Special Article

Recent advances in critical care: Part II

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ABSTRACT

With the increasing number of critically ill patients being admitted to intensive care units (ICUs), newer techniques and treatment modalities continue to evolve for their adequate management. Thus, it has become imperative to understand existing tools and resources, and utilise or repurpose them to achieve better results that can decrease morbidity and mortality. In this writeup, we chose five areas of interest, including analgosedation, role of colloids, recent advancements in the management of respiratory failure, the role of extracorporeal membrane oxygenation, and newer antimicrobials. The role of analgosedation in the critically ill has gained importance with focus on post-ICU syndromes, and albumin has re-entered the fray as a possible repairer of the injured glycocalyx. The coronavirus disease 2019 (COVID-19) pandemic forced us to relook at various ventilator strategies and mechanical support for the failing circulation has now become more common with clear end-points. Rising microbial antibiotic resistance has opened up the research on newer antibiotics.

Key words: Analgesics, colloids, critical care, opioids, respiratory failure

INTRODUCTION

A large number of critically ill patients are being admitted in our intensive care units (ICUs). With the aim of combating critical illness, a number of new techniques and pharmaceutical agents are evolving. It has also become important that we should understand existing tools and resources and utilise or repurpose them to achieve better critical care outcomes. We chose five such strategies, conducted a literature search on them, and have attempted to discuss them briefly in this article.

RELOOK AT ANALGOSEDATION

Pain and discomfort are observed in up to nearly 71% of critically ill patients. Analgesia and sedation practices remain highly variable, despite usage of the ABCDEF bundle approach to liberate a patient from mechanical ventilation.[1] Analgosedation is defined as either analgesia (i.e., an analgesic, usually an opioid, is used before a sedative to reach the sedation goal) or analgesia-based sedation (i.e., an analgesic, again an opioid, is used instead of a sedative to reach the same goal). It has been proved that a strategy that prioritises patient pain and discomfort before providing sedative therapy results in improved patient outcomes compared to standard sedative-hypnotic regimens. Difficult sedation, including situations of therapeutic failure, tolerance, and deprivation, has a negative impact on the outcome and occurs in one-in-four mechanically ventilated patients.[2] The implementation of ABCDEF bundle and Pain Agitation and Delirium (PAD) guidelines has been shown to definitely improve patient outcomes in terms of delirium and mortality, but patients continue to be more awake and often in pain.[3,4] Evidence is forthcoming about the

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association of opioid usage and delirium. Even though analgosedation practice reduces the side effects of sedatives, opioids themselves are deliriogenic. Hence, an analgesia-first approach needs to be strategised based on validated pain assessment tools. The pain has to be managed using a multi-modal technique with pharmacological and non-pharmacological approaches, thereby reducing opioid usage. Once pain has been addressed, sedation can be given using either propofol or dexmedetomidine.[3]

There are several advantages of analgosedation over analgesia or sedation alone.[2] These include decreased pain and discomfort, decreased drug-related adverse events, decreased duration of mechanical ventilation and length of ICU stay, improvement in psychological outcomes like post-traumatic stress disorder, and reduced amount of sedation requirement.

The disadvantages too are many and include delirium associated with opioid administration, high incidence of recall of unpleasant events before regaining consciousness, occurrence of nightmares and hallucinations, immunosuppression, tolerance and need for escalation of dose for same effect, and strong withdrawal effect including mydriasis, nausea/vomiting, abdominal cramps, diarrhoea, tachypnoea, hot flashes, chills, and sweating. Increased analgesic requirements and hyperalgesia following cessation of opioid infusions, malignant hyperthermia (rare, with volatile anaesthetics) and doubtful "analgo-economics" (e.g., remifentanil) are other concerns.[3,4] There exist a number of drugs/techniques used for administering analgosedation and a variety of tools and scales for the monitoring of analgosedation in the ICU [Tables 1-3].[5] It is recommended to use non-opioids, non-pharmacological methods, regional anaesthesia, and/or multimodal analgesia to reduce opioid-induced side effects.

Table 1: Analgosedation Monitoring in the Intensive Care Unit

Patient class	Monitoring tool
Pain in communicative patient	Patient's self-reported pain level (Numeric Rating Scale administered either verbally or visually) - "Gold-standard"
Pain in non-communicative patient, but with observable behaviour	Behavioural Pain Scale in intubated patients (BPS)
	BPS in non-intubated (BPS-NI) patients
	Critical Care Pain Observation Tool (CPOT)
	Proxy reporting of pain by family member
Sedation monitoring	Richmond Agitation Sedation Scale

The lowest opioid doses for the shortest possible time should be deployed for achieving the therapeutic goal and to prevent opioid-related side effects. Non-benzodiazepines are preferred over benzodiazepines for the prevention of delirium. For optimum patient recovery and outcome, multimodal analgesia is recommended to spare and/or minimise both opioids and sedatives.[1] During non-invasive ventilation (NIV), a small amount of analgosedation should be considered only after optimising ventilatory support, selecting the best interface for the patient, and selecting a proper interface rotational programme to prevent the development of a pressure sore and the related NIV intolerance. But there has been a lack of evidence regarding the choice of sedative and/or analgesia during NIV till date. Further research regarding analgo-economics of drugs vis-a vis the cost advantage of reduced ICU duration of stay is needed.

COMEBACK COLLOID: ROLE OF ALBUMIN IN THE CRITICALLY ILL

The scientific community has deliberated for decades in clinical and pre-clinical trials about the efficacy and volume-expanding capability of various resuscitation fluids, especially in sepsis.[7] Resuscitation fluids play a critical role in sepsis by augmenting the circulation volume and ensuring tissue perfusion. It has been often hypothesised that the resuscitation fluid has an impact on the endovascular endothelium and microcirculation, resulting in modulation of transvascular leakage, microvascular tone, inflammation, and interstitial oedema.[8] The approach to fluid resuscitation revolves around our recent understanding of the role of the glycocalyx which lines the vascular endothelium.. Endothelial glycocalyx regulates vascular permeability. Critical illness, sepsis, shock, and hyperglycaemia damage the glycocalyx layer. Shedding or damage to the endothelial glycocalyx, has a direct correlation with adverse outcomes in the critically ill, and it is potentially conceptualised that its restoration can improve outcomes. Albumin physiologically binds to the glycocalyx and prevents its shedding, thereby ensuring vascular integrity and normal capillary permeability.[6,9]

Clinically used albumin is non-glycosylated and negatively charged. With a single polypeptide chain of 585 amino acids, it has a molecular mass of 66.438 kD. Synthesised in the liver, it has a 21-day half-life and is slowly catabolised in the muscles, kidney, and liver.[9] The Surviving Sepsis Campaign Guidelines 2021 now

Table 2: Drugs/Techniques used for Analgosedation[6]

Analgesics/Sedatives	Drugs/Techniques	Significant Adverse Effects
Opioids 1st line drugs	Remifentanil Fentanyl	Increased requirement of analgesics and hyperalgesia after cessation, respiratory depression
Opioids 2nd line drugs	Morphine	Drug accumulation, longer duration of action, delirium, immunosuppression
Non-opioid analgesics	Paracetamol Non-steroidal anti-inflammatory drugs Ketamine	Adjunctive pain medications to reduce opioid requirements and opioid-related side effects
Regional-analgesia techniques	Epidurals Nerve blocks	Useful only in specific subpopulations of surgical patients, patients with rib fractures, etc.
Non-pharmacological methods	Injury stabilisation Patient repositioning Use of heat/chill Reassuring the patient Proper environment Music therapy Mindfulness Electrostimulation Massages	
Multi-modal analgesia	Pharmacological + non-pharmacological	

Table 3: Sedation

Type	Agent	Risks and benefits
Hypnotic agents	Dexmedetomidine Propofol	Sedation alone without analgesia may lead to agitation or delirium in critically ill.
Benzodiazepines	Midazolam	Delirium risk
Inhalational agents	Isoflurane Sevoflurane	Using in-line devices Sedaconda and Mirus; Not indicated for procedural pain management

recommend "using albumin in patients who received large volumes of crystalloids" in view of the recent evidence showing "higher blood pressure at early and later time points," "higher static filling pressures," and "lower net fluid balance" with albumin. Although most patients with sepsis and septic shock need high volume infusions, the critical threshold for initiating albumin therapy is yet to be established. Although the Albumin Italian Outcome Sepsis (ALBIOS) trial shows no difference in mortality with both crystalloids and 20% human serum albumin (HSA) solution, further subgroup analysis has established a decreased mortality with HSA in patients with septic shock.[9,10] The Chinese Society of Critical Care Medicine in 2021 recommended that in cases of persistent haemodynamic instability in septic shock, HSA infusion is a viable option after the transfusion of 30 mL/kg crystalloid and it can potentially reduce mortality. However, currently, there is no evidence that suggests the superiority of low- (4%–5%) or high-concentration (20%–25%) HSA for resuscitation in sepsis.[10] It is suggested that HSA can be discontinued on attaining haemodynamic stability or serum albumin levels above 30 g/L. Based on recent evidence, it is preferable to avoid HSA in acute brain injury or to reduce intracranial pressures in traumatic brain injury. There are also some recommendations for HSA in patients with acute respiratory distress syndrome with hypoproteinaemia.[10] Current expert opinion suggests that plasma is the currently preferred colloid in burns. However, 5% human albumin solution is a viable option if plasma is unavailable. Use of albumin prior to furosemide, compared to furosemide alone, potentiates diuresis in the critically ill.

Future research is needed to ascertain if the preservation or repair of the endothelial glycocalyx can improve clinical outcomes. It needs to be further established through large multicentric trials if HSA can be used as a therapeutic resuscitation strategy in sepsis.

RECENT ADVANCEMENTS IN THE MANAGEMENT OF RESPIRATORY FAILURE

Respiratory failure (RF) is the inability of the respiratory system to maintain its function of gas exchange. The management of RF is challenging, ever evolving, and has seen numerous advancements in recent times.

High flow nasal oxygen

High-flow nasal oxygen (HFNO) therapy involves delivering high flows, of up to 60 L/min, of oxygen-enriched gas at a fraction of inspired oxygen (FiO_2) ranging from 21% to 100%. The gas mixture is delivered through non-occlusive nasal prongs, humidified to full saturation, and heated

to core temperature.[11] HFNO reduces the patient's respiratory efforts by generating positive pressures in the upper airways, throughout the respiratory cycle, thereby aiding in recruiting and enhancing dynamic lung compliance. Additionally, the high flows wash out upper airway dead spaces, thereby reliably delivering adequate FiO_2 and reducing rebreathing.[12] By matching the patient's peak inspiratory flow rates, HFNO reduces inspiratory resistance and the work of breathing. The elevated respiratory rate and mouth breathing in patients with RF is known to hamper airway humidification. HFNO provides almost the same level of humidity as is found in the alveoli, thus optimising ciliary function, mucous hydration, improving patient comfort, and reducing inflammation.[13]

Non-invasive positive pressure ventilation

Non-invasive positive-pressure ventilation (NPPV) refers to mechanically ventilating the lungs using techniques not requiring an invasive artificial airway. Used early during RF, NPPV can reduce treatment failure, patient mortality, and the need for endotracheal intubation. The commonly used modes of NPPV include bilevel positive airway pressure (BPAP) and continuous positive airway pressure (CPAP) using oral, nasal, or facial interfaces. Recent years have shown significant improvements in sensor and microprocessor technology that have been incorporated in BPAP devices, thus providing variable ventilation modes that can self-adjust in response to respiratory variables.[14,15]

1. Adaptive servo-Ventilation/ Anticyclical Ventilation: This form of non-invasive ventilation provides automatically adjustable pressure support, with changes in inspiratory support on breath-by-breath basis. This mode is useful in managing patients with significant respiratory instability.
2. Volume-Assured Pressure Support: This mode provides variable inspiratory support, thus maintaining a target level of ventilation, despite alterations in airway resistance and changes in lung or chest wall compliance.
3. Automatic Expiratory Positive Airway Pressure (EPAP): Automatic EPAP auto-titrates EPAP, thus maintaining upper airway patency during BPAP or volume-assured BPAP. Use of auto-EPAP with BPAP is particularly beneficial in acute settings.

Recruitment manoeuvres

Recruitment is a dynamic process of reopening airless alveoli through an intentional transient increase in transpulmonary pressures.[16] Recruitment manoeuvres (RM) can be performed by various techniques. Traditionally, sustained inflation by setting the ventilator to the CPAP mode and increasing the pressure to 30–40 cmH_2O for 30–40 s has been used. Newer methods include continuing ventilation using stepwise increases in peak pressure and/or positive end-expiratory pressure (PEEP), thus mitigating the prolonged high transpulmonary pressures used in sustained inflation. This can be done by either incrementally increasing PEEP with a stable peak end-inspiratory pressure or a stepped and prolonged RM using a fixed driving pressure or tidal volume and a stepwise increase in PEEP.[16] Extended sigh manoeuvres (eSigh) also effectively improve lung aeration and are associated with lower mean airway pressures, with consequently less risk of haemodynamic compromise and hyperinflation.

Prone ventilation

This refers to delivering mechanical ventilatory support to the patient lying in the prone position. Proning improves lung perfusion and reduces lung compression, reduces difference between the dorsal and ventral transpulmonary pressures, decreases ventral alveolar over-inflation and dorsal alveolar collapse.[17] Thus, it decreases ventilator-associated lung injury and makes ventilation more homogeneous, thereby improving oxygenation.

Optimising mechanical ventilation

New technologies allow adequate bedside monitoring of critically ill patients on ventilatory support. This includes electrical impedance tomography, which is a non-invasive and radiation-free imaging tool used to do real-time, bedside, and continuous imaging of the distribution of pulmonary ventilation.

Stem cell therapy

Mesenchymal stem cell (MSC) therapy is a novel approach to managing severe respiratory illnesses. MSCs secrete various factors like prostaglandin E2 (PGE2), granulocyte-macrophage colony-stimulating factor, and cytokines, all of which promote alveolar macrophage phagocytosis and influence immune function.

MECHANICAL SUPPORT OF THE FAILING CIRCULATION AND RESPIRATION

Extracorporeal membrane oxygenation

Extracorporeal membrane oxygenation (ECMO) was used as rescue therapy in patients with

acute respiratory distress syndrome (ARDS) and refractory hypoxaemia in haemagglutinin type 1 and neuraminidase type 1 influenza A (H1N1)–infected patients, in neonates with respiratory distress.[18] After the CESAR(Conventional Ventilatory Support vs Extracorporeal Membrane Oxygenation for Severe Adult Respiratory Failure) trial showed an improved mortality and morbidity six months after patients with severe respiratory failure were treated with ECMO, it was further used during the coronavirus disease (COVID)-19 pandemic in patients with refractory ARDS and myocarditis.[19] The use of ECMO in the COVID-19 pandemic has reawakened interest in its utility in cardiorespiratory failure. There has been no randomised controlled trial in recent times that has proven the mortality benefit of ECMO, either during COVID-19 times or afterward. Moreover, it can only be performed by a multidisciplinary team with proper training, and best results are obtained if we choose the right patient and the right type of ECMO. It weighs heavily on resources and expense, which restrict its availability even at super-speciality hospitals.

Two types of circuits are commonly used for ECMO:

(i) Veno-arterial (VA) ECMO: allows gas exchange and haemodynamic support while blood is pumped from the venous to the arterial side.
(ii) Veno-venous (VV) ECMO: facilitates only gas exchange; blood is removed from the venous side and then pumped back into it but does not provide haemodynamic support.

The patient must be haemodynamically stable. Cardiac support can be given by ECMO. Only the VA ECMO can be used for this purpose. It provides both respiratory and haemodynamic support in cases of low cardiac output and hypotension despite adequate intravascular volume and high dose of ionotropic agents. The VA ECMO circuit is connected parallelly to the heart and lungs requiring arterial and venous cannulation. Blood bypasses both the heart and the lungs, so the pulmonary arterial pressure decreases. It is used in severe cardiac failure due to almost any cause, such as acute coronary syndrome, refractory arrhythmias, severe sepsis, drug overdose, toxicity, myocarditis, pulmonary embolism, primary graft failure in the heart or heart lung transplant, as a bridge to ventricular assist device support in chronic cardiomyopathy and as a bridge to heart transplant.

Respiratory support can be given by ECMO. Both VA ECMO and VV ECMO can be used for this purpose. VV ECMO is used to provide oxygenation or carbon dioxide removal or both while the lungs recover, or as a bridge to transplant in case of end-stage liver disease. It does not provide cardiac support and requires only venous cannulation. It is connected in series to the heart and lungs.

There are several contraindications to the use of ECMO. These include patients with minimal chances of improvement who are not candidates for transplant or ventricular assist device support, disseminated malignancy, known severe brain injury, and severe chronic organ dysfunction. VV ECMO is contraindicated in cardiogenic failure and in severe chronic pulmonary hypertension. VA ECMO is contraindicated in patients with peripheral vascular disease. Advanced age, obesity, and contraindication to use of anticoagulants is a deterrent to the use of ECMO.

The complications and limitations of ECMO have to be kept in mind. The complications per se are due to surgical insertion of the cannulae, circuit tubing, or anticoagulation. Incidence of bleeding and thrombotic events is high in VV ECMO, thus increasing the mortality.[20] Distal limb perfusion in femoral VA ECMO can be a challenge. ECMO is not a treatment modality for cardiopulmonary dysfunction but a device to support the lungs (VV ECMO) and both cardiac and pulmonary support (VA ECMO). It has its own limitations for use. Artificial membranes having polymethyl pentene have low resistance, are more biocompatible, and can be used for extended durations in ECMO.[21] The use of simulation should become a standard method for training and reinforcing technical skills.[22] Enhanced learning can be achieved by coupling mannequins and ECMO, with realistic scenarios making ECMO within reach for a more extensive list of patients.

NEWER ANTIMICROBIALS

In our daily practice, we face the challenge of treating multidrug resistance organisms (resistance to at least three different classes of antimicrobials) like multi-drug resistant tuberculosis (MDR-TB), methicillin-resistant *Staphylococcus aureus* (MRSA), carbapenem-resistant *Pseudomonas aeruginosa* (CRPA), etc.

With the development of drug resistance due to various mechanisms like target modification, drug inactivation, and limited uptake, introduction of newer antimicrobial drugs is challenging.

The AWaRe (access, watch, reserve) classification of antibiotics for evaluation and monitoring of its use was developed by the World Health Organization after taking into account the impact of different antibiotics on antimicrobial resistance.[23]

Monobactams

Aztreonam and carumonam belong to this group. They inhibit bacterial cell wall synthesis by blocking peptidoglycan cross-linking and have a spectrum of activity on gram-negative bacteria (GNB). They are poorly absorbed by the oral route and hence are preferably given by the intravenous, intramuscular, or inhalational route.

Cephalosporins

Some fifth generation cephalosporins such as ceftaroline fosamil, ceftobiprole medocaril, and ceftolozane/tazobactam act by disrupting the synthesis of the peptidoglycan by inhibiting multiple penicillin-binding proteins and have additional beta-lactamase activity.

Tetracyclines

Eravacycline, minocycline, and omadacycline belong to this group. They disrupt bacterial protein synthesis by binding to the 30S ribosomal subunit with high specificity, thereby preventing the incorporation of amino acid residues into elongating peptide chains that cause cell death/stasis. They act on broad spectrum gram-positive organisms.

Glycopeptides

Dalbavancin and oritavancin belong to this class. Among these, dalbavancin acts by inhibiting synthesis of cell wall peptidoglycan and cell membrane permeability, whereas oritavancin binds to the stem peptide of peptidoglycan precursors and inhibits transglycosylation.

Carbapenems

Faropenem, meropenem/vaborbactam, and imipenem/cilastatin/relebactam are penem class of antibiotics that inhibit bacterial cell wall synthesis.

Phosphonic acid derivatives

Fosfomycin IV inhibits an enzyme-catalysed reaction in the first step of the synthesis of the bacterial cell wall and it has a spectrum of activity on *Enterococcus faecalis*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Proteus vulgaris*, *Salmonella schottmuelleri*, *Staphylococcus aureus*, and *Streptococcus pyogenes*.

Trimethoprim derivatives

Iclaprim belongs to this class which are dihdro-folate reductase inhibitors active against GNB, gram-positive bacteria (GPB), atypical, bacteria, MRSA, and vancomycin-resistant *Staphylococcus aureus* (VRSA).

Pleuromutilins

Lefamulin derived from this class acts by inhibiting bacterial protein synthesis through interactive binding to peptidyl transferase in the centre of the 50S bacterial ribosome subunit which proved to be sensitive against GPB associated with CAP, MRSA, VRSA.

Oxazolidinones

Linezolid and tedizolid derived from this class act by inhibiting bacterial protein synthesis by binding to 23S ribosomal messenger RNA of the 50S subunit of the ribosome and act on facultative aerobic and anaerobic GPB, MRSA, and methicillin-sensitive *Staphylococcus aureus* (MSSA).

Polymyxins

Polymyxins include colistin and polymyxin B. These drugs disrupt the bacterial cell membrane. Colistin is also known to exert ant-endotoxin activity, while polymyxin binds and neutralises lipopolysaccharide and inhibits respiration of gram-negative bacterial cells.

SUMMARY

Analgosedation in the critically ill has gained importance in current times. While the colloid-crystalloid controversy is almost settled, albumin has re-entered the fray as a possible repairer of the injured glycocalyx. The COVID-19 pandemic forced us to relook at various ventilator strategies and recruitment manoeuvres. The application of mechanical support for the failing circulation has become more common and refined with clear end points. Rising resistance of microbia to current antibiotics has signalled the need for the repurpose of and research on newer antibiotics. Though we can deploy these skills and resources in the service of our patients, prudent utilisation of the same will increase their longevity.

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