

Challenges in Intensive Care Airway Management: A Comprehensive Review

Yoğun Bakım Havayolu Yönetimindeki Zorluklar: Kapsamlı Bir Derleme

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Abstract

This review delves into the complexities of difficult airway management in intensive care units (ICUs). We categorise difficult airway management into five classes according to the American Society of Anesthesiologists guidelines. The review highlights the higher incidence of difficult airway cases in ICUs compared to operating rooms, attributed to various factors such as the critical status of ICU patients, fluid therapy complications, and the emergency nature of many intubations. We discuss the effectiveness of traditional anatomical indices in predicting difficult airways, noting their limited predictive value. We also propose a difficult airway algorithm for ICU settings, which adapts to three potential scenarios: anticipated, unanticipated, and critical "Can't Intubate Can't Ventilate" situations. This algorithm is complemented by the Vortex Approach, a cognitive tool designed to streamline decision-making in difficult airway scenarios. We conclude with best practice recommendations adapted from the National Audit Project 4, emphasising the need for specialised training, equipment readiness, and a collaborative team approach in ICU airway management.

Keywords: Airway management, intensive care, intubation

Öz

Bu derleme, yoğun bakım ünitelerinde (YBÜ) zor havayolu yönetiminin zorluklarını ele almaktadır. Amerikan Anestezi Uzmanları Derneği kılavuzlarına göre zor havayolu yönetimini beş sınıfa ayırıyoruz. Derleme, zor havayolu olgularının YBÜ'lerde operasyon odalarına kıyasla daha yüksek oluşunu vurgulamakta; bu durumun nedenleri arasında yoğun bakım hastalarının kritik durumu, sıvı terapisi komplikasyonları ve birçok entübasyonun acil niteliği bulunmaktadır. Geleneksel anatomik indekslerin zor havayollarını tahmin etmedeki etkinliğini tartışıp, bunların sınırlı tahmin değerlerine dikkat çekmeyi amaçlıyoruz. Ayrıca, YBÜ için üç potansiyel senaryoya uyum sağlayan bir zor havayolu algoritması öneriyoruz; öngörülen, beklenmeyen ve kritik "Entübe Edememe-Havalandıramama" durumları. Bu algoritma, zor havayolu senaryolarında karar almayı kolaylaştırmak için tasarlanmış bilişsel bir araç olan Vortex Yaklaşımı ile tamamlanmaktadır. YBÜ havayolu yönetiminde uzmanlaşmış eğitim, ekipman hazırlığı ve işbirlikçi ekip yaklaşımı ihtiyacını vurgulayan Ulusal Denetim Projesi 4'ten uyarlanan en iyi uygulama önerileriyle sonuca varıyoruz.

Anahtar Kelimeler: Havayolu yönetimi, yoğun bakım, entübasyon

Introduction

The approach to the airway in the intensive care unit (ICU) is a complex procedure, placing this subgroup of patients in a high-risk category for difficult airway (DA) management (1).

In a Closed Claims analysis (2,3) by the American Society of Anesthesiologists (ASA) Closed Claims Project—a database that records all anesthetic events leading to legal complaints – it was found that for events related to the airway, occurrences outside the operating room environment, such as in the emergency room

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or ICU, resulted in a fatal outcome in approximately 87% of cases, with permanent brain injury in the remaining cases. These findings were recently supported by a multicenter observational project in the United Kingdom (1).

Definitions and Prevalence

The difficulty in airway management can be classified into 5 distinct categories, according to ASA recommendations (4):

a) Difficult mask ventilation or supraglottic device use [e.g., laryngeal mask airway (LMA), laryngeal tube, or intubating LMA (ILMA®)]: when adequate ventilation by an Anesthesiologist is not possible due to inadequate mask sealing, excessive leakage, or excessive resistance to gas flow.

b) Difficulty in supraglottic device placement: with the need for multiple placement attempts in the presence or absence of tracheal pathology.

c) Difficult direct laryngoscopy (DL): when no portion of the vocal cords can be visualised after multiple attempts of conventional laryngoscopy.

d) Difficult tracheal intubation: when tracheal intubation requires multiple attempts in the presence or absence of tracheal pathology.

e) Failed intubation: when the placement of the endotracheal tube (ETT) fails after multiple attempts.

According to the literature, the incidence of DA is higher in the ICU compared to the operating room, ranging between 10 to 22% of all intubations (5-8).

Why do patients in ICUs experience DA?

Various factors can explain this:

- Patients in ICUs are at the limit of their functional reserves, particularly in terms of cardiorespiratory function, often experiencing multi-organ failure and a significant need for vasopressors, making them more susceptible to hypoxia or sedatives and with a poorer response to fluids (9);

- These patients often have a positive fluid balance due to the need for abundant prior fluid therapy. This can lead to airway oedema or interstitial pulmonary oedema (10).

- Patients need to be more adequately positioned for airway management, and often access to the head is limited by the presence of monitoring/infusion pumps or extracorporeal therapies, making DL difficult (11).

- In ICUs, Orotracheal Intubation can potentially occur as an emergent procedure, either due to the reasons mentioned above or due to ventilatory weaning failure [in 26-42% of all weaning attempts (12-14)] or accidental extubation in up to 15% of cases (15).

- These patients have an increased risk of regurgitation because they traditionally are not fasted (considered "full stomach") (16).

- DA/Invasive equipment is not frequently immediately available in the ICU, and the use of EtCO₂ for confirmation of the correct ETT positioning is limited (17).

The addition of these factors may reflect in a greater need for multiple attempts at endotracheal intubation. According to Mort (19), it is observed that several attempts of intubation using DL are associated with a dramatic increase in the incidence of hypoxemia, regurgitation of gastric contents, aspiration, bradycardia, and cardiorespiratory arrest (Figure 1) in patients in a non-operating room environment (18).

Prediction of DA

Numerous clinical conditions predict a DA (20,21), summarized in Table 1.

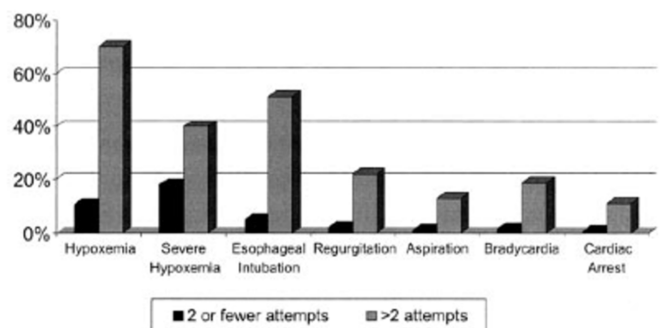


Figure 1: Graphic display of complications by intubation attempts

Table 1: Clinical conditions that predict a difficult airway (35,54)			
Anomalous facial anatomy	Limited mouth opening	Cervical restriction	Larynx/Pharynx anomalies
<ul style="list-style-type: none"> • Small mouth and/or macroglossia • Dental anomalies • Prognathism • Obesity • Advanced pregnancy • Acromegaly • Congenital syndromes (e.g., treacher collins syndrome) 	<ul style="list-style-type: none"> • Masseter spasm (dental abscess) • Temporomandibular joint dysfunction • Facial burns • Post-radiation fibrosis • Scleroderma 	<ul style="list-style-type: none"> • Obesity/short neck • Limited cervical mobility (e.g., ankylosing spondylitis) • Previous surgery of the cervical spine • Presence of cervical collar • Post-radiation fibrosis 	<ul style="list-style-type: none"> • High or anterior larynx • Deep vallecula • Anatomical changes of the epiglottis or hypopharynx • Subglottic stenosis

A previous history of difficult intubation or the presence of signs or symptoms suggestive of cervical/pharyngeal/mediastinal pathology is relevant in anticipating a likely difficulty in the airway. On the other hand, despite being universally used, it has not yet been demonstrated a significant positive predictive value for the use of common anatomical indices, such as inter-incisor distance, Mallampati index, cervical mobility, or distances between various cervical anatomical point (11,22-27). The low predictive value of individual anatomical indices has led to the structuring of combinations of indices and the creation of scores, also with variable sensitivity and specificity. Additionally, in the context of ICU, the use of these methods can be time-consuming and often impractical. A method for predicting DAs outside the operating room, called the MACOCHA score (Table 2) (28), has been described and has undergone external validation. To rule out the probability of a DA, a cut-off of 3 seems appropriate.

Considering that the prevalence of DA is challenging to establish among populations and most tests and scores have a low negative predictive value, it is accepted by several authors (29-33) that the systematic planning of an intubation strategy is crucial for addressing unexpected problems that may occur during the intubation attempt. The structured planning of this strategy is suggested in the form of an algorithm.

DA Algorithm in the ICU

Each patient poses a unique airway challenge, making the teaching of complex algorithms on airway management often unrealistic and counterproductive (34). While the ASA DA algorithm (4) is universally known and taught among anesthesiologists, it has faced various criticisms, being designed for the operating room environment and challenging to execute in emergencies. Additionally, it is not widely disseminated among nurses and non-anesthesiologist physicians, limiting communication and teamwork in an emergent situation (35). Therefore, many authors consider it unsuitable for difficult or emergent airway situations outside the operating room, particularly in locations such as the emergency room or the ICU (29,36).

	Points
Factors related to the patient	
Mallampati ≥ 3	5
Obstructive Sleep Apnea Syndrome (OSAS)	2
Reduced cervical spine mobility	1
Reduced mouth opening (<3 cm)	1
Factors related to pathology	
Coma	1
Severe hypoxemia ($\text{SaO}_2 < 80\%$)	1
Factors related to the operator	
Non-anesthesiologist	1
Total	12

An alternative strategy aligning with the approach proposed by the DA Society (DAS) (31), considers three scenarios:

1. Anticipated DA

This represents the least lethal "scenario" since there is time to consider a strategy, optimize the situation, and obtain appropriate adjuvants/supplemental assistance. In this case, two fundamental questions must be addressed: "Should the patient be intubated awake, or can there be an anesthetic induction?" and "Which intubation technique should be used?"

- **Awake intubation:** It is more time-consuming, requires trained personnel, is less comfortable for the patient, and may need to be abandoned due to a lack of cooperation. However, it is significantly safer, considering the maintenance of pharyngeal and laryngeal muscle tone and spontaneous ventilation. It is commonly used in situations involving fiberoptic intubation and retrograde intubation.

- **Intubation under anesthetic induction:** This involves inducing deep anesthesia sufficient to allow for DL and orotracheal intubation without the use of muscle relaxants and optimally with the maintenance of spontaneous ventilation. Intubation without muscle relaxation can be facilitated by the prior application of lidocaine spray. Patient preparation, equipment readiness, and the involvement of all personnel are crucial in this scenario (Table 3).

2. Unanticipated DA

In this case, there is only a small time-window to address the problem, aiming to prevent hypoxemia, hypoventilation, hemodynamic instability, and potentially cardiorespiratory arrest (37). The patient is already anesthetised, often apnoeic, relaxed, and may have undergone several unsuccessful intubation attempts. If the appropriate equipment and assistance are not immediately accessible, there may not be time to obtain them! If a depolarizing relaxant, a short-acting non-depolarizing agent,

Table 3: Requirements for the approach to DA with intubation under anaesthesia induction, adapted from Lavery and McCloskey (11)

Fasted patient
Anti-acid therapy
Optimal positioning
Monitoring of vital signs and capnography
Availability of endotracheal tubes and laryngoscope blades in various shapes and sizes
Availability of adjunct devices, ideally bougies, stylets, introducers, laryngeal masks (of various sizes), or Combitube [®]
Availability of a cricothyroidotomy kit or mini-tracheostomy kit
Preoxygenation of the patient
Maintenance of spontaneous ventilation until the airway is secured
Use of bimanual laryngoscopy or BURP (Backward, Upward, Rightward, Pressure) maneuver if necessary
DA: Difficult airway

or a reversible relaxant has been used and ventilation is easy, it may be appropriate to allow the patient to regain consciousness, with the option to plan a delayed awake intubation. However, in most cases, due to the need to establish a definitive airway for respiratory failure, altered consciousness, or other reasons, alternative techniques to DL are often employed to improve the chances of visualising and intubating the trachea (38). The following are a set of techniques and devices alternative to DL. For a better understanding of their potential, it is suggested to search for illustrative videos online or attend a DA course.

Bimanual Laryngoscopy (BURP)

This corresponds to the initials of Backward, Upward, Rightward, Pressure, (BURP) which can improve the visualization of the vocal cords under DL (39), when performed by the laryngoscopist and subsequently maintained by the assistant.

Bougie or Modified Bougie (Frova Catheter)

Bougie is a malleable, thin, and elongated plastic cylinder that can have a blunt distal tip in the shape of a "hockey stick" to facilitate direction and entry through a less visible or even non-visible glottis (blind introduction). The correct placement of the Bougie in the tracheobronchial tree is revealed by transmitting the contact of the tip with the successive tracheal rings, which is felt as a series of bumps. At this point, the ETT can be introduced, according to the Seldinger technique (40) through the Bougie, which acts as an introducer/guide. It is, for many authors (41,42), the first alternative adjunct in a Ventilation-Associated Device (VAD) situation because it is cost-effective, disposable, enables ventilation (in the case of the Frova catheter), and has a quick learning curve.

Stylus with Light Source (Light Wand)

The stylus with a light source corresponds to a flexible introducer with an optical fiber light source, which is inserted into the ETT to later allow intubation when the light source is in the trachea. It is a device that facilitates blind intubation because it distinguishes the tracheal lumen (more anterior) from the esophageal lumen through transillumination of cervical tissues when the light source passes beyond the vocal cords (43). An important disadvantage is the requirement for low ambient lighting, which is not desirable (and often not possible) in the intensive care environment. Additionally, it is contraindicated in patients with anatomical airway alterations or cervical tissue. The intubation failure rate appears to be similar that of the lighted stylet.

Supraglottic Devices

- LMA®: The classic LMA (cLMA®) is a small rubber mask shaped like a spoon with an inflatable elliptical cuff, connected to a hollow plastic tube. It is blindly placed in the hypopharynx, adapting obliquely to the pharyngeal opening. Despite providing a seal for ventilation, the cLMA® does not protect against the

risk of aspiration. However, compared to intubation, it can be placed more successfully and quickly, especially by operators with limited training (44,45), making it useful as an alternative device in VAD situations.

- Modified laryngeal masks: The technology of laryngeal masks has seen significant differentiation in recent years, with various modified laryngeal masks available in the market. These include the ILMA®, Proseal LMA®, and several variations, including disposable formats.

The ILMA has a more rigid, angled, and larger-diameter tube with an insertion handle (see figure). These masks allow the introduction of a modified wire-reinforced endotracheal tube that can be inserted through the mask for blind intubation or with the assistance of a fiberoptic. Due to their characteristics, they can be used in trauma situations with suspected cervical injury or limited airway access (46). The Proseal LMA® (47) was introduced to overcome the risk of aspiration and improve adaptation to the anatomical structures of the hypopharynx. It features a larger and more concave mask, and the cuff is positioned posteriorly.

Additionally, it incorporates a working channel parallel to the tube, allowing the introduction of a suction catheter for esophageal content aspiration, thus limiting the risk of regurgitation.

Videolaryngoscopes: C-Mac, Glidescope®, McGrath®

Videolaryngoscopes are modified laryngoscopes that incorporate a rigid optical fiber with a camera at the distal end of the blade. The blade is inserted into the oral cavity along the midline and directed toward the base of the tongue until the epiglottis is visualized. The distal end of the endotracheal tube can then be directed through the glottis under indirect visualization. These devices appear to improve the approach to airway management in Anaesthesiology and Intensive Care, reducing the incidence of difficult laryngoscopy and intubation (48). A major disadvantage is their costliness.

Combitube® (Dual-Lumen Esophagotracheal Airway)

The Combitube® is a modified blind-insertion tube that includes an esophageal obturator and a tracheal tube (Figure 1). Regardless of its placement in the trachea or esophagus, it allows ventilation with partial protection against aspiration. Potential disadvantages include the inability to aspirate the trachea if the distal end is in the esophagus (more frequent position) and the possibility of airway trauma during placement. For these reasons, it is contraindicated in patients with known esophageal pathology, intact laryngeal reflexes, or after ingestion of caustic substances.

3. "Can't Intubate-Can't Ventilate"

This is an absolute emergency situation. In this scenario, it is crucial to remain calm and follow an appropriate algorithm

that includes only two options: a “minimally” invasive approach with a satisfactory method of ventilation without intubation, or an invasive approach with a decision for a surgical airway (cricothyroidotomy vs. emergency tracheostomy). The choice should depend on the operator's familiarity with the technique and the availability of materials/human resources in each institution.

Cognitive Aid: “The Vortex Approach” (29)

In an emergency, having a protocol for action serves to organise a team's response systematically and prevent delays or lapses in certain therapeutic options. However, adherence to guidelines may be challenging in a stressful environment with limited time. As discussed above, in an emergency, protocol-based action should be simple (for quick recall) and universal, shared by all team members, allowing for anticipating treatment priorities. In the case of DA, creating such guidelines is complicated by the existence of various possible devices and the understanding that the clinical context certainly influences the most appropriate approach. In this context, guidelines need to be both simple and robust to guide the approach in a wide range of situations. Despite this, the guidelines (4,31) from societies dedicated to DA remain relatively complex and are designed for the operating room environment.

Therefore, all ICU staff need a simple and effective cross-sectional mental model for DA management during a critical event. The Vortex cognitive model (29) is one such suggested method, conceptualizing the DA approach as a funnel based on the following assumptions:

The primary goal is to ensure that oxygen delivery to the alveoli is maintained, associated with airway patency (patient kept in the “Green Zone”). This can be achieved by:

1. Facial mask – Non-surgical extra-glottic airway,
2. LMA – Non-surgical supraglottic airway,
3. ETT – Non-surgical transglottic airway,
4. Surgical infra-glottic and definitive methods (surgical airway and definitive airway).

Preferably, up to three “optimized attempts” should be made to secure the airway with each of the non-surgical techniques described above.

The order in which each technique should be used depends on the operator and the airway maintenance objective (Figure 2).

The inability to establish airway patency after exhausting the previous possibilities should prompt an immediate transition to a surgical airway, regardless of SaO₂.

The “green zone” is conceptualized as a horizontal surface that reinforces the idea that in the presence of a difficult airway (VAD), there is no immediate imperative to proceed with successive airway manipulations. Instead, the focus is on ventilation/oxygenation, providing an opportunity to pause and devise a strategy while keeping the patient in a “safety zone”.

Proposal for an “Protocol” for Orotracheal Intubation in Intensive Care

It has recently been demonstrated that the use of an airway management protocol in intensive care has led to a reduction in complications associated with tracheal intubation (49). The protocol, the Montpellier algorithm, includes the interventions described in the Table 4. Implementing this protocol has resulted in a significant reduction in complications associated with intubation (9% vs. 21%) (49,50).

Table 4: Orotracheal intubation protocol in the ICU [modified from (49)]

Pre-intubation
<ol style="list-style-type: none"> 1. Presence of two operators 2. Administration of “Fluid Loading” (recommended 500 mL of 0.9% NaCl) in the absence of cardiogenic oedema 3. Preparation of long-term sedation and noradrenaline infusion 4. Pre-oxygenation for 3 minutes with NIV in case of respiratory failure (FiO₂ 100%, pressure support ventilation between 5-15 cmH₂O to achieve tidal volume between 6-8 mL/kg, and PEEP of 5 cmH₂O)
Peri-intubation
<ol style="list-style-type: none"> 5. Rapid sequence intubation: <ul style="list-style-type: none"> • Propofol 0.1 mg/kg or ketamine 1.5-3 mg/kg • Succinylcholine 1-1.5 mg/kg (in the absence of known allergy, hyperkalaemia, severe acidosis, neuromuscular disease, burns over 48 hours, spinal trauma, and organophosphate poisoning) • Rocuronium: 0.6-0.9 mg/kg in case of succinylcholine contraindication, prolonged stay in the ICU, or risk of neuropathy 6. Sellick maneuver (also known as cricoid pressure is used for endotracheal intubation to prevent the occurrence of gastroesophageal reflux)
Post-Intubation
<ol style="list-style-type: none"> 7. Immediate confirmation of tube placement by capnography 8. Immediate initiation of noradrenaline infusion if diastolic blood pressure <35 mmHg 9. Initiation of long-term sedation 10. Initiation of “protective ventilation”: Tidal volume 6-8 mL/kg, PEEP>5cm H₂O , respiratory rate 10-20 cycles/min, P_{plateau}<30 cmH₂O 11. Recruitment maneuver: CPAP 40 cmH₂O for 40s, FiO₂ 100% (if the patient does not have cardiovascular collapse) 12. Maintenance of cuff pressure at 25-30 cmH₂O
NIV: Non-invasive ventilation, CPAP: Continuous positive airway pressure, ICU: Intensive care unit, PEEP: Positive-end-expiratory pressure

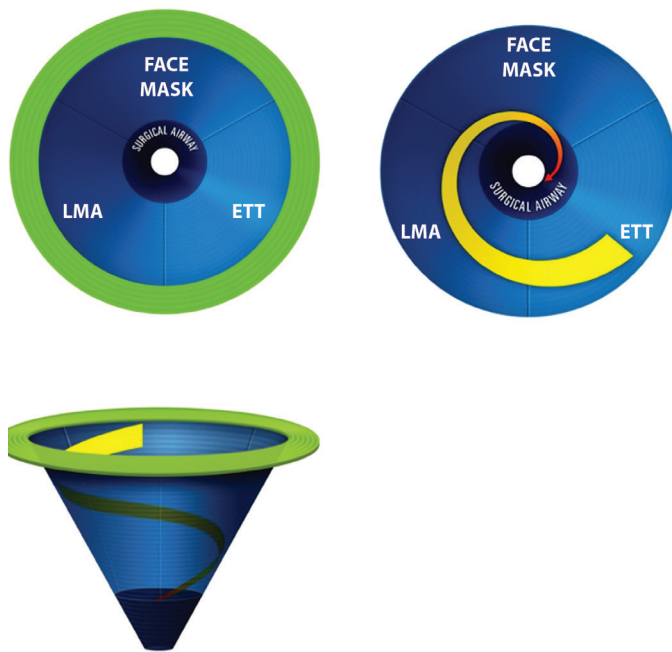


Figure 2: Concept of "Green Zone"

ETT: Endotracheal tube, LMA: Laryngeal mask airway

Delayed Sequence Intubation (DSI)

Unlike rapid sequence intubation, which involves the simultaneous administration of a hypnotic agent and a muscle relaxant without providing ventilation until endotracheal intubation, DSI involves the administration of specific sedative agents with minimal attenuation of spontaneous ventilation or airway reflexes. Another way to conceptualise DSI is to promote mild sedation of the patient while effectively pre-oxygenating under non-invasive ventilation. This technique often uses Ketamine and Continuous Positive Airway Pressure, as described in the Montpellier algorithm (49). After achieving $SpO_2 >95\%$, the muscle relaxant can be administered, and ETI can be performed. In the case of patients in respiratory failure, DSI appears to be a safe and effective alternative to conventional pre-oxygenation (51-54).

Best Practice Recommendations for Airway Management in the ICU [Adapted from the National Audit Project 4 (NAP4) Recommendations (1)].

The NAP4, conducted in the United Kingdom in 2011, was a national project to record all airway-related complications that occurred in the previous year. From this project, which is available for consultation, emerged best practice recommendations in the field of intensive care, described in the Table 5, aiming to

Table 5: NAP4 best practice recommendations for airway management in the ICU	
Capnography	Capnography should be used during endotracheal intubation in all critical patients, regardless of their hospital location. Continuous capnography should be used in all ICU patients who are intubated and ventilator-dependent (including those with tracheostomies). When capnography is not used in the aforementioned situations, there should be documentation of the clinical reason for non-use and regular review of the situation. Training for all ICU staff should include capnography interpretation. The focus of the training should be on airway identification or displacement, as well as recognition of the capnography waveform during cardiac arrest.
Intubation	An intubation checklist should be developed and used for all intubations of critically ill patients. The checklist should include alternative plans.
Anticipation of difficulty and planning	Each ICU should have an algorithm for airway management during intubation, extubation, and reintubation. Patients at risk of airway-related events should be identified early and clearly recognized by the staff. There should be a documented plan for these patients, including the primary plan and alternatives, as well as the necessary additional strategies and equipment. This information should be communicated and validated at each shift change.
Displacement of the endotracheal tube	Staff training should emphasize the recognition and risks of displacement of the endotracheal tube/tracheal cannula. This event is more common in obese patients, those with tracheostomies, during mobilisation, and when sedation is interrupted.
Obesity	Obese critically ill patients should be identified as individuals with an increased risk of airway complications and an elevated risk of associated morbidity (55).
Airway equipment	All ICUs should have immediate access to a difficult airway cart. This cart should have the same content and layout as the one in the operating room. The difficult airway cart should be checked regularly (56,57). A fiberscope should be immediately available for use in the ICU.
Cricothyrotomy	Training for the staff involved in advanced airway management should include regular practice of cricothyrotomies on manikins. Regular identification of anatomical landmarks should be encouraged, especially in obese patients.
Transfers	There should be recognition that intra or inter-hospital transfers are high-risk events, and it is recommended to assess the airway and establish an airway management plan before the transfer.
Staff	Specialty trainees responsible for managing critically ill patients should be proficient in basic management of emergency airways. Additionally, they should always have access to a senior professional with advanced airway expertise.
Training	Specialty trainees responsible for managing critically ill patients should learn basic emergency airway management. This training should include basic airway management, familiarity with algorithms for handling predictable complications, and the use/interpretation of capnography. This training should also serve to identify the limits of each trainee's experience and teach the early need for seeking help from more experienced clinicians. Team training and simulation should be included in this education. Regular audits of airway management issues and other critical events in the ICU should be conducted.

NAP: The National Audit Project 4, ICU: Intensive care unit

improve the quality of care and limit morbidity and mortality related to airway management.

Conclusion

If difficulty in endotracheal intubation is anticipated, consider the feasibility of an alternative initial approach. The use of ILMA, videolaryngoscopy, or bronchofibroscope is associated with high success rates but requires time and the patient's functional reserve.

If the lighted stylet is the chosen technique for initial intubation, it is important to note that the first attempt is always the best. After the second attempt, the risk of complications increases by 85%. Positioning should be optimised as much as possible, and pre-oxygenation is crucial.

Competent airway management depends on integrating individual knowledge, clinical judgment, appropriateness for the patient, and technical skills—factors that evolve throughout each professional's career.

Airway management is a team effort where everyone speaks the same language: training in cognitive tools among all team members and early recognition of the need for a senior anaesthesiologist is crucial to prevent fatal outcomes.

Airway management is not learned in theory: all techniques should be practised in elective settings (in the operating room) or in simulation. Attendance at a DA course is strongly recommended.

Ethics

Authorship Contributions

Surgical and Medical Practices: J.B.-E., B.C.M., Concept: M.K.B., B.C.M., Design: J.B.-E., B.C.M., Data Collection and/or Processing: E.K., M.K.B., Analysis and/or Interpretation: J.B.-E., M.K.B., Literature Search: E.K., B.C.M., Writing: J.B.-E., E.K.

Conflict of Interest: There is no potential conflict of interest to declare.

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