What's New in Critical Care Medicine?

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Learner Objectives:

- Update on management of vasodilatory shock, including vasopressin, selective vasopressin analogs, methylene blue;
- Update on management of acute lung injury, including new approaches to mechanical ventilation, HFO and ECMO;
- Update on renal protection, including new biomarkers and the evidence basis for pharmacologic interventions;
- Update on palliative care, and its role in the intensive care unit.

VASODILATORY SHOCK AND VASOPRESSOR THERAPY

Vasopressin and its Analogues

Arginine vasopressin (AVP) is a nonapeptide produced in the paraventricular and supraoptic nuclei of hypothalamus as a prohormone, cleaved to AVP and stored in secretory vesicles in the posterior pituitary1. AVP has a plasma half-life of 6-20 min and is rapidly metabolized by vasopressinases in the liver and kidney. Vasopressin receptors, sites of action and actions are summarized in Table 1.

Increased serum osmolality (> 1%), generates plasma AVP levels of 1-5 pg/mL that act on V2 receptors, inducing an antidiuresis. Severe hypotension generates plasma AVP levels of 10-100 pg/mL that act on V1 (formerly called V1a) receptors, inducing peripheral vasoconstriction as a component of the baroreflex response. Activation of V3 (V1b) receptors induces ACTH and insulin release and may reflect the relationship between AVP and glucocorticoid metabolism (see below). At high levels, AVP may activate purinergic (P2) receptors in the cardiac endothelium, inducing coronary vasoconstriction.[1] Oxytocin is a nonapeptide that differs from AVP by only two amino acids, yet its actions are very different (uterine contraction, milk let-down) and there is little cross-reactivity.

Table 1: Receptors, Sites of Action and Actions of Endogenous Vasopressin (AVP)[1]

Receptor	Site of Action	Action
V1 (V1a)	vascular smooth muscle	vasoconstriction
V2	collecting duct of nephron	antidiuresis
V3 (V1b)	anterior pituitary, pancreas	ACTH, insulin release

Pathogenesis of vasodilatory shock:

Vasodilatory shock has multiple pathways for induction[2]. Contact activation with any foreign surface, e.g. cardiopulmonary bypass (CPB), ECMO, ventricular assist device (VAD) triggers Hagemann (Factor XII) activation and simultaneously activates the intrinsic pathway of coagulation, fibrinolysis and the complement system. Severe sepsis or systemic inflammatory response syndrome (SIRS) cause massive activation of inducible nitric oxide synthase (iNOS) and release of endogenous nitric oxide (NO). Protracted intracellular acidosis opens potassium-dependent ATP (KATP) channels in cell membranes, which allows potassium egress and hyperpolarization of the cell membrane, inactivating calcium channels and inhibiting the vasoconstrictor response to catecholamines such as norepinephrine (NE) or epinephrine, a syndrome known as vasoplegia. There is considerable evidence that in protracted shock, there is depletion of endogenous AVP from posterior pituitary, so that plasma AVP declines to < 3 pg/mL3.

Actions, benefits and limitations of AVP infusion in vasodilatory shock:

Low dose AVP infusion (1-4 u/hr, or 0.015-0.067 u/min) has a number of potentially beneficial effects in vasodilatory shock.[2] AVP appears to inhibit activation of inducible nitric oxide. It binds to and closes KATP channels, restores membrane polarity and the vasoconstrictor response to catecholamines. Depleted endogenous AVP levels are restored: infusion of 1-4 u/hr achieves plasma AVP levels of 20-30 pg/mL.

These actions consistently result in increased blood pressure and decreased catecholamine requirement. Diminution of high-dose NE decreases pulmonary vascular resistance (PVR) and cardiac arrhythmias. Compared to NE, AVP preferentially induces efferent arteriolar constriction and thereby may enhance glomerular filtration rate (GFR) and renal function.

The 2008 Surviving Sepsis Campaign recommends that AVP infusion (0.03 u/min) may be added to NE (still recommended for initial therapy) if the mean arterial pressure (MAP) cannot be maintained above 65 mmHg.[4]

Infusion of AVP must always be via a central line because extravasation may cause intense cutaneous vasoconstriction and injury. At excessive doses (> 6 u/hr) especially in low flow states, AVP infusion may cause acral cyanosis and cutaneous necrosis, and at higher doses still it promotes mesenteric vasoconstriction (thus its erstwhile use in variceal bleeding), hepatic dysfunction and even coronary vasoconstriction.

Evidence basis for use of AVP and its analogues in vasodilatory shock

The most definitive randomized controlled study (RCT) performed on AVP thus far is the Vasopressin and Septic Shock Trial (VASST).[5] It was designed to test the hypothesis that low-dose AVP infusion (0.01-0.03 u/min or 0.6-1.8 u/hr) would decrease 28-day mortality among patients with septic shock who were being treated with NE 5-15mcg/min. In the 778 patients studied, there was no significant difference in mortality between the AVP and NE (35.4% vs. 39.3%). However, in patients with less severe septic shock (prospectively defined as requiring NE 5-14 mcg/min), there was a significant improvement in mortality with AVP over NE (26.5% vs. 35.7%, $p < 0.05$). It is possible that the lack of benefit in more severe septic shock (NE > 14 mcg/min) was due to an inadequate dose of AVP or late intervention.

Role of corticosteroids in vasodilatory shock

An retrospective analysis of the VASST study by its authors demonstrated that the concomitant administration of corticosteroids with AVP significantly decreased mortality (35.9% vs. 44.7%, $p = 0.03$), and increased plasma AVP levels by one to two thirds[6]. This further implicates the relationship between AVP and steroid metabolism, considering that V3 receptor activation increases ACTH release and cortisol levels. It also warrants future prospective studies.

Indeed, the role of steroids in septic shock remains in flux.[7] The use of ACTH-stimulation tests to evoke adrenal hyporesponsiveness as an indication for hydrocortisone therapy has been discredited by subsequent equivocal outcomes, intra-study use of etomidate (which impairs cortisol synthesis), and the observation that these studies were based upon total rather than free cortisol levels.[8] The 2008 Surviving Sepsis Campaign recommends the administration of hydrocortisone (≤ 300 mg/day) when hypotension responds poorly to adequate fluid resuscitation and vasopressors , and that it should be weaned once vasopressors are no longer required.[4]

Terlipressin

Terlipressin (tricyl-lysine vasopressin) is an AVP analogue used in Europe but not currently available in the US or Canada. It is twice as potent at the V1 receptor than AVP, but has a much more prolonged half-life (4-6 hr), which makes it more difficult to titrate1. A small European RCT (TERLIVAP) compared continuous infusion of AVP (0.03 u/min) and terlipressin (1.3 mcg/kg/hr) with NE (15 mcg/min) as first-line therapy in septic shock in 45 patients[9] Terlipressin appeared superior to AVP in decreasing NE requirements, with lower bilirubin levels and less rebound hypotension, but had a greater effect in lowering platelet count.

METHYLENE BLUE

Actions of methylene blue

Methylene blue appears to inhibit guanylate cyclase, the enzyme that catalyzes the conversion of guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP), which mediates the vasodilator effect of NO. It may also cause selective inhibition of iNOS.

Evidence basis for use of methylene blue in vasodilatory shock

Anecdotal observations of the benefits of methylene blue (MB) in severe vasodilatory shock have been made for many years.[10,11]

Dosing has ranged between 1-4 mg/kg given as a single dose infused over 30 min to 4 hrs. MB increases MAP and cardiac index (CI). The latter may be due to increase preload secondary to venoconstriction, or a decrease in the impact of high levels of NO, which is a myocardial depressant that impedes the inotropic effect of catecholamines. Arterial lactate decreases, but this may be in part from its effect as a reducing agent. However, PVR also increases and arterial oxygenation may decrease![12,13] Although decreases in endogenous production of NO, interleukins and tumor necrosis factor (TNF) have not been noted,[14] urinary excretion of NO metabolites is substantially lower.[15] Attenuation of the urinary excretion of renal tubular injury markers has also been noted.

Most recently a small dose-ranging RCT on 15 patients evaluated MB at 1mg/kg, 3mg/kg or 7mg/kg over 20 min. The authors noted a dose-dependent enhancement of hemodynamic function even at the lowest dose, but cautioned that high doses of MB may compromise splanchnic perfusion.[16] We have observed occasionally dramatic responses to MB 2 mg/kg administered over 30 min in severe vasoplegia. However, because of its potential to increase PVR, in our practice we restrict its use to patients who are already receiving inhaled NO.

MANAGEMENT OF ACUTE LUNG INJURY

Protective Lung Ventilation

During mechanical ventilation, progressive lung parenchymal injury (ventilator-induced lung injury or VILI) is induced by excessive alveolar distension (large tidal volumes) alternating with collapse (low or inadequate PEEP). The primary mechanism for VILI appears to be surfactant depletion with loss of its barrier function, and a subsequent cytokine-induced inflammatory response.[17]

The compliance, or pressure–volume ((PV) curve of the lung is sigmoid-shaped, with a lower and upper inflection point. Between the inflection points, alveoli have the best compliance and a small pressure increase results in large volume increase. Below the lower inflection point, the alveoli are collapsed, and above the upper inflection point, excessively distended. In both regions the alveoli are “stiff”, i.e. a large pressure increase results in minimal volume

increase. Protective lung ventilation implies alveolar ventilation between the lower and upper inflection points, i.e., relatively small tidal volumes with moderate PEEP.[18]

This concept was supported by evidence from the first ARDSNet trial that demonstrated a significant mortality benefit (31.0% vs. 39.8%, p <0.007) with the use of low tidal volume (6 mL/kg) plateau pressure (<30 cmH2O) versus high tidal volume (12 mL/kg) and plateau pressure <50 cm H2O).[19] This approach has since become the paradigm for protective lung strategy.

THE OPEN LUNG CONCEPT

Physiologic basis

However, low tidal volumes are not very effective in recruiting collapsed alveoli. The open lung concept is based on achieving an ideally inflated lung, by opening up collapsed alveoli with an initial sustained recruitment maneuver that overcomes a critical opening pressure, then followed by high levels of PEEP with low tidal volumes.[20] Of note, studies comparing lower vs. higher levels of PEEP alone have not demonstrated an outcome difference. The goal is to sustain ventilation between the lower and upper inflection points of the lung pressure–volume curve, minimize airway pressures during inflation and avoid alveolar collapse during deflation. When all alveoli are equally expanded, oxygenation is maximized and shear force (and potential for VILI) is minimized.[21]

Evidence basis

There are only limited data available on open lung ventilation in patients. The most widely quoted study is that reported in 1998 by Amato et al., who performed an RCT on 53 patients with early ARDS comparing protective and conventional lung ventilation.[22] Their strategy included a recruitment maneuver (35–40 cmH2O for 40 sec), PEEP above the lower inflection point of static PV curve, a tidal volume of < 6 ml/kg, peak pressures <20 cmH2O above PEEP and permissive hypercapnia. 28-day mortality was 38% vs. 71%, ventilatory weaning more successful (66% vs. 29%), and barotrauma much less common (7% vs. 42%).

Using computed tomography (CT) studies, Gattinoni found that peak airway pressures of 45 cm H2O recruited anything from 0% to 50% of atelectatic lung, and that about 25% was not recruitable.[23] The "potentially recruitable lung" was inversely proportional to the severity of ARDS. However, it has been suggested that total alveolar recruitment might have required higher airway pressures.[24] Subsequently, the Amato group demonstrated that recruitment pressures of up to 60 cmH2O could permanently reverse hypoxia and collapse in the majority of patients with early ARDS.[25]

Peter Papadakos in Rochester, NY, has been a strong advocate of the use of pressure controlled inverse ratio ventilation (PC-IRV) to achieve open lung strategy.[26] He advocates an initial recruitment maneuver with peak airway pressures 40–60 cm H2O on PC for 10–30 ventilator cycles, using IRV with in inspiration:expiration (I:E) ratio of 1:1 or 2:1 and PEEP of 10–20 cm H2O. Success in recruitment is largely determined by an improvement in oxygenation. The PC is then adjusted to decrease the peak airway to the lowest that will sustain a stable tidal volume or oxygenation, usually 15–30 cm H2O below the recruitment maneuver.

HIGH FREQUENCY OSCILLATORY VENTILATION (HFOV)

Mechanisms and delivery

High frequency oscillatory ventilation (HFOV) potentially provides lung protection in ARDS by avoiding alveolar distension and collapse.[27] Oscillation is provided at rates of 180–900 cycles per minute, or 3–15 Hz (1 Hz = 60 cycles per minute or 1 cycle per second), with sub-dead space tidal volumes (0.1– 0.3 mL/kg), high gas flow, and an active expiratory phase.

During HFOV there are multiple potential mechanisms of gas exchange other than direct ventilation, including convective transport, "pendeluft" (inter-regional to-and-fro gas flow), longitudinal dispersion, and diffusion.[28] High mean airway pressures (25-30 cmH2O) are necessary to support and maintain alveolar recruitment and an open lung. The HFOV device has an adjustable power control that determines the amplitude of piston displacement and peak and trough pressure excursions (delta P) above and below the mean airway pressure. The piston sets up a body "wiggle" that typically extends to the thighs. The oscillation frequency (Hz) determines the time for piston displacement, thus a lower Hz will lead to larger bulk tidal volumes. The FiO2 and mean airway pressure determines oxygenation, whereas delta P and Hz determined ventilation and CO2 elimination. Occasionally it may be necessary to create a small endotracheal tube cuff leak to facilitate CO2 washout. HFOV provides a number of management challenges, including the necessity for a firm bed surface with increased risk of pressure injury, and difficulty in adequate hydration of inspired gas.

HFOV has established itself as a ventilatory mode in pediatric ICUs and trauma units, where it facilitates ventilation in the presence of abdominal compartment syndrome and constrained lung volume.

Evidence basis

In adults, HFOV has been reported primarily as a rescue mode that enhances oxygenation in ARDS in patients failing to improve with conventional ventilation.[29]

Thus far, only one large RCT has compared HFOV with conventional ventilation. After 2–4 days of conventional ventilation, 148 patients were

randomized to HFO or PC-IRV (tidal volume 6–10 mL/kg).[30] Patients who received HFOV required higher mean airway pressure but had improved oxygenation in the first 24 h, but there was no statistical difference in mortality (37% vs 52%). The only other RCT was abandoned because of low recruitment without detecting any difference between HFOV and conventional ventilation.[31]

More recently a small study was performed that combined lung recruitment with HFOV. Three sustained inflations at 40 cm H2O for 40 secs were followed by a decremental titration of FiO2 and then mean airway pressure with HFOV.[32] Recruitment maneuvers were repeated for hypoxemia and routinely at least twice daily if the FiO2 was >0.4. This resulted in a significant improvement in oxygenation compared with standardized conventional ventilation.

In short, there remains a need for a large randomized trial where HFOV is instituted at an early stage of ARDS, before VILI occurs, is combined with lung recruitment maneuvers, and is continued until the lung is no longer susceptible to VILI.[33]

EXTRACORPOREAL MEMBRANE OXYGENATION (ECMO)

Types of ECMO

Extracorporeal membrane oxygenation (ECMO) for pulmonary support is provided most often via a veno-venous circuit (VV-ECMO) that creates an oxygenated circuit in parallel to the venous system. From an internal jugular cannula, venous blood is pumped through an extracorporeal membrane oxygenator and thence returned to the femoral vein. More recently, an adult double-lumen bicaval internal jugular cannula has facilitated single cannula placement for VV-ECMO; it simultaneously withdraws blood from the superior and inferior vena cavas and returns it to the right atrium. Circulatory support is not provided by VV-ECMO, so the patient needs to be relatively hemodynamically stable, or supported by a right ventricular assist device (RVAD), into which the VV circuit can be inserted. The goal is to oxygenate venous blood returning to the heart, which in turn enhances arterial oxygenation sufficiently to sustain tissue metabolism.

In our hands, we have found VV-ECMO to be a life-saving intervention in selected patients with ARDS, especially ischemic-perfusion injury after double lung transplantation. A salutary outcome is predicated on good cardiovascular function, the absence of multisystem organ failure, and relatively rapid (< 72 h) lung function improvement.

If oxygenation is not sufficiently supported by VV-ECMO, or the patient is hemodynamically unstable, ECMO is provided via a veno-arterial circuit (VA-ECMO). This provides partial or near complete circulatory assist (analogous to CPB) and more complete oxygenation of arterial blood. However it requires cannulation of a major artery (most often, the femoral artery) with increased risk of vascular injury, embolism, and limb ischemia.

ECMO is an expensive, complex, resource intensive modality that requires considerable expertise. It requires systemic anticoagulation to prevent contact activation-induced thrombosis, and there is high risk of major bleeding and coagulopathy, thromboembolism, stroke, sepsis, and multisystem failure.

More recently, a poly-methylpentene (PMP) membrane oxygenator (Quadrox D) has become available that is very small and portable, driven by a centrifugal pump.[34] This system avoids the plasma leakage associated with conventional standard hollow-fiber oxygenators. Studies are underway at our institution to use this form of VV-ECMO as a bridge to lung transplant in decompensated patients.

Evidence basis

Initial studies, such as the U.S. ECMO trial (1974–1977) used ECMO with complete lung collapse, and dismal survival (9%). Over the next 10 yr, Gattinoni demonstrated the effectiveness of maintenance of low frequency positive pressure ventilation (LFPPV, pressure limit 35 cm H2O, rate 3–5/min), utilizing low flow VV-ECMO for CO2 removal (ECCO2R).[35] This approach was associated with a 49% survival in very severe ARDS; in survivors, lung function improved within 48 h. In a subsequent randomized study in the U.S., Morris compared LFPPV-ECCO2R with PC-IRV, using computerized protocols in 40 patients.[36] There was no statistical significance in 30-day survival (33% vs 42%).

The most recent large scale RCT is the CESAR trial (Conventional ventilatory support versus ECMO for Severe Adult Respiratory failure) performed on 180 adults in the UK.[37] An independent central randomization service randomly assigned patients to either treatment modality within 7 days of the onset of severe ARDS (Murray score > 3.0, pH < 7.20). Patients who were referred to a specialty center for consideration of ECMO had significantly improved 6-month survival (63% vs. 47%). However, 20% of the referred patients did not undergo ECMO and had an 80% survival, thus some of the benefit was likely due to the provision of protective lung ventilation in a highly specialized center.

RENAL PROTECTION: BIOMARKERS AND PHARMACOLOGIC INTERVENTIONS

Biomarkers

Ischemic acute kidney injury (AKI) progresses through several phases (prerenal, initiation, extension, maintenance and recovery). The success of any intervention to restore GFR thus depends on its timing – the earlier, the better. However, traditional renal function tests do not allow early recognition of AKI. Development of robust, easily detectable and prompt biomarkers of renal injury might allow us to assess the site, duration, etiology, prognosis and course of renal injury, and the effect of prophylactic or therapeutic interventions.[38,39]

Serum Creatinine

Serum creatinine (SCr) is not a marker of renal injury, but of renal function, and reflects the balance between muscle creatinine production and renal excretion.[40] SCr is a useful marker of glomerular filtration rate (GFR) in a steady state, but it is important to appreciate that the relationship between SCr and GFR is inverse and exponential. A doubling of the serum creatinine implies a halving of the GFR. There are numerous limitations to SCr as a reflection of steady state GFR as well as of acute changes in GFR.

Many physiologic molecules (e.g. glucose, protein, ketones) or drugs (e.g. cephalosporins) interfere with the chromogenic assay for creatinine. N-acetylcysteine (NAC), an antioxidant renoprotective agent in radiocontrast nephropathy (RCN) actually decreases SCr levels.

SCr does not increase above the normal range until GFR is <50 mL/min, so any decrease in GFR above this level will still be associated with a "normal" SCr. This is pertinent in the elderly (whose normal GFR is 50-80 mL/min) and cachectic patients (who have very low creatinine generation). Creatinine is freely soluble and distributes throughout the total body water (TBW), so perioperative increases in TBW are reflected by artifactually low SCr immediately after surgery.

Importantly, it may take 2 to 7 days before the SCr reaches a new steady state that reflects acute changes in GFR. This explains why intraoperative AKI is so often reflected by a postoperative SCr that does not peak until 5-7 days after surgery. Indeed, after a transient renal insult (e.g. suprarenal aortic cross-clamping) SCr may increase for a few days while GFR is actually recovering.[41]

Cystatin C

Cystatin C is a cysteine-protease inhibitor that is released into the circulation by all nucleated cells. It is completely filtered by the glomerulus, reabsorbed and not secreted by the tubules; thus, increased serum cystatin C levels reflect decreased GFR, and increased urinary levels reflect tubular injury.[42] Elevation of urinary cystatin C within 6 hr of cardiac surgery has been shown to have a strong correlation with AKI defined by subsequent elevation of SCr.[43] Unlike creatinine, cystatin C levels are not affected by muscle mass, age or gender, and there is evidence that it more accurately tracks GFR and responds more quickly.[44,45] However, certain factors such as cigarette smoking, inflammation and immunosuppressive therapy do independently elevate cystatin C.[46]

Classic biomarkers of tubular injury

Beta-2 microglobulin (B2M) is a small protein component of the major histocompatibility complex that is present on the surface of almost all cells.[47] It is normally filtered by the glomerulus and then undergoes partial tubular reabsorption. The ratio of serum to urine B2M may help distinguish glomerular from tubular injury. In the former, serum B2M increases because it is not filtered. In the latter, urinary B2M increases because it is not reabsorbed.

Increased urinary concentration of the tubular enzyme, N-acetyl beta D-glucosaminidase (NAG) is an index of subclinical tubular injury.[48] Urinary NAG levels, or the ratio of its isoenzymes, is used in the early detection of rejection after renal transplantation. However, the relationship between tubular enzymuria and clinical AKI is not known.

New biomarkers of tubular injury

Neutrophil gelatinase-associated lipocalin (NGAL) is a small 25 kDA polypeptide expressed in proximal tubular cells. Within minutes after ischemic tubular injury NGAL expression is dramatically up-regulated - 3-4 fold within 2-3 hrs, and up to 10,000 fold by 24 hrs.[49] NGAL is readily detected by ELISA in tiny (micromililiter) amounts of urine almost immediately after renal injury, preceding the appearance of NAG and beta2-microglobulin.

Urinary NGAL increases significantly within two hr of CPB in pediatric or adult patients who subsequently go on to develop a 50% increase in postoperative SCr, whose peak is delayed until 2-5 days after surgery.[50] However, the sensitivity and specificity in individual patients is much greater in pediatric (AUC 0.98) than adult cardiac surgery (0.74).[51] This may be explained by pediatric patients having a single insult imposed upon previously normal renal function, whereas, adults have varying preoperative GFR and co-morbidity, with multiple disparate renal insults. Thus although urinary NGAL may represent an early, sensitive, noninvasive urinary biomarker for ischemic and nephrotoxic AKI, it is not yet useful for management decisions in an individual patient.

Interleukin-18 (IL-18) is a pro-inflammatory cytokine that is involved in ischemic AKI. After CPB, urinary IL-18 is elevated within 4-6 hrs (i.e. later than NGAL), and levels may reflect the severity and duration of ischemic AKI.[52]

Kidney injury molecule-1 (KIM-1) is an immunoglobulin that normally resides in proximal renal tubular cells. After ischemic or nephrotoxic AKI, KIM-1 levels become dramatically elevated, perhaps because the protein plays a role in scavenging apoptotic and necrotic tubular cells.[53] However, compared with NGAL and IL-18, the levels of KIM-1 peak considerably later, at about 12-24 hrs.

Conclusions

Despite their promise, individual biomarkers of AKI have not yet replaced traditional markers in clinical and investigational studies. There is considerable interest in the development of a panel of early markers of acute tubular injury (NGAL, IL-18, KIM-1) together with a more reliable marker of GFR (cystatin C).[38] The hope is that these panels will be

more useful for timing the initial insult and duration of AKI, and in predicting outcome (requirement for dialysis, mortality). Much work remains to be done to validate their sensitivity and specificity in large, diverse patient populations.

PHARMACOLOGIC PROTECTION

Osmotic and Loop Diuretics

Mannitol (25-50 g) is routinely added to the pump prime, although there are few clinical data that define its true role in renal protection during CPB. It does not prevent subclinical renal injury (microalbuminuria, tubular enzymuria), but AKI after uncomplicated CPB in patients with previously normal renal function is rare. Mannitol increases urine flow during infra-renal cross-clamping but does not prevent intraoperative decreases in GFR Postoperative osmotic diuresis can exacerbate hypovolemia and hypokalemia; persistent isosthenuria actually is predictive of CPB-induced tubular injury.

Loop diuretics (furosemide, bumetanide, torsemide, ethacrynic acid) have long been used to "convert" oliguric to nonoliguric AKI. However, it is most likely that oliguric patients who respond to diuretics have a lesser renal injury than those who do not, with an intrinsically more favorable outcome. Once dialysis is required, high dose furosemide does not alter the natural history of AKI.

Dopaminergic Agonists

Dopaminergic agents (dopamine, fenoldopam) potentially confer renal protection by increasing renal blood flow (RBF), diuresis and saliuresis. By activating cyclic AMP they "turn off" the energy-dependent tubular sodium pump and thereby decrease tubular oxygen consumption; increased intratubular urine flow protects against tubular obstruction.

Low dose (1-3 µg/kg/min) dopamine, added to high dose furosemide and mannitol, can also convert oliguric to nonoliguric states if given within a few hours of injury. However there is little evidence that "prophylactic" low dose dopamine has any role in cardiac surgery. In part this may be because there is very wide variability in dopamine pharmacokinetics, i.e. some patients given low dose dopamine may achieve high plasma levels, i.e. in the beta- or alpha-adrenergic range.[54] When oliguria is associated with slow heart rate and low blood pressure in a volume repleted patient, initiation of dopamine as an inotropic agent can be very helpful. However, its usefulness is limited by its propensity to induce supraventricular arrhythmias especially postoperative atrial fibrillation.[55]

Fenoldopam is a phenol derivative of dopamine that is selective for the DA-1 receptor and lacks any beta- or alpha-adrenergic effects. There is increasing evidence that prophylactic perioperative administration at low doses (0.5-1.0 mcg/kg/min) can preserve GFR during and after CPB and decrease the requirement for postoperative dialysis.[56,57]

Natriuretic Peptides

The natriuretic peptides are formed by the endogenous synthesis of chains of 22-32 amino acids. They specifically oppose the sympathoadrenal, renin-angiotensin, aldosterone, and arginine vasopressin (AVP) systems, and induce vasodilation and natriuresis via activation of cyclic GMP. A-type (atrial) natriuretic peptide (ANP) is released by atrial stretch; B-type (brain) natriuretic peptide (BNP) is released by ventricular dilation. Assay of BNP (and its precursor, N-terminal-pro-BNP) is an established diagnostic tool for acute cardiac failure.[58] C-type natriuretic peptide (CNP, great vessels) and urodilatin (kidney) are endogenous analogs.

Human recombinant ANP (anaritide) infusion during CPB significantly decreases renin-angiotensin and aldosterone responses, and preserves GFR. Preliminary data suggested that administration in patients with severe AKI it could decrease dialysis requirement and mortality.[59] However, mortality was increased in nonoliguric patients, perhaps because the surviving nephrons are more sensitive to hypotension induced by ANP. A subsequent trial in oliguric patients showed no difference in outcome.[60]

Human Recombinant BNP (nesiritide) is FDA-approved for the parenteral treatment of patients with advanced decompensated CHF (ADCHF). Infusion decreases cardiac preload and afterload, promotes diuresis and relieves pulmonary edema and anasarca. Considerable controversy has been elicited by implications that nesiritide may adversely affect renal function in ADCHF.[61] However, in a prospective, controlled study in patients undergoing coronary revascularization of mitral valve surgery with CPB, a perioperative infusion of nesiritide (0.01 mcg/kg/min) was associated with lower SCr and 6-month mortality.[62]

N-Acetylcysteine

N-acetylcysteine (NAC) is naturally occurring glutathione precursor and free radical scavenger. It is well established in the treatment of acetaminophen toxicity, and there is considerable experimental evidence of its effectiveness in ameliorating nephrotoxic AKI. When combined with hydration, prophylactic oral NAC (600 mg PO bid x 2 days) provides significant renal protection in radiocontrast nephropathy (RCN).[63,64] However, NAC may decrease creatinine production and thereby give a false impression of the extent of its benefit.[65]

No renal benefit has been demonstrated by the perioperative infusion of NAC during cardiac surgery.[66] NAC must pass through the liver to be converted to glutathione, so in part this may be due to inadequate knowledge regarding the appropriate parenteral dose of NAC to protect against clinical IRI.[67]

Sodium Bicarbonate

It is well established that urinary alkalinization (pH > 6.5) protects against tubular injury in myoglobinuria (rhabdomyolysis) as well as RCN. There is now preliminary clinical evidence that urinary alkalinization can ameliorate AKI during cardiac surgery.[68]

PALLIATIVE CARE

Benefits of a Palliative Care Service in the ICU

Intensive care and palliative care might appear to be contradictions: the former focuses on restoration of health or at least prolongation of life; the latter focuses on control of symptoms and relief of suffering.[69] However, these are not opposite ends of a spectrum – there is considerable overlap. There is considerable evidence that integration of palliative care experts into the ICU is of benefit to patients, families and caregivers. It has been estimated that nearly 50% of Americans who die in hospitals spend time in the ICU in their last 3 days of life, and about 15% of patients admitted to an ICU (half a million patients a year in the US) will die in the ICU.[70]

Palliative care in the ICU may be associated with improved quality of life, higher rates of formalization of advanced directives and utilization of hospices, and lower use of certain non-beneficial life-prolonging treatments for critically ill patients who are at the end of life.

For example, at Montefiore Medical Center in the Bronx, New York a palliative care team integrated into the operations of an ICU included an advance practice nurse (APN) – who attended rounds - and social worker.[71] The team provided recommendations on pain management; education on the death process; guidance for formalized advance directives (especially non-English speaking patients of low socio-economic status); helped with withdrawal of support such as mechanical ventilation, inotropic support, artificial nutrition, or dialysis; and referred patients to hospice with access to formal bereavement services. Charges for opioid medications increased but use of laboratory and radiology tests decreased.

An important emphasis of palliative care is to enhance communication between the ICU team and families. Palliative care staff can facilitate more in-depth meetings to allow families to express concerns and emotions, which may reduce posttraumatic stress reactions and to allay misconceptions regarding the ICU team's recommendations to limit or withdraw care. The "ABCDE" approach has been advocated to enhance communication with families of diverse cultural origin. The team should explore attitudes to death and dying (ethnically based); beliefs (religious); context (historical and political origins and experiences); decision-making style (individual or family-centered); and environmental resources.[70]

The Palliative Care Consult

Common symptoms triggering a palliative care consult include delirium, dyspnea, pain, fatigue and anxiety. In addition to counseling, interventions offered include opioid management, steroids, antipsychotic drugs, do not resuscitate conversion, withdrawal of invasive and non-invasive ventilatory support.[72]

Attempts have been made to systematize the criteria for a palliative care consult. This is an area where disagreement persists. For example, a group of surgical intensivists offered criteria primarily on family request, or evidence of medical futility such as poor Glasgow coma scores, death expected during same SICU stay, median expected survival <6 months, SICU stay >1 month, and so on.[73] The editorial accompanying the report expressed concern at the lack of any reference to management of treatable pain, delirium or depression by the palliative care team and wondered whether intensivists and surgeons fear sending patients or families "the wrong prognostic message".[74]

At the other end of the spectrum are practitioners of palliative care who believe that "all ICU patients experience … suffering regardless of prognosis or goals, thus palliative therapy is a requisite approach for every patient, of which pain management is a principal component".[70]

End-of-Life Care

Palliative care can help with the three aspects of "good dying" advocated by the Institute of Medicine in 1997: avoidance of distress and suffering; accordance with the patient's preferences and wishes; and consistent with clinical and cultural standards.[70] It can help in the shift to comfort-oriented care for dying patients; it can enhance communication and cultural sensitivity with the patient and family; it can help resolve misconceptions about opiate escalation to alleviate pain and suffering. It can also address family and caregiver stress. It may facilitate the use of standardized instruments to gauge pain and discomfort.

Palliative care teams can help to educate caregivers and families that aggressive palliation of pain, even though it might shorten survival, is ethically justifiable as long as the primary goal is the relief of suffering. This is the so-called doctrine of the "double effect". In fact, relief of uncontrolled pain and its severe systemic effects may delay demise. However, a European survey suggested that there is no clear-cut distinction between treatments administered to relieve pain and suffering and those intended to shorten the dying process, which many intensivists feel directly leads to patient demise.[75] Specific guidelines or orders for analgesia and sedation may be helpful during withdrawal of life-support; these may include protocols for palliative (total, terminal or controlled) sedation for patients in extreme distress.

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