is 30%. A similar number occur each year in Europe. The incidence of severe sepsis is increasing as the population ages, more patients live longer with severe comorbidities, and the number of patients on chronic immunosuppressive therapy increases. Forty percent of patients with severe sepsis originate in the community and are admitted to the hospital through the ED; the other 60% develop severe sepsis while hospitalized, either as a progression of already present infection or the emergence of infections, especially in the postoperative setting.

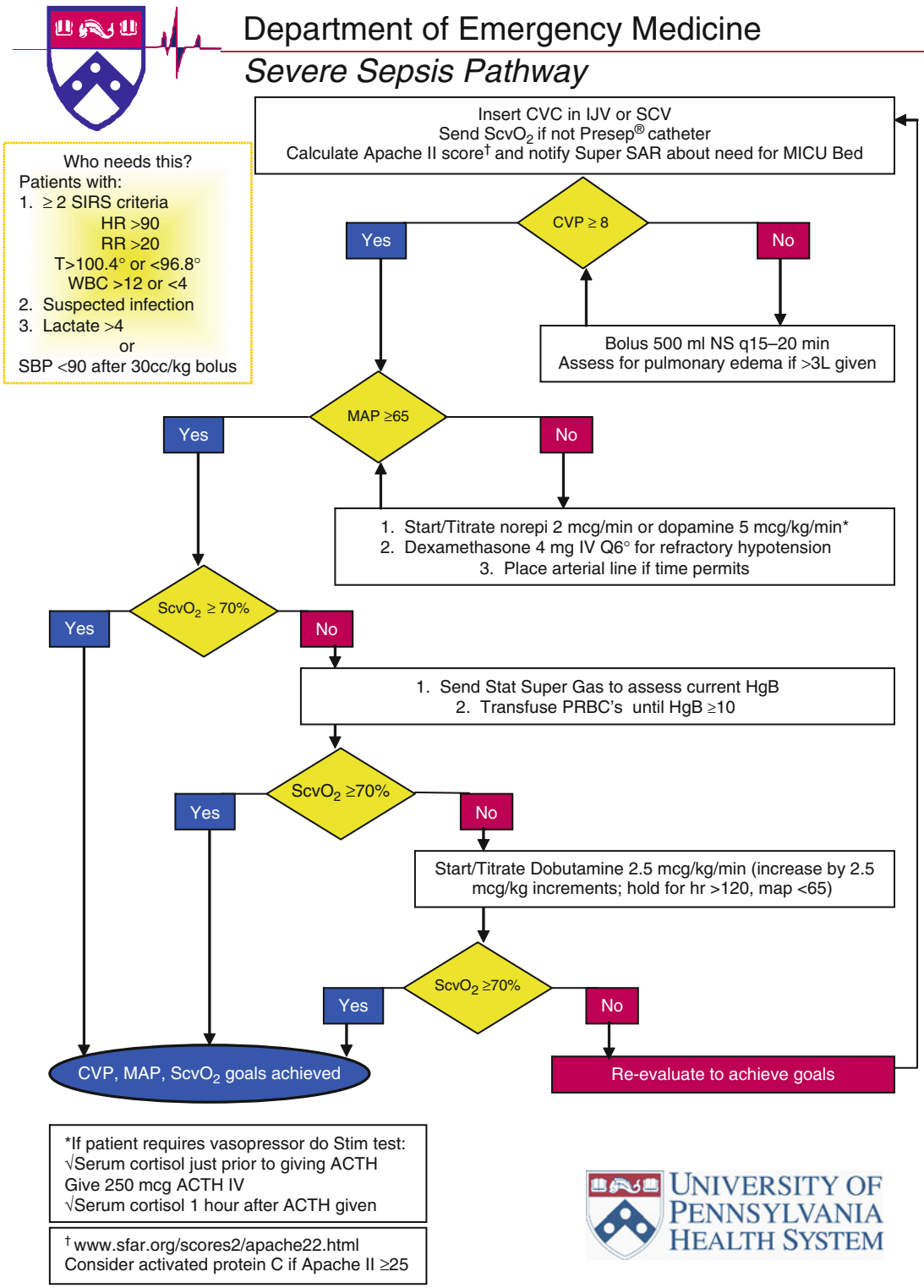
Antibiotic therapy and supportive care are the key components of the management of patients with sepsis. The intensity of therapy required increases as the patient moves along the continuum of severity of illness. When an imbalance between oxygen delivery and oxygen consumption occurs, tissue-level hypoperfusion and shock ensue. Hypoperfusion can manifest itself as increased production of lactate or as hypotension. With the development of shock, sepsis becomes a time-sensitive disease and rapid intervention is required.

Conceptualizing Early Goal-Directed Therapy

The concept of EGDT grew out of insights from hemodynamic optimization trials in high-risk surgical patients. Dr. Shoemaker observed that patients admitted for high-risk valve replacement surgery had unacceptably high mortality. He hypothesized that the patients would do better if their hemodynamics were optimized prior to the physical stress of surgery. Using invasive monitoring, Dr. Shoemaker attempted to increase oxygen delivery to supratherapeutic values in a systematic fashion. This approach lowered mortality in this patient cohort from 33% to 4% [1]. Subsequent studies attempting to apply a similar approach to a mixed group of critically ill ICU patients showed no efficacy to a hemodynamic optimization strategy. Dr. Gattinoni and colleagues randomized more than 750 ICU patients to receive either normal therapy, therapy targeting supranormal cardiac output (CO), or therapy normalizing oxygen delivery, measured by mixed venous oxygen saturation (SvO_2). No difference was seen between the three groups. However, the patients enrolled in Dr. Gattinoni's trial had been in the ICU for at least 24 h and, on average, had already attained the resuscitation goals related to central venous pressure (CVP), mean arterial pressure (MAP), and SvO_2. It can be argued that when aggressive, targeted therapy is applied to an already optimized patient population, the risk of the therapy will outweigh the potential benefits because the patients are no longer in a supply-dependent phase of oxygen consumption.

The 1999 ACCM guidelines for the management of patients with severe sepsis and septic shock suggested several hemodynamic goals in this patient population including pulmonary artery occlusion pressure of 12–15 mmHG, adequate MAP, preload, and contractility; however, these guidelines were largely based on expert consensus because of a lack of clinical trials. In 2001, in *The New England Journal of Medicine*, Dr. Rivers and colleagues published their landmark study on EGDT, which revolutionized the approach to treating patients with severe sepsis and septic shock [2]. Dr. Rivers and colleagues designed a study to test a number of insights into severe infections: (1) severe sepsis and septic shock are time-dependent diseases and a window of opportunity exists to reverse pathophysiologic changes developing at the organ and tissue levels before damage becomes irreversible; (2) when severe sepsis and septic shock patients present to the ED, they are often in a supply dependent phase of oxygen consumption and will consume more oxygen if supplied; (3) serum lactate levels can be used to identify patients with severe tissue-level hypoperfusion who have not yet developed SBP criteria for shock.

The trial published by Dr. Rivers and colleagues is a single-center, randomized, partially blinded trial of standard therapy compared to an algorithmic, goal-directed hemodynamic optimization strategy in patients with severe sepsis or septic shock. To qualify for the trial, patients had to have a suspected or confirmed source of infection, at least two SIRS criteria as a marker of sepsis, organ dysfunction, and either a lactate ≥ 4 mmol/L as a marker of tissue-level hypoperfusion or an SBP ≤ 90 mmHg after a fluid challenge of 20–30 cc/kg over a 30 min period. It is important to emphasize that a novel approach of the EGDT enrollment criteria was the use of serum lactate as a marker of tissue-level hypoperfusion, organ dysfunction, and impending cardiovascular collapse. For both groups adequate IV access was obtained, supplemental oxygen was delivered (including intubation if clinically indicated), a central venous catheter (CVC) and arterial pressure monitoring catheter (a-line) were placed; antibiotics were administered and source control was pursued as indicated.



Goal-Directed Therapy. Figure 1 The hospital of the University of Pennsylvania's severe sepsis pathway

Specifics of the Protocol

In the trial, 263 patients were enrolled. For the 133 randomized to standard therapy the following were addressed: CVP was checked at some time in their ED course and attempts were made to increase the CVP to 8–12 mmHg; a MAP of >65 mmHg was targeted; a urine output of >0.5 mL/kg/h was pursued using IV fluid boluses. The patients were transferred to the ICU when a bed became available. For the 130 patients randomized to the EGDT group, a 6-h algorithmic resuscitation strategy addressing hemodynamic goals in a systematic fashion was pursued and the patients remained in the ED the entire 6 h. The first hemodynamic variable addressed was CVP, as a marker of preload. If the CVP was <8 mmHg, IV boluses of crystalloid solution were given. After adequate volume resuscitation, MAP, as a marker of appropriate afterload, was addressed, with a target goal of 65–90 mmHg. Inappropriately low MAP was corrected with vasopressor infusion; inappropriately high MAP was treated with vasodilators. The third hemodynamic variable addressed was the central venous oxygen saturation ($ScvO_2$), a marker of the balance between oxygen delivery and oxygen consumption. This variable was not addressed at all in the standard therapy arm. In the EGDT arm of the trial, if the patient's $ScvO_2$ was $\leq 70\%$, packed red blood cells (pRBC) were transfused to increase the patient's hemoglobin (Hgb) to ≥ 10 mg/dL. If an Hgb level of ≥ 10 mg/dL already existed, an inotrope was started.

After 6 h of algorithmic care, the patients were transferred to the ICU where the ICU physicians were blinded to which study arm the patients were enrolled in. Using this resuscitation strategy, Rivers and his colleagues demonstrated a 16% absolute reduction in in-hospital mortality in patients treated with EGDT versus standard therapy (46.5% vs 30.5%). This survival benefit remained at 28 and 60 days after treatment. The mortality benefit of EGDT was twofold: (1) EGDT patients had a 50% reduction in sudden cardiovascular collapse as a cause of death, 12/117 (10.3%) vs 25/119 (21.0%); and (2) post-hoc analysis of stored serial blood samples from the EGDT trial demonstrated significant reductions in inflammatory markers associated with progression of organ dysfunction and these reductions were noted as early as 3 h after the onset of therapy [3]. This suggests that early restoration of tissue-level perfusion is an immunomodulatory intervention.

Significant differences between the EGDT and standard therapy groups during the first 6 h of care included: (1) crystalloid infusion, EGDT, 5.0 L vs standard therapy, 3.5 L; (2) inotropes, EGDT, 13.7% versus standard therapy, 0.8%; and (3) pRBC transfusion, EGDT, 64.1% vs 18.5%.

The potential for a significant reduction in severe sepsis mortality demonstrated in this single center trial was acknowledged in the Surviving Sepsis Campaign's (SSC) 2004 recommendations for the initial resuscitation bundle, which gave EGDT a high priority (see Fig. 1 for an example of a hospital's EGDT protocol). The same level of evidence was assigned to EGDT when the SSC guidelines were revised in 2008 [4].

Controversies

Significant controversy has surrounded the translation of the EGDT algorithm used in the original trial to the management of severe sepsis patients in diverse settings. These concerns include: (1) the level of evidence assigned by the SSC to a single center trial, (2) the contribution of each step of the algorithm to patient outcomes, and (3) the generalizability of results to patient populations at increased risk for severe sepsis (transplant; oncology patients receiving chemotherapy; need for immediate surgical intervention) who were excluded from the original trial.

Pooled data of EGDT implementation studies (either without controls or with historic controls) have demonstrated similar mortality reduction as the original trial; the SSC's initial publication addressing increased worldwide compliance with their resuscitation and management bundles demonstrated significant mortality reduction (37% prior to initiation; 31% after) when the bundles, including EGDT, were employed [5]. A recent trial by Jones et al. demonstrated the non-inferiority of a goal-directed resuscitation strategy substituting lactate clearance for $ScvO_2$ as the third resuscitation goal [6].

An NIH-funded, multicenter, three-arm trial comparing EGDT as performed in the Rivers et al. trial to less-invasive, protocolized care to standard therapy, known as the Protocolized Care in Emergency Department Septic Shock (ProCESS) trial, began enrolling patients in January 2008. The trial hopes to test the survival benefit seen with protocolized care.

Conclusions

Several fundamental insights from the original EGDT trial remain central to currently accepted "standard of care" for managing patients with and improving outcomes from severe sepsis and septic shock: (1) early recognition of severity of illness, (2) implementing aggressive resuscitation at the most proximal phase of critical illness, (3) systematically targeting specific resuscitation goals in an algorithmic fashion, (4) increasing oxygen delivery during the supply-dependent phase of critical infections reverses shock, limits

inflammation, and prevents sudden cardiovascular collapse. Further investigations are needed to refine EGDT, define the importance of different hemodynamic resuscitation goals, and elucidate the optimal resuscitation strategy for severe sepsis and septic shock.

References

1. Shoemaker WC et al (1998) Prospective trial of supranormal values of survivors as therapeutic goals in high-risk surgical patients. Chest 94(6):1176–1186
2. Rivers E et al (2001) Early goal-directed therapy in the treatment of severe sepsis and septic shock. NEJM 345(19):1368–1377
3. Rivers EP et al (2007) The influence of early hemodynamic optimization on biomarker patterns of severe sepsis and septic shock. Crit Care Med 35(9):2016–2024
4. Dellinger RP et al (2008) Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock. Crit Care Med 36(1):296–327
5. Otero RM et al (2006) Early goal-directed therapy in severe sepsis and septic shock revisited: concepts, controversies, and contemporary findings. Chest 130(5):1579–1595
6. Jones AE et al (2010) Lactate clearance vs. central oxygen saturation as goals of early sepsis therapy: a randomized trial. JAMA 303 (8):739–746

"Golden Hour" in Trauma Management

► Initial Trauma Management: Primary Survey

Goodpasture's Disease

► Pulmonary-Renal Syndrome

Group A Streptococcal Toxic Shock in Gynecology

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Synonyms

GAS in gynecology

Definition/Diagnosis

Group A streptococcus (GAS) is a common cause of both pharyngitis and skin and soft-tissue infections. It can also occasionally be the causative agent of overwhelming sepsis in the general medical as well as the obstetric and gynecologic patient population in which it produces a toxic shock syndrome which shares some similarities to staphylococcal toxic shock syndrome. GAS is an uncommon cause of bacteremia and a rare cause of sepsis and shock, accounting for just over 10,000 cases of invasive disease and roughly 1,700 deaths in the United States during 2003 [1]. However, sepsis due to GAS and toxic shock syndrome (TSS) is the most severe form of GAS infection, the latter of which is mediated by toxin releasing group A streptococcus. GAS infections appear to have been a frequent cause of mortality long before the understanding of microbiologic origins of infections. Peurperal sepsis, likely caused by GAS, has been recorded as early as 500BC but became epidemic in the mid 1600s. This coincided with the centralization and "modernization" of obstetric care which transformed the process of childbirth from home birth with a lay provider to a hospital birth attended by clinicians. For approximately the next 200 years, women succumbed to child bed fever in staggering proportions. During this time, reports suggest that as many as 10% of women died in childbirth from childbed fever [1]. Since the development of modern germ theory, the introduction of significant improvements to basic hand hygiene, and the discovery of antibiotics, the rate of GAS sepsis decreased dramatically. In recent years, however, there appears to have been a resurgence of severe cases secondary to Group A Strep in obstetrics for unclear reasons.

A case of Group A streptococcal toxic shock is defined as the isolation of this pathogen combined with clinical evidence of toxic shock syndrome. TSS is a syndrome of hypotension combined with the presence of two of the following: renal impairment, coagulopathy, liver abnormalities, adult respiratory distress syndrome (ARDS), generalized erythematous macular rash with occasional desquamation, soft tissue necrosis including necrotizing fasciitis, myositis, and tissue gangrene. TSS plus the presence of GAS isolated from a normally sterile source is defined as a definite case whereas GAS isolated from a non sterile site (throat, vagina, skin lesion) is defined as a probable case [2].

Group A Streptococcus is an exotoxin-producing, gram positive cocci which causes a wide variety of illnesses including strep pharyngitis as well as aggressive skin and soft tissue infections. The virulence of GAS is attributed to a variety of factors, most importantly the production of

a toxin. The antiphagocytic M protein expressed on the surface has properties which aid the pathogen in avoiding destruction by the host immune system. GAS can also produce a pyrogenic exotoxin which induces cytokine synthesis, leading to fever and increased susceptibility to endotoxins as well as serving to suppress the host immune response. Additionally, the M protein may act as a super antigen, further amplifying the systemic response to the infection. The resurgence of cases of GAS invasive infections are theorized to be due to shifting antigenicity of the M proteins to more virulent subtypes. Infection may present following an obvious breach of epithelium or mucosa such as after vaginal delivery, cesarean section, hysterectomy, or other major gynecologic surgery. Patients may also occasionally present without any obvious antecedent trauma or injury in addition to the fact that cases following viral illnesses such as varicella and influenza have also been reported. While GAS pharyngitis is common, rarely does GAS toxic shock syndrome follow GAS pharyngitis. GAS was traditionally thought to affect those at the extremes of age. However, newer reports have shown that GAS is seen in all age groups with pertinent risk factors being age dependent. GAS in young adults to middle-aged people is most commonly associated with IV drug use, HIV, and puerperal sepsis. Risk factors in patients over 40 include burns, immunosuppression, and diabetes mellitus. Importantly, several reports of nosocomial infections and outbreaks have been linked to healthcare workers who were subsequently noted to be GAS carriers [2].

Pain is the most common presenting symptom in GAS toxic shock. One fifth of patients will report a flu-like prodrome with fevers, chills, nausea, and vomiting 1–2 days prior to the onset of sepsis. Most patients report sudden onset, severe pain which typically is out of proportion to the physical findings on exam, and often develops before any other clinical signs. Fever is another of the most common early signs of TSS. The majority of patients also manifest signs of soft tissue infection including erythema and induration at the site of infection which may progress over hours to dusky appearing tissue and bullae. Patients with progressive GAS invasive infection will commonly develop hypotension and multi-organ failure in a very rapid manner after initial presentation. Because early symptoms of GAS sepsis and toxic shock syndrome are vague and nonspecific, clinicians must remain vigilant for the rare cases of GAS sepsis and TSS that occur. Patients with GAS TSS quickly develop toxin mediated sepsis and require prompt, aggressive resuscitation and surgical debridement of the infected area as well as the use of broad- spectrum antibiotics.

Treatment

Survival of patients with GAS sepsis and toxic shock syndrome is dependent upon aggressive surgical resection of the necrotic tissue, rapid commencement of broad spectrum antibiotics, and prompt supportive care with aggressive fluid rescusitation and use of vasoactive agents for hemodynamic support as needed. This aggressive surgical resection often means urgent lifesaving hysterectomy and/or extensive skin and soft tissue resection. Septic-appearing patients in whom there is a suspicion of GAS should be evaluated carefully for a possible source of infection. If there is evidence of skin or soft tissue involvement or any evidence of necrotizing fasciitis, surgical debridement should be undertaken without delay and should be managed as described in the section on necrotizing fasciitis. Aggressive supportive care should be started immediately and often coincides with making the diagnosis of GAS TSS.

Broad spectrum antibiotics should be promptly started in cases of septic shock and tailored based on culture results. All cases of sepsis without a clear source should be evaluated for possibility of Group A Strep TSS and appropriate coverage should be instituted. For patients with known GAS TSS, most studies recommend a beta-lactam agent in combination with clindamycin. Clindamycin is used for both its antimicrobial and anti-inflammatory/antitoxin properties. Antibiotics can be tailored when the culture results produce sensitivity profiles. Duration of therapy should be individualized for each case, but should be continued for a minimum of 14 days.

References

1. Bisno A, Stevens DL (2000) *Streptococcus pyogenes*, Chapter 186. In: Mandell GL, Bennet JE, Dolin R (eds) Principles and practices of infectious diseases, 5th edn. Churchill Livingstone, Philadelphia, pp 2101–2116
2. Gibbs RS, Sweet RL (eds) (2002) Toxic shock syndrome, Chapter 11. In: Infectious diseases of the female genital tract, 4th edn. Lippincott Williams & Wilkins, Philadelphia, pp 317–336

GRVs

▶ Gastric Residuals

αGST

▶ Tubular Enzymuria

πGST

► Tubular Enzymuria

Guideline-Based Sepsis Therapy

► Sepsis: Management, Including Sepsis Bundles

Guidelines

► Resuscitation Endpoints

Gustilo-Anderson Type IIIB or IIIC Open Fracture

► Mangled Extremity

Gut Dysfunction

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Synonyms

Intestinal barrier dysfunction; Intestinal failure; Leaky gut

Definition

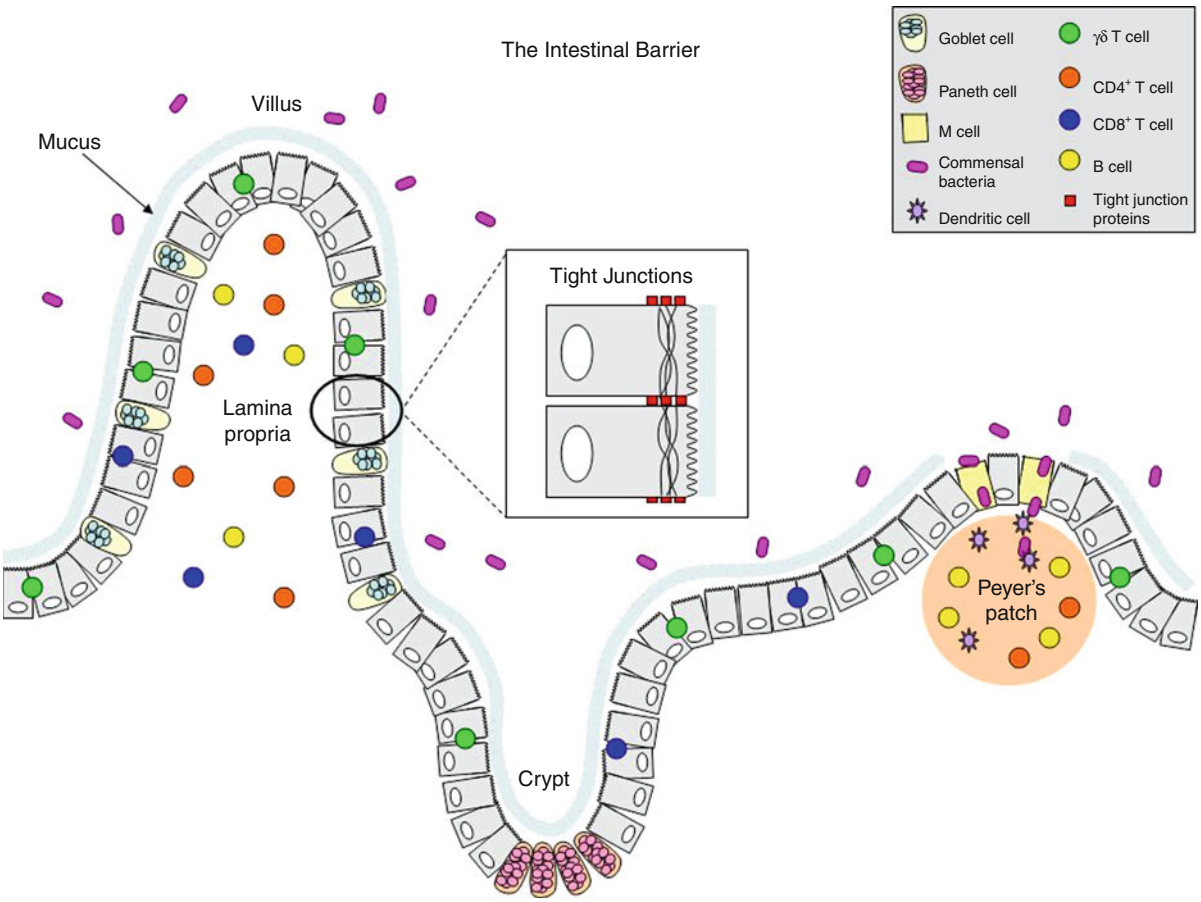
Gut dysfunction is a frequent occurrence among critically ill patients and is thought to contribute significantly to morbidity and mortality. Despite this, there is no uniform, objective, clinically relevant definition of gut dysfunction. Furthermore, none of the scoring systems used to assess organ dysfunction and severity of illness take gastrointestinal function into account. Therefore, a clear objective definition of gut dysfunction is warranted. This article will focus on the pathophysiology, clinical features, and management of gut dysfunction in critical illness.

The gut has been hypothesized to be the "motor" of multiple organ dysfunction syndrome (MODS) for more than two decades. As critical care research has evolved, numerous studies have further defined how the gut plays a role in the origin and propagation of critical illness. The gastrointestinal tract has several important functions which can influence the clinical outcome of critically ill patients. First, digestive functions are performed by the intestinal epithelium. Absorption of nutrients by the epithelium is necessary for host well-being; however, the presence of nutrients in the gastrointestinal tract is also essential for maintaining intestinal integrity. This is highlighted by the observation that provision of enteral nutrition and specific nutrients such as glutamine attenuates increased intestinal permeability seen in critically ill patients. Secondly, the gut functions as a barrier to protect against invasion of potentially harmful antigens. In addition, the gut is home to an enormous number of bacteria, and can be a source of infections among critically ill patients. Lastly, the gastrointestinal tract is the largest lymphoid organ in the body, and therefore plays an important role in the immune response of critically ill patients.

The Normal Intestinal Barrier

The gut, in broad terms, is comprised of portions of the gastrointestinal tract ranging from the mouth to the anus. It contains the esophagus, small intestine (duodenum, jejunum, and ileum), colon, and rectum. Within the gut, there are three entities: the epithelium, the mucosal immune system, and the commensal microflora (Fig. 1). Each of these components interacts in a tightly regulated complex ecosystem that is under constant surveillance [3].

The Epithelium. The epithelium of the gastrointestinal tract represents the largest body surface in contact with the outside world. This mucosal lining consists of a single layer of columnar epithelial cells that are constantly renewed from multipotent stem cells. This has been best studied in the small intestine, where stem cells originate in the crypts of Lieberkühn. These stem cells give rise to four major epithelial lineages: absorptive enterocytes, mucous-producing goblet cells, enteroendocrine cells, and Paneth cells, which function in host defense. Over the course of a 3–5 day lifespan, enterocytes, goblet cells, and enteroendocrine cells migrate upward along the crypt-villus axis where they differentiate and ultimately die of apoptosis or are exfoliated as a whole into the lumen. In contrast, Paneth cells migrate downward over the course of 5–8 day to the crypt base where they reside for approximately 3 weeks. Each epithelial cell is in intimate contact with its neighbors, and the integrity of the epithelium is maintained by apical junctional complexes.



Gut Dysfunction. Figure 1 The intestinal barrier in the distal small intestine. The epithelium, immune cells, and commensal bacteria work together to prevent invasion of potentially harmful substances

Tight junctions are the most apical components of the complex and create a dynamic barrier to the paracellular movement of water, solutes, and immune cells.

The mucosal immune system. The gut-associated lymphoid tissue is the largest lymphatic organ in the body and is composed of four distinct compartments: Peyer's patches, mesenteric lymph nodes, the lamina propria, and intraepithelial lymphocytes (IELs). Importantly, the intestinal lymphoid cells secrete cytokines and other mediators that stimulate and regulate the mucosal immune system. The mucosal immune system has three main functions: (1) to prevent pathogens from penetrating the epithelium; (2) to prevent uptake of foreign antigens from a variety of sources including commensal bacteria, food, airborne, or particulate matter; and (3) to prevent pathologic immune responses against luminal antigens if they are successful in crossing mucosal barriers.

The commensal microflora. The gut's endogenous microflora plays a significant role in host homeostasis and can profoundly influence healthy and diseased states. The adult human intestine is home to more than 100 trillion bacteria, which is greater than the total number of somatic and germ cells in the entire human organism. There are estimated to be between 500 and 1,000 species of bacteria present within the gut. Aerobic, facultative, and anaerobic bacteria are all part of the enteric microflora; however, their distribution changes throughout the length of the gut with anaerobes not present in the stomach but making up greater than 99% of the flora in the distal colon.

Pathogenesis of Gut Dysfunction in Critical Illness

The gut plays an important role in the pathophysiology of critical illness, and any perturbations to the intestinal epithelium can ultimately lead to distant organ damage and development of MODS. The pathogenetic mechanisms of gut dysfunction are multifactorial; however,

there are ultimately only a limited number of ways in which the gut can initiate or propagate a physiologic state that leads to increased mortality. The first is to allow something that already exists within the gut lumen (bacteria, endotoxin, other preformed toxins) access to the remainder of the body where it can have harmful effects. Next, the gut can produce and then release something (cytokines, toxins) that might have direct or indirect harmful extra-intestinal effects. Finally, alterations in gut mucosal integrity can cause significant volume and electrolyte abnormalities via losses of gastrointestinal fluid (via excessive vomiting or diarrhea) or by anemia caused by gastrointestinal bleeding.

There is significant evidence that both residents of the gut and factors newly produced within the gut leave the intestine via the systemic circulation and/or the mesenteric lymph to cause propagation of critical illness. Specifically, whatever substance leaves the gut (either escaping from the lumen or being produced by the epithelium or immune system) can subsequently either primarily injure distant tissue, or secondarily alter the host response.

The immune response in critical illness is complex, with an early hyperimmune state followed by a late hypoimmune state [5]. Inflammatory mediators are key modulators of epithelial permeability due to their ability to alter tight junction expression and localization. Increased intestinal permeability, due to compromised epithelial integrity, can lead to persistent activation of systemic inflammation, and importantly, loss of intestinal barrier function is an early event in critical illness. While conclusive data that intact bacteria translocate from the gut in critical illness is lacking, there is significant evidence that luminal contents (bacterial products, cytokines) have distant injurious effects; thus, intestinal hyperpermeability may be a critical component in the pathophysiology of critical illness.

Both cellular proliferation and death are also altered in the intestinal epithelium during critical illness. Sepsis and noninfectious inflammation cause increased apoptosis in the gut epithelium in numerous animal models as well as in patient autopsy studies, and prevention of apoptosis leads to improved survival in preclinical models of sepsis. Increased sepsis-induced intestinal apoptosis may contribute to increased intestinal permeability. Despite the fact that there is increased cell death in sepsis, there is no compensatory increase in intestinal proliferation. In fact, there is a marked decrease in crypt cell proliferation in sepsis. In addition to its effects on the gut epithelium, critical illness also has a profound effect upon the number of cells in the mucosal immune system with increased sepsis-induced apoptosis in lamina propria lymphocytes, IELs, and Peyer's patches.

Interactions between host and bacterial pathogens in the intestine contribute to gut-derived sepsis. In critically ill patients, increased intestinal permeability, immunosuppression, and antibiotic usage can alter the delicate balance of the enteric microflora, leaving the intestinal mucosa with less "beneficial" bacteria such as *Bifidobacterium* and *Lactobacillus* and higher "pathogenic" bacteria such *Staphylococcus* and *Pseudomonas*. Since commensal bacteria are believed to be an essential part of host homeostasis, there is significant interest in the use of probiotics to recreate the normal gut flora. Probiotics have been studied in over 50 trials (most not in critical illness) with varying success. However, a recent prospective randomized trial in patients with severe acute pancreatitis showed increased mortality in patients treated with probiotics. This was associated with increased bacterial translocation and enterocyte damage in patients with organ failure [1]. In contrast to studies attempting to give exogenous bacteria to regain homeostasis, there is also preclinical data that downregulating or eliminating commensal bacteria is beneficial in murine models of critical illness, although the relevance of this in patients is unclear.

The gastrointestinal tract is especially susceptible to ischemic injury in critical illness. Even when cardiac output is maintained or increased in the intensive care unit, the body preferentially maintains perfusion to the heart, brain, and kidneys while shunting blood away from the intestine. In addition, while pressors raise blood pressure, they also frequently have splanchnic vasoconstrictive effects. Hypoperfusion of the intestine can ultimately result in severe gut dysfunction, whether measured globally, regionally, locally, or on a cellular or subcellular basis. In addition, intestinal reperfusion following ischemia can lead to production of inflammatory mediators that can amplify the systemic inflammatory response.

Treatment

Nutritional treatment. The most important stimulus for intestinal epithelial growth, function, and preservation of intestinal integrity is the presence of nutrients within the gut lumen. Therefore, providing enteral nutritional support is a crucial component of patient management in the intensive care unit. Importantly, enteral nutrition should be initiated early (within 24–48 h if possible) in a patient's course in the intensive care unit. Parenteral nutrition should be used in patients who are unable to tolerate enteral nutrition; however, parenteral nutrition lacks the immunological benefits of enteral nutrition and should not be used as a first line method of feeding critically ill patients.

Patients who are fed enterally should receive polymeric solutions [2]. These should not be supplemented with

arginine. In specific patient populations, immunonutrition has been demonstrated to be beneficial. Specifically, both burn and trauma patients should be supplemented with glutamine and patients with ARDS should receive fish oil, borage oil, and antioxidants. Patients should be fed into the stomach unless they cannot tolerate feeds, in which case strategies to optimize the chance of success include beginning a prokinetic agent or placing a small bowel feeding tube. Of note, feeding protocols may improve compliance with evidenced-based nutrition guidelines, but there is no evidence that these protocols improve mortality in critically ill patients.

Selective decontamination of the digestive tract (SDD). In the critically ill patient, loss of bacterial homeostasis is a characteristic feature of gut dysfunction. Selective decontamination of the gastrointestinal tract is a clinical strategy commonly used that decreases commensal microflora. In theory, SDD prevents both secondary colonization and preemptively treats infection caused by either respiratory flora or commensal gut flora. This, in turn, should decrease the incidence of both pneumonia and bacteremia in ICU patients, which could lead to lower mortality.

Although the term SDD implies that it is selective for the gut, the term is actually a misnomer since the majority of SDD studies use a 4-day course of intravenous antibiotics (most commonly cefotaxime) in combination with non-absorbable enteral antibiotics (most commonly polymixin E or colistin, tobramycin, and amphotericin B). This combination attempts to target aerobic gram-negative bacteria, *Staphylococcus aureus,* and enteric fungi while maintaining anaerobic gut flora.

In practice, SDD is controversial, with wide variance in usage depending on geography. Advocates of SDD point to over 40 randomized trials and 10 meta-analyses demonstrating decreased pneumonia and bacteremia in patients randomized to receive SDD. In addition, many of these trials demonstrate decreased mortality in patients who receive SDD. In fact all meta-analyses studying the effects of SDD published after the year 2000 demonstrate decreased mortality in patients receiving SDD except for a single meta-analysis of the use of SDD in liver transplant patients. However, it is important to note that the majority of benefit seen in these meta-analyses is based upon a single prospective, randomized, unblinded study by deJonge et al. in a med-surg intensive care unit demonstrating a decrease in intensive care unit mortality from 23% to 15% with SDD.

More recently, a study of nearly 6,000 patients in the Netherlands (by far the largest study to date on the topic) compared SDD to selective oropharyngeal decontamination (SOD, no intravenous antibiotics given) to standard care in 13 intensive care units [4]. Each of the three regimens was given in random order over 6 months. When accounting for confounders, SDD reduced mortality by 3.5% and SOD reduced mortality by 2.9%. Since SDD cost 12 times more than SOD ($12/day vs. $1/day) and they reduced mortality by a similar degree, the authors concluded that SOD may be preferable to SDD. Of note, neither SDD nor SOD was associated with the emergence of resistant microorganisms or *Clostridial difficile* colitis over the length of the study.

Despite the potential benefits of SDD, it is used sparingly, if at all, in the United States. Opponents of SDD highlight the concern for the development of resistant organisms in patients who receive this therapy. There is little efficacy data on the use of SDD in intensive care units with high baseline rates of multidrug-resistant organisms. Additionally, although the literature is mixed, there are some studies demonstrating increased selection of resistant organisms in intensive care units where they are endemic.

Enhancement of intestinal perfusion. Hypoperfusion of the gut is common in critically ill patients. The intestinal mucosa has a high metabolic demand and a unique microvascular anatomy that leads to heterogeneous blood distribution. Unfortunately, the gut is therefore particularly susceptible to inadequate perfusion, and attempts to enhance gut perfusion may have variable effects within the different layers of the intestinal wall.

The first treatment for intestinal hypoperfusion is simply to make sure the patient has adequate intravascular volume. While intravascular volume repletion does not guarantee that intestinal blood flow will be adequate, inadequate intravascular volume repletion guarantees that intestinal blood flow will be inadequate.

Once intravascular volume is repleted, attention must be paid to the cause of inadequate perfusion. This can be related to a refractory vasodilatory state (as might be seen in septic shock or the systemic inflammatory response syndrome), inadequate cardiac output (as might be seen in cardiogenic shock), or a combination. While the physiology of shock is beyond the scope of this chapter, shock should be treated by attempting to reverse the underlying cause and by pharmacologically supporting the patient with pressor agents. While the specific type of agent needed varies depending upon the underlying clinical condition, pressors do not have the same effects on splanchnic blood flow. There is significant conflicting data on the effects of various pressor agents on splanchnic perfusion. Norepinephrine increases systemic blood flow with increasing cardiac output; however, these effects are not seen in parallel in the splanchnic beds where norepinephrine has either minimal effect on mesenteric

blood flow or may actually decrease it. However, the combination of norepinephrine and dobutamine increases splanchnic blood flow in septic shock. Dopamine may also cause a small increase in splanchnic blood flow, although this may be associated with negative hepatic energy balance at higher doses, and the effect is minor compared to its systemic effects. Phenylephrine appears to have minimal effects on mesenteric blood flow. In contrast, both vasopressin and epinephrine have negative effects on splanchnic blood flow. The newer inodilator levosimendan is less well studied, but appears to preferentially improve mesenteric blood flow.

Clostridial difficile colitis. C. difficile is a gram-positive spore-forming anaerobic bacterium. Although many people in the community are asymptomatic carriers of *C. difficile*, the incidence of disease arising from the bacteria has greatly increased over the past decade. Importantly, both disease severity and mortality have increased recently due to the emergence of a new strain of *C. difficile* with increased toxin formation. Although commonly thought of as antibiotic-associated diarrhea, the development of *C. difficile* colitis does not require previous antibiotic exposure and can occur either in the healthcare setting or in the community.

Treatment for *C. difficile* colitis is dependent on its severity. Risk factors should be minimized. While both oral vancomycin and metronidazole have been used as first line agents, there is increasing evidence to suggest that oral vancomycin is superior and should be the first drug started for *C. difficile* colitis. Combination therapy is appropriate in more severe cases. Fulminant *C. difficile* colitis can be rapidly lethal, and total abdominal colectomy can be lifesaving in the most severe cases.

Stress gastritis. Critically ill patients are at increased risk for stress gastritis and subsequent gastrointestinal bleeding. Commonly used agents to prevent stress ulceration include H2 blockers and proton pump inhibitors. Common risk factors for the development of stress ulceration include respiratory failure requiring mechanical ventilation for greater than 2 days, coagulopathy, major burns, acute renal failure, head injury, acute liver failure, and administration of high-dose corticosteroids. Patients with these risk factors may benefit from stress ulcer prophylaxis, and no class of drugs has been demonstrated to be superior in preventing bleeding from stress ulcers. Simply being in an intensive care unit is not an indication for stress ulcer prophylaxis. The role of enteral feeding to prevent stress ulceration is evolving, and some experts suggest that enteral nutrition represents an alternative to pharmacologic therapy for prevention of stress ulceration.

Evaluation and Assessment

There is no single method to assess for gut dysfunction. Methods used in preclinical studies (permeability, blood flow, tight junction proteins, immunohistochemistry, proliferation, apoptosis, etc.) are not measurable at the bedside. In patients, a commonly used surrogate is tolerance to enteral feeding; however, like all other bedside measures of gut function, this is not necessarily reflective of specific abnormalities in the gut on a microscopic level. Tonometry has been performed in multiple locations in the gut, with gastric tonometry being the most common. In theory, tonometry provides some reflection of the adequacy of splanchnic perfusion. However, it is not typically used outside of the research setting since it does not measure gut function directly. In addition, the methodology is susceptible to technical and operator variability and it has not been shown to be a useful tool for directing clinical therapy.

Prognosis

The prognosis of patients with gut dysfunction is dependent on the underlying etiology of their critical illness, as well as the presence and number of comorbidities. Global improvements in systemic perfusion are generally accompanied by improvements in gut barrier function and restoration of gut homeostasis.

References

1. Basselink MG et al (2009) Intestinal barrier dysfunction in a randomized trial of a specific probiotic composition in acute pancreatitis. Ann Surg 250(5):712–719
2. Cahill NE et al (2010) Nutrition therapy in the critical care setting: what is "best achievable" practice? An international multicenter observational study. Crit Care Med 38(2):395–401
3. Clark JA, Coopersmith CM (2007) Intestinal crosstalk: a new paradigm for understanding the gut as the "motor" of critical illness. Shock 28(4):384–393
4. de Smet AM et al (2009) Decontamination of the digestive tract and oropharynx in ICU patients. N Engl J Med 360(1):20–31
5. Hotchkiss RS, Karl IE (2003) The pathophysiology and treatment of sepsis. N Engl J Med 348(2):138–150

GVHD

Graft versus host disease. Complication of bone marrow transplants in which T cells in the donor bone marrow graft attack the host's tissues. It is seen most often in cases where the blood marrow donor is unrelated to the patient or when the donor is related to the patient but not a perfect match. There are two forms of GVHD: an

early form called acute GVHD that occurs within the first 3 months after the transplant when the white cells are on the rise and a late form called chronic GVHD. Acute GVHD typically can affect the skin, liver, stomach, and/or intestines and chronic GVHD causes symptoms similar to those of autoimmune disorders.

Gynecological Infections

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Definition

Severe gynecologic infections requiring critical care are relatively uncommon but carry significant morbidity and occasional mortality. Most practitioners will encounter sporadic cases of critically ill gynecologic patients secondary to infectious morbidity in their career, and familiarity with the diseases and their treatment is paramount. See also ► Tubo-Ovarian Abscess, ► Necrotizing Fasciitis and Group A Streptococcal Sepsis, and ► Toxic Shock Syndrome for details.