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Chapter

Airway Management Outside the Operating Room

Shakeel Moideen

Abstract

An anesthesiologist is an expert at airway management in the clinical environment. He or she has mastered knowledge of the anatomy and physiology of the normal and potentially abnormal airway. The environment of the operating room (OR) has been considered to be their most familiar area of work, where they feel most confident. Airway management outside this area is known to put patients at an increased risk of complications. This chapter addresses the important facets of this indispensable skill when used outside the operating room, taking into consideration both anesthesiologists and non-anesthesiologists as operators. Since the intensive care unit (ICU) is a similar environment to the OR, a separate chapter has been written for airway management in the ICU. Therefore, this chapter will concentrate on other areas outside the OR. It will not address resuscitation scenarios.

Keywords: outside OR, remote locations, airway complications, sedation, standalone anesthesia

1. Introduction

*The most compelling educational effort for the anaesthesia community should be to reduce the frequency and severity of complications related to managing the airway—Benumof 1995.*

Airway management outside the operating theater is associated with increased risks when compared with the management of the airway done in the operating theater setting [1]. Except for the resuscitation scenario, airway management is always associated with the administration of sedative medication to facilitate a procedure being performed. This could be diagnostic or therapeutic in nature. It is understood that the responsibility of managing the airway lies on the physician who prescribes the sedative drug, unless there is the presence of an assigned anesthesiologist to that area. The anesthesiologist is considered the expert for airway management in the clinical environment, who has mastered knowledge of the anatomy and physiology of the airway, usually with years of experience in dealing with the normal airway. They are also trained to handle the potentially abnormal airway and are most familiar with the newer equipment available for the management of the airway. The operating room has always been associated with terms such as being the anesthesiologist’s home or backyard. It is their most familiar area of work, where they feel most confident. The reason for this is that this area is most prepared to handle problems with the airway, not only in terms of equipment and available expert help, but also in terms of ergonomics. Airway management outside this area is known to
Special Considerations in Human Airway Management

put patients at an increased risk of airway complications. This chapter addresses the important facets of this invaluable skill when used outside the operating room, taking into consideration both anesthesiologists and non-anesthesiologists as operators. Since the intensive care unit is a highly specialized area, similar to the OR, a separate chapter has been written for airway management in the ICU. Therefore, this chapter will concentrate on other areas outside the OR. It will not address resuscitation scenarios where immediate airway management is unplanned and is a life-saving procedure, and may be needed in any area of the hospital and beyond.

2. Anticipating difficulty is key

As with any skill, preparation is fundamental and is the secret to avoiding harm to patients. Ideally, all patients needing airway manipulation outside the OR should be assessed for potential difficulty, and prepared just as they would be for an elective procedure in the OR. One of the reasons airway management is more difficult outside the OR than inside is due to the fact that there may not be enough time to learn about the patient's physical condition and to predict risk of difficult airway or aspiration. Whenever possible patients should be assessed for comorbidities, drug allergies and fasting status. An airway assessment should be completed. There are many aides-memoires to help with a quick but relatively thorough assessment of the airway to predict difficulty with mask ventilation and intubation. These should be available in all areas for the physician to refer to, ideally attached to the difficult airway trolley. Risk factors for difficult mask ventilation include an increased body mass index (BMI), history of obstructive sleep apnea (OSA), presence of a beard that may disrupt the seal of the face mask, being edentulous and having limited mandibular protrusion. A difficult laryngoscopy is anticipated when a patient has limited mouth opening, a Mallampati score of III or IV, limited head and neck movements, is obese and has an increased neck circumference.

Patient preparation is also important. A patient who is not fasting adequately is at a higher risk of aspiration of gastric contents during induction of anesthesia and intubation. Standard airway equipment and monitoring that conforms to international safety standards should be readily available. These are discussed below. For intubating patients, it is sometimes difficult to get optimal positioning of the patient outside the OR. The OR tables allow all kinds of position changes, but the trolleys and ward beds are not as versatile. In obese patients, one has to try to achieve the ramp position to aid intubation. Outside the OR, one may need to improvise to achieve this. The Oxford HELP® (Head Elevating Laryngoscopy

Figure 1. Troop Elevation Pillow® System.
Pillow) and the Troop Elevation Pillow® System (Figure 1) are examples of adjuncts used to achieve optimal laryngoscopy position in obese patients.

3. Areas outside the OR

There are many areas in hospitals outside of operation theaters and ICUs where sedation or general anesthesia is given for various reasons. This could be to aid uncomfortable diagnostic or therapeutic procedures or for patients who do not have the capacity to understand the need for such essential procedures. The medication that a patient receives defines where on the continuum of sedation (Table 1) they lie, which in turn decides the airway support needed.

Every hospital facility will have different areas where airway management will be required or needed to be on standby. Airway management in some areas such as the ICU and prehospital setting will be discussed in other chapters. These are some of the other areas:

3.1 The radiology suite

Most hospitals have a very large radiology suite. It can consist of MRI scanners, CT scanners and interventional radiology suites. Patients requiring both diagnostic and therapeutic procedures in these areas may need some form of sedation or analgesia to tide over the procedure. They may even need a general anesthetic. These areas need to be equipped from the start with all the airway kit that is required in an operating room setting. It is important to have MRI compatible airway equipment, as airway difficulties can arise when the patient is in the scanner tunnel. Laryngoscopes need to be non-ferromagnetic and MR compatible anesthetic machines, ventilators and vaporizers are available. Having long breathing circuits is the alternative to having MR compatible machines.

Another problem faced in scanner suites is the inability to prop-up the head-end of the patient. This can sometimes lead to partial airway obstruction in the deeply sedated patient who is spontaneously breathing. Partial obstruction to breathing causes movement artifacts on the head and neck scans. Nasal or oral airways can be carefully used in these deeply sedated patients (Figure 2).

The coils used in MR magnets need to be kept cold in order to maintain superconductivity. This is often achieved by immersing them in liquid helium. If the machine gets quenched (usually an emergency process involving the rapid boil-off

<table>
<thead>
<tr>
<th>Signs</th>
<th>Minimal</th>
<th>Moderate</th>
<th>Deep</th>
<th>General anesthesia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responsiveness</td>
<td>Alert/awake</td>
<td>Responds to verbal stimuli</td>
<td>Responds to painful stimuli</td>
<td>Unresponsive</td>
</tr>
<tr>
<td>Ventilation</td>
<td>Unaffected</td>
<td>Adequate</td>
<td>Maybe inadequate</td>
<td>Frequently inadequate</td>
</tr>
<tr>
<td>Airway</td>
<td>Unaffected</td>
<td>No intervention</td>
<td>Intervention maybe needed</td>
<td>Intervention often required</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Unaffected</td>
<td>Maintained</td>
<td>Usually maintained</td>
<td>Maybe impaired</td>
</tr>
</tbody>
</table>

Table 1. Sedation continuum.
of the cryogen that causes an immediate loss of superconductivity, to shut down the magnetic field) and if there is damage to the quench pipe, the build-up of helium within the scanning room could potentially lead to asphyxiation. The use of oxygen sensors is vital to the safe conduct of anesthesia.

3.2 The neuroradiology suite

The neuroradiology suite would require a special mention, as they may be stand-alone from the rest of the radiology suite. These are very similar to the interventional radiology suites used by radiologists for other procedures, but the incidence of the patient needing intubation and a general anesthesia over just deep sedation is more here. Apart from the general risks of working in a dark environment with high radiation as is mentioned in the general risks below, these areas should be set up to mirror an OR as far as possible. It is comparable to the hybrid CT/MRI ORs that exists in many hospitals these days.

3.3 The gastroenterology suite

The gastroenterology suites conduct many procedures that can warrant the patient to be either sedated or anesthetized. These include endoscopic retrograde cholangiopancreatography (ERCP) and papillotomy, esophageal or colonic dilatation and stenting, enteroscopies, and endoscopic sleeve gastoplasties. ERCP procedures need to be done with the patient in the prone position and in a fluoroscopy room. These rooms are usually small and crowded with equipment other than airway equipment. Apart from doing these under GA, these procedures have also been done under deep sedation with no adjunct airway device except supplemental oxygen via nasal prongs. One has to bear in mind the difficulty of airway access in these cases and plan airway management at the outset based on the expected duration of the procedure and expertise of the operator. Frequent suctioning of the oral cavity may be required in the unprotected airway.
The gastroenterology suites have started doing more bariatric work than in the past. These include simple procedures like intra-gastric balloon insertions and removals, and also complicated longer procedures like the sleeve gastroplasties. Obesity is by itself a pointer of airway risk and this should be taken into consideration when planning to intubate these patients. This includes having trained staff familiar with the bariatric airway, proper preparation of the patient, positioning the patient well using a ramp, good pre-oxygenation, and having a skilled person for post procedure monitoring.

### 3.4 Electroconvulsive therapy (ECT) suite

ECT is still being used in patients who have severe major depression or bipolar disorders who have not responded to maximal medical management strategies. Small electrical currents are passed through the brain, intentionally triggering a brief seizure, which has been known to alter brain chemistry, reversing symptoms. This procedure requires a GA, with the patient given an induction agent and a small dose of muscle relaxant to prevent trauma during seizures. It is vital to establish that the patient is fasting (some patients do not have mental capacity and are not able to give proper history) to avoid aspiration of gastric contents. These are very brief procedures and do not usually require an extensive airway armamentarium, but backup airway equipment should be standard. Since suxamethonium, a depolarizing muscle relaxant is used to achieve safety during the brief period of seizure (and therefore a short period of apnea), it is vital to pre-oxygenate the patient well to increase the safe apneic time.

### 3.5 The in-vitro fertilization (IVF) suite

The IVF suite usually requires sedation and analgesia for egg retrieval. Mild to moderate sedation is usually sufficient, but some patients slip into deep sedation and airway support may be warranted. These areas need to be equipped with a dedicated airway trolley as airway problems are not uncommon.

### 3.6 Oncology

Stand-alone oncology units do procedures that usually require general or spinal anesthesia, or at times deep sedation. These include brachytherapy and bone marrow aspirations, among other procedures. In spite of being a stand-alone facility for the immunocompromised, these areas usually have OR setups with the usual airway kit.

### 3.7 Cardiology

The cardiac catheter lab provides an area for interventional procedures and has similarities to the neuro-interventional suite although deep sedation or general anesthesia is not usually necessary in adult patients. Apart from interventional cardiology, sedation is also given for Transesophageal Echocardiograms (TEE). This is similar to having an esophagogastrosopy and the airway needs are that of the gastroenterology suite. Cardioversions may be done in this area or as an emergency in the ED. These patients usually get a dose of sedative medication, but muscle relaxants are not necessary.

Ventilation in some patients needs the use of room air to study the blood gases physiology in certain critical congenital heart lesions.
3.8 ENT procedure room

The Ear, Nose and Throat clinic usually has a procedure room to carry out minor procedures. Local anesthesia of the airway is usually used to access the laryngeal inlet for vocal cord injections. The clinic also performs tracheostomy tube changes and tracheostomy wound management. Routine tracheostomy changes must be done only during the daytime and during working hours except in an emergency. At least two trained practitioners are required during the tracheostomy tube change procedure. No drugs are usually given to hamper the patient’s respiratory efforts, but the difficult airway trolley should always be available along with a good functioning suction machine.

3.9 Emergency department

The resuscitation areas in the ED are usually equipped to intubate and ventilate patients. In the other acute areas of the ED, procedures may be done for non-fasted patients (such as cardioversions, TEEs and fracture reductions). These areas should be well equipped with anesthetic machines and airway trolleys. One needs to keep in mind the need for a fiberoptic scope in case of airway swelling in severe allergies or burns.

3.10 Wards and other areas

The resuscitation team may need to intubate a patient in any area of the hospital. Basic airway kit and intubation equipment are available in all ward areas (Figure 3).

Figure 3. A resuscitation trolley with airway equipment on the ward.
Ventilation is usually achieved with the use of a bag-valve-mask device until a definite portable ventilator is made available for transfer of the patient to the ICU.

4. Challenges in these areas

Working in different areas outside the OR comes with its own difficulties. These may be specific to the area like the radiology suite or can be general differences to the OR.

**Dark rooms:** Rooms where fluoroscopy or ultrasound is used tend to have low lighting to enable visual clarity of the images for the operator (Figure 4). This makes it difficult to observe the patient and to monitor notes. An alternate source of light should always be available [2]. The monitor should be clearly visible in this environment (Figure 5).

**Remote location:** When airway management is undertaken away from other trained personnel and specialist equipment, it is important to formulate a plan to get help quickly in case of a crisis.

**Unfamiliar equipment:** Different areas are equipped with different airway kit. The anesthetic machines may be basic models with minimal monitors. It is important to familiarize oneself with the equipment available prior to use, as they may be very different to those available in the OR.

**Lack of skilled staff:** As mentioned above, skilled support staff may be at a distance, and having a plan to inform and seek help needs to be in place before starting.

**Limited patient access during procedures:** Whether the patient is in the MRI tunnel or fully draped on the interventional radiology table, it is difficult to manipulate the patient’s airway once the procedure has begun. The decision to maintain the patient’s airway using a particular technique should be taken keeping this in mind.

**Crowded rooms:** The rooms mentioned above can be very crowded with equipment essential to the procedure being performed (Figure 4). In the

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**Figure 4.**
*A dimly-lit crowded interventional radiology room.*
fluoroscopy rooms, the C-arms of the fluoroscope will move in multiple axes and can come in the way of airway or monitoring equipment intra-procedure. Very little consideration is given to airway equipment placement in these areas as not all procedures require patient sedation or airway manipulation. It is therefore important to reshuffle equipment, in discussion with the operator, to make sure airway maintenance and management is kept safe throughout the procedure.

**Radiation exposure:** Patients and staff are exposed to high doses of ionizing radiation in the radiology suite. Radiation exposure poses a significant health risk. Measures taken to minimize exposure and risk during the procedure include wearing protective lead aprons, thyroid shields, eye protection, radiation exposure badges (to log exposure) and distancing oneself as far as possible from the radiation source.

5. Sedation outside OR

With respect to administrating sedation outside the OR environment two aspects need to be emphasized:

**Oxygen therapy modalities:** These could be either low-flow administration or high-flow administration [3]. Low-flow methods are usually employed for the majority of sedation that happens outside the OR. These may be via nasal cannulae with flow rates between 2 and 6 L/min or face masks, including simple masks, venturi masks, or non-rebreathing masks, with flow rates up to 15 L/min. High-flow nasal cannula (HFNC) is a nasal cannula with the capability of delivery humidified oxygen at flow rates that exceed the inspiratory pressure of the patient (60–70 L/min). It allows delivery of 100% oxygen, and can be given to achieve transient apneic oxygenation.

**Medication for sedation:** Choosing sedative agents that cause minimal depression of the ventilatory drive is safer when dealing with patients away from the OR. Fentanyl and Midazolam are the most commonly used sedative agents, with an added advantage of having antagonists available. Ketamine and Ketamine-Propofol mixtures are also used. Dexmedetomidine is known to preserve upper airway reflexes and the ventilatory drive. Propofol should be used only with the option...
of airway rescue available, as the patient may move from deep sedation to general anesthesia (Table 2).

6. Monitoring

Maintaining standards of monitoring is the most important modality used to ensure the safety of the patient and to avoid airway complications. Adherence to the current best practice guidelines [4] is essential when planning and equipping areas outside the OR. This should include the pulse oximeter and capnograph. Failure of capnography contributed to 74% of cases of death or persistent neurological injury [5]. Figure 5 shows a snapshot of a monitor used in a patient who is deeply sedated with a Target Controlled Infusion (TCI) of Propofol, spontaneously breathing with supplemental oxygen delivered via a nasal cannula. No other airway adjuncts were necessary. The nasal cannula is incorporated with a sampling port for expired gases (Figure 6) and a clear ET\( \text{CO}_2 \) (end tidal carbon dioxide) trace and value is displayed on the monitor. In a fully open circuit as is with nasal prongs, the value displayed is dependent on the flow of oxygen delivered and the depth of breathing. Although the exact value displayed is not of true significance always, the characteristics of the trace and the trend of the number displayed warns clinicians of impending airway compromise and the need to intervene.

Capnography use has the highest potential to prevent deaths from airway complications outside of the operating theater complex [6, 7].

Monitoring depth of sedation has been looked at using a bispectral index (BIS) monitor. The depth of sedation is calculated by measuring cerebral electric activity via an electroencephalogram (EEG). The BIS algorithm processes the frontal EEG and converts the signal to a waveform on the BIS monitor, and displays a number between

<table>
<thead>
<tr>
<th>Drug</th>
<th>IV dose in Adults</th>
<th>Onset</th>
<th>Duration</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam</td>
<td>1–2 mg titrated boluses (+3)</td>
<td>1–5 min</td>
<td>30–90 min</td>
<td>Usually used along with Fentanyl</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>0.5–2 mcg/kg</td>
<td>2–3 min</td>
<td>20–30 min</td>
<td>Can cause hypoventilation</td>
</tr>
<tr>
<td>Propofol</td>
<td>1 mg/kg then 0.5 mg/kg q5 min</td>
<td>&lt;1 min</td>
<td>3–10 min</td>
<td>Causes drop in BP, reduced inotropy (caution in hypovolemic patients and HF patients) Can cause hypoventilation or apnea</td>
</tr>
<tr>
<td>Ketamine</td>
<td>0.25–1 mg/kg</td>
<td>30 sec</td>
<td>5–10 min</td>
<td>Does not depress ventilatory drive Has bronchodilatory effects Can cause hypersalivation (may need anticholinergic) Can cause increase in HR, BP, ICP and emergence delirium</td>
</tr>
<tr>
<td>Dexmedetomidine</td>
<td>0.5–1 mcg/kg over 10 min</td>
<td>5–30 min</td>
<td>1–2 h</td>
<td>Minimal respiratory depression Can decrease SVR and HR</td>
</tr>
</tbody>
</table>

Table 2. Commonly used drugs for sedation (BP-blood pressure, HF-heart failure, HR-heart rate, ICP-intracranial pressure, SVR-systemic vascular resistance).
100 (fully awake) and 0 (no brain activity). This has proved very useful during general anesthesia in avoiding awareness due to inadequate hypnosis, by keeping values between 40 and 60, but its use to achieve a particular level of sedation on the continuum of sedation has proved difficult to interpret. Levels of 60–70 have been postulated and the aim should be to avoid letting the patient slip into general anesthesia from deep sedation, risking apnea and hypoxia. This has not always correlated to an adequate level of sedation and most operators adjust the level of sedation based on response to any stimulus the patient experiences during the procedure.

7. Improving airway management outside the OR

At least 25% of major airway events are from outside of the OR environment [8]. Complications are associated with hypoxia, aspiration, unrecognized esophageal intubation, airway trauma and obesity.

As we have seen above, areas outside the OR need to be prepared with equipment to manage the airway in a patient who may need it. We should plan and equip every area where this is anticipated, usually due to the fact that we as clinicians give patients drugs to aid procedures to happen, putting them in harm’s way. Apart from eternal vigilance and monitoring, we should be prepared to step up the management of the airway that can become compromised.

Capnography is a tool that has become part of the basic standards of monitoring the world over, in patients having sedation or general anesthesia. It is a very important tool to detect a deterioration in ventilation in a spontaneously breathing patient due to increasing levels of sedation. All staff involved with sedating patients need to be trained in its use.

Checklists have improved patient care [9]. In areas where intubations are not routinely carried out, an intubation checklist has proved invaluable. Checklists have also helped in pre-assessment of patients and has helped recognize potential difficulties. For example, obesity is recognized as an increased risk factor for airway complications. These allow for thorough back-up strategy planning, both for intubation and extubation, as it may not be routine in areas outside the OR.
The availability of the difficult airway trolley (Figure 7 and Table 3) is paramount in areas where airway maneuvers are planned. These require regular checking and maintenance with replacement and stocking done every day. Since many areas exist outside the OR for airway procedures and since not every area is used on a daily basis unlike the OR, a designated person should be responsible to oversee this task. Every area should also have a plan to access video-laryngoscopes and fiberoptic bronchoscopes without much delay. Front of neck access equipment should always be available on the difficult airway trolley, and regular training should happen among the staff who look after the airway of patients.

Apart from airway equipment that is routinely used in the OR, certain newer developments in airway management have potential roles in areas outside the OR [11]. These include Laryngeal Mask Airways (LMA) modified with a separate channel to allow endoscope access into the esophagus, and high flow nasal oxygen delivery devices. Examples of the separate channel devices include the LMA® Gastro™ Airway from Teleflex, and the Gastro-Laryngeal Tube from VBM Medizintechnik GmbH (Figure 8). These modified airway devices have made it easier to anesthetize patients for ERCPs and upper endoscopy procedures.

The use of heated and humidified high flow nasal cannula (HFNC) with flows of 60–70 L/min has also become increasingly popular in deeply sedated patients outside the OR [12]. This can be used in various areas and addresses the concerns of transient apneas and hypoventilation and hypercarbia. It is recommended to use transcutaneous carbon dioxide (TcCO₂) monitoring during prolonged use of HFNC in patients who may go apneic.
8. Human factors and team working

Human factors such as poor team working, poor communication and failure to call for help all contribute to airway critical events. Human factors extend to institutional organization and structure, equipment availability and use of standard operating protocols (SOP) [13].
Junior staff should always have senior help readily available, and non-anesthesiologists should have a system in place to get anesthetic help in case of problems. All staff involved in airway management outside the OR should undergo airway training, both basic and advanced, and have annual refresher practice sessions of the less used skills, preferably in a dedicated simulation lab. They should also be familiar with the interpretation and use of capnography along with other monitoring equipment.

Communication channels and links should be established between various departments and senior clinicians in the Emergency Department, Anesthesia, Intensive Care Unit and ENT (Ear Nose and Throat surgery department). Regular audits should take place of airway management problems or events, in all areas.

High-fidelity simulator training provides anesthesiologists and other doctors involved in sedating patients outside the OR with the opportunity to develop their technical and non-technical skills for managing rare and dangerous scenarios related to airway management. It provides a safe multidisciplinary learning environment, and simulators can replicate a specific aspect of airway management, or the entire outside OR working environment.

### 9. Post-procedure care

Post-procedure care should be the same as that required after an anesthetic in the operating room. This should be the rule, irrespective of the procedure done. If the patient has had sedative drugs or a general anesthetic, they are prone to having airway complications in the recovery phase. The risk is dependent on the drugs used, airway technique applied intra-procedure, and the duration of the procedure.

Ideally a designated area of the corresponding suite should be available for patient recovery. This should be adequately equipped with facilities and trained personnel like a theater recovery room. This is an area that needs to cater to the monitored recovery of different kinds of patients, from those who may have had only moderate sedation, all the way to the patient who has had a full general anesthetic (with an indwelling endotracheal tube) for a few hours.

For most, such a facility may not be available, and depending on the area, may not be possible. This would require patients to be transported to the main theater recovery room (the post-anesthetic care unit-PACU). For safe transfer one must ensure that adequate equipment and personnel are available in advance, and organized with the PACU team. It is vital to have the location of recovery and logistics of transfer if required, planned in advance, before embarking on anesthetizing in a remote location.

Safe post procedure discharge from the intervention unit to the ward or home should be done following local discharge criteria. At the least patients should have vital parameters (Heart rate, blood pressure, oxygen saturation on room air and respiratory rate) within 20% of pre-procedure baseline levels, not be too sedated (either alert or responding to verbal stimulation), have a core temperature of more than 36°C, have no nausea or vomiting, and be pain free. The patient should be able to sip fluids orally without features of aspiration or coughing.

### 10. Conclusion

Airway management outside the OR can be a challenging task, not just due to the situationally difficult airway that can arise, but also due the different environments having different SOPs, differences in equipment availability and expertise of personnel present. It is crucial to standardize equipment availability in all areas where sedation will be given. This has to be drawn up and agreed upon with the anesthetic
department. The need for the availability of special equipment like the video-laryngoscope or the fiberoptic bronchoscope will be decided depending on local protocols. Having capnography in all these areas is of utmost importance for patient safety in this day and age. Staff involved in monitoring these patients need to be educated in its use. The importance of eternal vigilance cannot be emphasized enough. Airway management can be more of a challenge in these areas and in an attempt to prevent a deterioration in the airway of a patient, constant monitoring by a dedicated member of staff is paramount throughout the procedure and into the recovery phase. The ability to manage airway emergencies must be a skill mastered by all staff involved in sedating patients outside the OR and this can only be made possible through regular training. Airway management outside the operating room is challenging. Difficult airway management guidelines from the Difficult Airway Society (DAS), UK, or the American Society of Anesthesiologists (ASA) remain the standard reference guide [14].

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