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Fatigue and the paediatric anaesthetist

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Introduction

The healthcare environment in the state and private sectors is currently very challenging for clinicians. This may compound the problem of occupational fatigue that we currently face as a community.

The problem of occupational fatigue is not unique to the healthcare industry or anaesthesia specifically. To prevent industrial accidents, many industries such as seafaring, mining, public safety, nuclear power, military and transportation have put measures in place to reduce occupational fatigue and improve occupational health.[1] We could learn a lot from them.

Although a search of the literature did not reveal studies relating to paediatric anaesthetists specifically, much research has been done in relation to the impact of fatigue on performance in medicine and anaesthesia in general. What follows is a brief review of some of the literature and how I think it relates to paediatric anaesthesia.

Definition and types of fatigue

Occupational or work-related fatigue is extreme tiredness and reduced functional capacity that is experienced during and at the end of the workday, incorporating dimensions of physical, mental and emotional work fatigue.[1] Howard et al.[2] define fatigue as inability or unwillingness to continue effective performance of a mental or physical task and is a summary descriptor for the varied effects and labels used to describe the cognitive, behavioural, and physiological outcomes of sleep loss and circadian disruption.

Why is (paediatric) anaesthesia more prone to occupational fatigue?

Our work as anaethetists demands sustained mental focus at high levels for long periods which contributes to fatigue, both mental and physical.[1] Paediatric anaesthesia requires the same if not hyper-vigilance and thus this cohort may be at higher risk for occupational fatigue. Although this is recognised as a fact, fatigue among anaesthesiologists is accepted as norm or mostly ignored.[1] However, the risk to patient safety cannot be ignored and is well described.

Anaesthesiology by its nature involves crises.[3] We work in a complex and dynamic environment where surgery and the patient constantly challenge even the best anaesthetist.[3] This is more pronounced in paediatric anaesthesia, where the heterogeneity of the patients, among other characteristics, often adds to the complexity.

Patients often have poorly structured underlying problems and their responses to interventions cannot always be accurately predicted. Vigilance is required in terms of the progress of surgery because catastrophic complications cannot always be anticipated.[3] Added to this patient and surgical stress is time pressure, where the scarcity of theatre time requires anaesthetists to make hasty decisions at times in an attempt to meet efficiency goals, which may not always be for a particular patient's benefit.[3]

Factors predisposing to fatigue in (paediatric) anaesthesia

In addition to the sustained mental focus anaesthesia demands, the following factors are cited as major contributors to occupational fatigue[1,4]:

- Long working hours (more than 12.5 hours) and the duration and frequency of night shifts and the sleep deprivation linked to it
- Physical demands (standing for long periods, volume and turnover of patients)
- Undiagnosed hypovolaemia and hypoglycaemia due to lack of adequate breaks to allow for food and fluid intake
- Unrelenting cognitive demands especially linked to patient acuity and the complexity of surgical procedures undertaken
- Interpersonal dynamics
- Prevailing environmental factors (noise, temperature, shortages etc.)
- Reduced tolerance to night shift work (seen as prolonged recovery times) with advancing age
- Personal and family challenges

Individuals working in state hospitals are subject to government regulations on working hours and an overburdened health system teeming with patients, which may not always align with recommendations based on scientific research. Individuals working in the private sector are forced by various factors to make poor choices in personal scheduling in order to 'please' the surgeon and thus keep their list. These factors contribute to fatigue due to the prolonged periods of work which may result and the reduced time for rest between shifts.[1]

Sanders et al. reported Epworth Sleepiness Scale scores in the mild sleepiness category among trainees in the Wits Anaesthesia department, which were still much higher than the average population in keeping with the long working hours and regular night shifts required of trainees.[5]

Why should we be concerned about occupational fatigue?

Fatigue has been shown to reduce several aspects of cognitive performance required for the delivery of safe anaesthesia, by 25% from baseline after more than 24 hours of being awake.[4] Reduced cognitive performance can include any of the following:

- Reduced attention and vigilance with attention lapses
- Impaired memory and decision-making
- Slowed cognitive throughput
- Prolonged reaction time with lowered optimal responding
- Lapses in attention to detail
- Errors of omission
- Compromised problem solving
- Reduced motivation and disrupted communications[4]

Anger and depression culminating in absence of compassion for the patient can also result.[4]

Patient safety is compromised when fatigue-related errors occur, namely drug errors, errors in medical judgment and delayed reaction to events.[1] In United States (US) and Australian studies, anaesthetists reported fatigue as a contributing factor to 2.7% of anaesthesia incidents and 50% of medical judgment errors.[1] In the South African context, Sanders et al.[5] reported that 48.6% of anaethetists in their study admitted to making clinical errors related to sleepiness.

Of equal importance is the danger a fatigued anaesthetist poses to themselves and the general public when they drive home after a night shift for instance, running the real risk of causing a car accident.[1] In June 2016, a similar incident was reported in South Africa, where a fatigued intern caused a fatal car accident.[6]

Another potential danger to the anaesthetist is percutaneous injury, although this may have other causes such as sudden patient movement, poor lighting or lapses in concentration.[4,5]

Countermeasures to fatigue

It is impossible to eradicate fatigue and its consequences but measures can be employed to reduce it. Fatigue risk management (FRM) uses our current understanding of sleep physiology to develop a set of countermeasures that can reduce the impact of sleep deprivation or circadian shifts on physician performance.[7] The transportation sector has utilised such programmes for years to deal with fatigue among pilots, commercial drivers and train engineers to name a few.[7]

The average adult requires approximately eight hours of sleep in a 24-hour period, which is difficult to ensure given our long hours and night shift work as anaesthetists in most settings.[4] Reduction of overall work hours would be the most effective strategy against the negative effects of fatigue, but for obvious reasons, it is the most difficult to implement.[7] The disablers to this strategy include existing nursing and support staff schedules, the demand for service delivery in the state sector and the requirements of surgeons for instant service in the private sector. In general, studies suggest an association between long work shifts of more than 24 hours' duration and a reduction in alertness and performance compared to shorter shifts.[7] Thus, scheduling which allows for adequate breaks during shifts in suitable rest facilities as well as power napping at work may help stave off the resultant fatigue.[1]

In the South African Society of Anaesthesia (SASA) Practice Guidelines on workload, corrective strategies to mitigate fatigue are outlined in detail and are in keeping with international literature.[4] Of particular importance are the fatigue-alleviating strategies suggested in this document which include: day sleeps before a night shift, naps of at least 40 minutes when feeling excessively fatigued and before driving home, and improved structuring of call and shift rosters. Regarding scheduling in particular, the following suggestions are made:

- Work activities should not exceed 80 hours per week averaged over six weeks
- A minimum of 10 hours' rest between consecutive duties should be allowed for
- Ensuring that continuous shifts on call do not exceed 17 hours of anaesthesia provision at any one time
- Between 10–25% of available working time should be allocated towards non-clinical activities such as continuous professional development (CPD) courses etc.

Mental strain at work could be reduced by creating awareness about the effects of external stressors on work performance and active attempts to reduce them.[1] Assistance with work for women, decreasing demands for older colleagues and increasing flexibility of scheduling for those with families have all been suggested as strategies for reducing fatigue.[1]

Other strategies for mitigating fatigue include: caffeine, strategic naps, controlled exposure to bright or blue-enriched light during extended or overnight shifts and appropriate use of recovery sleep.[7] The judicious use of alarms and timers on monitors can also be seen as helpful in offsetting the negative effects of fatigue, although studies to prove this are lacking.

Strategically planned naps prophylactically before sleepiness occurs have been found to briefly reduce the results of fatigue from sleep deprivation on long night shifts for up to 30 hours.[7] It appears that a short 20 to 60 minute nap during a night call shift can yield better psychomotor vigilance, performance and alertness.[7] Sleep inertia, which is an impairment in alertness and performance that is present immediately on waking from sleep as the brain transitions to complete wakefulness (which can take up to four hours), should be considered when planning these strategic naps especially when response to emergency situations upon immediate awakening is required.[7] Caffeine

intake, exposure to bright light and washing ones' face with cold water have been suggested as countermeasures to sleep inertia.[7]

Microbreaks including a short walk and some brief shoulder, back and neck exercises have been studied among surgeons but could possibly improve alertness in anaesthetists performing anaesthesia for very long surgeries.[7]

Caffeine at a dose of 200 mg six hourly can enhance performance and alertness in fatigued individuals during night shifts.[7] Caution is advised as it may impair the quality of rest during breaks.[4]

Bright and/or blue-enriched light has been shown to counter fatigue by resetting the circadian phase and rapidly increasing alertness and cognitive performance. These benefits are dependent on intensity, duration and the wavelength of the light. Most benefit is derived from the combination of bright light and either stimulants (i.e. caffeine) or strategic napping.[7]

The relevance of these strategies varies depending on whether the (paediatric) anaesthetist is still in training or a qualified consultant, and whether said consultant is in state or private practice. This is because generally, like our international counterparts, our registrar training years are characterised by long work hours mainly due to night call shifts and the need to prepare for examinations.[7] In addition, a (paediatric) anaesthetist in private practice, depending on how they have structured their practice, may have either very little after hours work or a large amount if they work with a busy surgeon in solo practice. Thus, each anaethetist can utilise whichever measures are relevant to them.

Culture and awareness

As clinicians, we often continue to work when most other professionals would either call in sick or get medical advice, presumably because of the demands of our caring profession. This culture of deifying continuing to work while impaired needs to be discouraged. Instead, we must foster a safe culture of vulnerability by speaking out when impaired, by any factors including fatigue, without fearing stigmatisation.

A workplace culture that promotes help-seeking behaviour needs to be nurtured, where a fatigued individual feels no shame in requesting help when feeling vulnerable, and accepts help when others observe fatigue-related behaviour.[1] However, it is essential that fighting fatigue is not kept as a 'matter between colleagues' but that organisational structures are involved to effect change at policy level.[1]

Similar to the aviation industry where pilots use a mnemonic checklist to screen for impairment by analysing the influence of potential performance-shaping factors and remaining grounded if impaired, we could use the I'M SAFE approach. I'M SAFE is a simple personal checklist to determine one's ability to perform safely concerning these factors: **I**llness, **M**edication, **S**tress, **A**lcohol/drugs, **F**atigue, **E**ating and **E**limination.[3] The reality though is that it is not always possible to be excused from work on account of impairment owing to these factors due to various real and perceived pressures, especially in private practice. A change in culture at individual and organisational levels is needed.

Summary

Occupational fatigue must be addressed as a matter of urgency at individual and institutional level for the sake of both patient and clinician safety. A culture of awareness and support must be encouraged especially in our resource-constrained environment where strategies and guidelines for reducing fatigue suggested in the literature are not able to be implemented.

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Neonatal pharmacology

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Neonatal physiology differs from that of older children and adults and has a direct implication on the use of anaesthetic drugs. Their clinical pharmacology is dynamic and diverse as there is ongoing maturation of enzymes, anatomical and physiological systems which leads to drug response variability. In order to properly dose anaesthetic drugs in this patient population it is important to appreciate their unique physiological characteristics, pharmacokinetics, pharmacodynamics and consider potential drug adverse effects. The use of postmenstrual rather than postnatal age has been shown to be a valid measure for maturation. In this article, the unique neonatal pharmacological features pertaining to anaesthesia will be reviewed.

Keywords: neonate, anaesthesia pharmacology, pharmacokinetics, pharmacodynamics

Introduction

While specifically defined as birth to one month of age, neonates are in practice a heterogenous group including extreme pre-term babies born at 22 weeks up to those 50 weeks post menstrual age (PMA) and weights varying from 0.5–5kg.[1] They have well recognised pharmacological differences from older children and adults and their biological systems evolve with maturity. This variability is a core component of their clinical pharmacology. Providers caring for neonates should pay close attention to factors contributing to variability specifically patient size, maturation and, to a lesser extent, organ function.[2,3] Pharmacokinetic (PK) and pharmacodynamic (PD) variability is also due to differences in patient age, genetic polymorphisms, inter-individual variation, comorbidities and drug co-administration. Appreciation of these differences is essential to provide safe and effective pharmacotherapy.

Disasters due to poor understanding of neonatal pharmacology (chloramphenicol and gray baby syndrome; benzyl alcohol toxicity and gasping syndrome) historically remind us how critical it is to pay close attention to differences in neonates.[1] Unfortunately, evidence-based pharmacotherapy in neonates is still limited. Clinical studies in this population remain restricted by difficulties with ethics, recruitment of adequate numbers, technical challenges, perceived high vulnerability, and concerns of potential adverse effects later in life. Advances in population-based modelling, micro-sampling, pooling of data from multiple institutions, and improved computer programs have helped address some of these challenges.[4] This article will attempt to summarise our understanding of PK and PD in neonates undergoing anaesthesia. Appreciation of these differences may help to improve pharmacological safety and further research in neonatal anaesthesia.

Pharmacokinetics (PK) and the neonate: *"What the body does to the drug"*

By definition PK is the study of drug disposition by patients. It considers absorption (a), distribution (d), metabolism (m), and elimination (e) of administered drugs.[4]

Absorption

Absorption links a drug's physicochemical properties and patient considerations that influence translocation from its exposure site to either the blood stream or effect compartment.[2] Absorption can occur via various routes.

Enteral route: Administration by mouth is a common route for drug administration in neonates. Gastric pH and volume of secretions is variable after birth, and absorption is therefore often delayed. Gastric emptying and motility do not mature until six to eight months. This can directly affect the ability of a drug to dissolve, altering the ionised/unionised components.[2] This is worsened by feeds that are calorie dense or containing long-chain fatty acids and in congenital gastrointestinal abnormalities such as pyloric stenosis and duodenal atresia. Slower gastric emptying and reduced clearance may influence dosing of medications commonly administered enterally. For example, paracetamol should be administered in decreased doses and frequency in neonates. Co-administration of opioids can further slow down emptying.

Transdermal route: Compared to older children neonates have increased absorption. Exposure to commonly administered drugs such as corticosteroids, local anaesthetic creams, and antiseptics like betadine can easily reach toxic levels. This is due to a greater relative skin surface area, higher cutaneous perfusion, and thinner stratum corneum. Lidocaine-prilocaine creams can be especially toxic as neonates are predisposed to forming higher amounts of methaemoglobin due to reduced methaemoglobin reductase activity and the presence of foetal haemoglobin which is more readily oxidised. This has resulted

in a general unwillingness to use lidocaine-prilocaine cream in neonates.[5]

Rectal route: In neonates, administration via this route results in variable plasma concentrations because of irregular motility of the lower gastrointestinal tract and inconsistent depth of drug insertion. Varying depth of insertion affects plasma concentration because absorption via the upper rectal veins undergoes first pass metabolism unlike the middle and inferior veins which bypass this.[2]

Inhalational and intramuscular route: Anaesthetic delivery by the inhalational route is determined by functional residual capacity (FRC) and alveolar ventilation. In the neonate there is higher minute ventilation (MV) to FRC (MV:FRC) ratio and alveolar ventilation. Rapid wash-in is further supported by the presence of higher cardiac output with a greater proportion distributed to the vessel-rich organs. In the presence of cardiac right-left shunt (intrapulmonary or cyanotic heart disease), inhalational induction is slower especially with the least soluble agents like sevoflurane and nitrous oxide. However, left-right shunting has a minimal effect on induction unless there is reduced cardiac output or peripheral perfusion.

Drug effect after intramuscular administration is faster because of increased neonatal muscle capillary density and higher cardiac output.[5,6]

Epidural route: The epidural space in infants compared to adults has increased vascularity and a smaller absorptive surface for local anaesthetics. Epidural levobupivacaine absorption T ½ decreases from birth till six months of age. There is also reduced levobupivacaine clearance (via CYP3A4) leading to delayed time to maximum plasma concentration (T_{max}). In combination, this may contribute to increased rostral spread and subsequent longer duration of caudal analgesia seen in this population.[7] Chloroprocaine is a potentially safer alternative to bupivacaine in neonates because of its much shorter elimination T ½.

Distribution (V_d)

Distribution relates to transfer of a drug from one location in the body to another.[6,8]

$$V_d(\text{l/kg}) = \frac{\text{total amount of a given drug}}{\text{concentration}}$$

V_d is a theoretical value and does not necessarily represent uniform drug distribution throughout the body. Maturational physiological changes that occur in body composition, regional blood flow, organ size and plasma protein concentration can all affect distribution. Many of the drugs used in anaesthesia do not have one simple volume of distribution.[6,8]

Body composition: For preterm and term neonates the V_d of water-soluble drugs is larger as compared to older children and a larger loading dose is required (e.g. aminoglycosides, cefazolin, paracetamol and neuromuscular blocking drugs [NMBD]).[8] (See Table I for the fluid composition of neonates compared to adults).

Despite having a higher initial dose, reduced clearance capacity results in lower maintenance dose to avoid accumulation. Fentanyl (lipophilic) will have a much higher V_d compared to total body volume because fat holds more drug compared to the same volume of blood. If V_d is large then the dose required to achieve a target concentration is also large. However, larger doses may cause more significant adverse effects and are not given because a prolonged effect can result from reduced clearance.[2]

Table I. Fluid composition in neonates compared to adults[2]

	Preterm	Term	Infant (1 year)	Adult
TBW*	85%	80%	60%	60%
ECF†	60%	45%	25%	20%
ICF‡	25%	35%	35%	30%

* Total body water
† Extracellular fluid
‡ Intracellular fluid
All as % of total body weight

Fat contributes 3% of total body weight in a 1.5 kg premature neonate and 12% at term. By the time the infant is four to five months old this would have doubled.[5] Drugs relying on redistribution to fat and muscle like thiopentone and propofol can have prolonged and higher concentration in plasma in the preterm.

Cerebrospinal fluid contributes a greater proportion of body composition in neonates as compared to older children explaining the larger doses of spinal anaesthesia drug required in this population (1 mg/kg in infants < 5 kg compared to 0.3 mg/kg for those > 15 kg).[9]

Protein binding: Protein binding is decreased in neonates. Concentrations of albumin and α_1-acid glycoprotein (AAG) are lower in neonates (0.32–0.92g/l) but by six months values are similar to adults.[10,11] Decreased quantity of drug-protein binding results in increased free drug concentrations and subsequent enhanced effect for drugs with typically high protein binding.

Albumin concentrations are lowest in preterm neonates. Drugs such as thiopentone that typically bind to albumin, have lower induction doses in neonates than children due to less protein binding (13% unbound drug in newborns versus 7% in adults).[12] Jaundice is also common in premature infants. Elevated bilirubin competes with drugs like phenytoin for protein binding. Phenytoin administration in jaundice may lead to higher free drug concentration and increased risk of kernicterus (immature blood-brain barrier).[12]

Bupivacaine is typically highly bound to AAG. With the decreased levels in neonates, a higher proportion of the drug is unbound; therefore, bolus epidural dosing is lower (1.5–2 mg/kg vs 2.5 mg/kg) to decrease the risk of toxic levels. AAG is an acute phase reactant and will increase after surgical stress hence, bupivacaine concentration in the first 24 hrs post-surgery may increase in neonates on continuous epidural infusion but theoretically the unbound fraction should remain the same.[13] However, there have been reports of seizures in infants on continuous bupivacaine epidural infusions leading to the recommendation to discontinue infusions at 24 hrs.[14] For bupivacaine, clearance

(CYP3A4) is the main parameter reduced in infants and there is more inter-individual variability in concentration as compared to reduced protein binding. In neonates, continuous epidural infusions will not generally run beyond 48 hrs (dose of 0.2 mg/kg/hr less than 0.4 mg/kg/hr in older children).[13,14]

Blood-brain barrier (BBB): The integrity of the BBB improves gradually with age. Foetal and neonatal brains may be more easily accessed by small molecules and even more so with certain disease states such as sepsis, hypoxia, and acidosis. Unbound lipophilic drugs such as bupivacaine can passively diffuse across the BBB.[2] Combined with reduced protein binding, this may explain the increased risk of toxic levels leading to seizures in neonates.

Fentanyl is actively transported across the BBB by an ATP-binding cassette protein like P-glycoprotein. Modulation of this glycoprotein can influence onset of action, maximum effect, and duration of analgesic response.

Metabolism and elimination

Significant covariates, when considering neonatal drug metabolism are size, maturation and the effect of disease on organ function. Allometry describes the non-linear relationship between size and function. Use of allometric models enables prediction of paediatric doses from adult ones and target-controlled infusions have the potential to use allometric scaling.[1,5] With the exception of remifentanil, allometry alone is insufficient in predicting clearance of most drugs in neonates and infants and there is a need to add a model accounting for maturation. Since maturation of clearance starts before birth, PMA is probably the better predictor than postnatal age (PNA) for drug elimination.[5] For example, CYP2D6, CYP3A4, CYP1A2 display ontogeny in the second and third trimester of pregnancy.[15] Organ function changes associated with normal growth and development can be determined from pathological changes as function decreases with disease.[1] Organ function may be increased by enzyme inducers like phenobarbitone (CYP1A2, CYP2C9, CYP2C19, CYP3A4, UDP glucuronsyltransferase [UGT]).[1]

The hepato-biliary (metabolic clearance) and renal (elimination clearance) systems are the main routes of clearance for drugs and metabolites. Immaturity in these two systems has an effect on neonatal drug handling.

Hepatic metabolic clearance: Hepatic elimination is governed by phenotypic variation and relates to inherent, disease-related and genetic factors. During infancy the main determinant is age-dependent phenotypic enzymatic activity. Development of these systems can alter drug clearance significantly.

There are three categories of isoenzymes in neonates with most being in class iii[16-18]:

i. Mature at birth with decreasing activity with age (CYP3A7, SULT1A3/1A4)
ii. Moderate maturation at birth with increased activity with increasing age (CYP3A5, CYP 2C19, SULT1A1)
iii. Little to modest maturation at birth with increasing activity with age (CYP2D6, CYP3A4, CYP2C9, CYP1A2)

Metabolising enzymes are divided into Phase I (non-synthetic reactions like oxidation, reduction and hydrolysis) and Phase II reactions (synthetic or conjugation reactions making water soluble compounds excreted in urine).

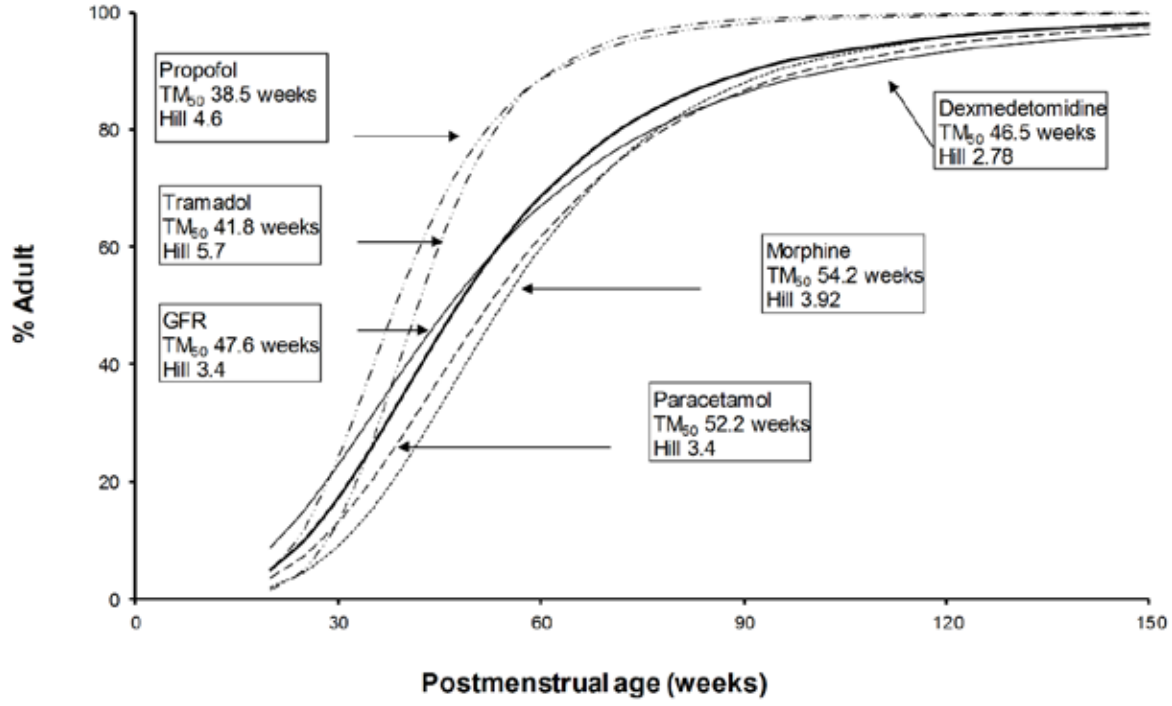

Figure 1. Clearance maturation, expressed as a percentage of mature clearance, of drugs for which glucuronide conjugation (paracetamol, morphine, dexmedetomidine) plays a major role. (Note how the profiles correlate to glomerular filtration rate [GFR]). Cytochrome P450 isoenzymes also contribute to propofol metabolism as shown by the faster maturation profile than expected from glucuronide conjugation alone. Tramadol and levobupivacaine clearance maturation (CYP2D6, CYP3A) is also rapid.[5] Reproduced with permission.

Important for the Phase I reactions are the cytochrome P450 group of enzymes which are often not fully mature in the neonate and also subject to variation due to genetic polymorphisms. Clearance of levobupivacaine depends on CYP3A4 and CYP1A2 for ropivacaine which are both immature in the neonate. This means this population requires reduced epidural infusion rates of these drugs.[7] Altered phenotypic expression of CYP2D6 enzymes affects tramadol metabolism and formation of the major (M1) metabolite.[19] Plasma cholinesterase activity influencing succinylcholine metabolism is also influenced by genetic polymorphism.[5]

Phase II reactions show limited activity during foetal life and some reactions like acetylation, glycination and glucuronidation are not mature at birth.[2] These systems are complicated. For example, UGT clearance is immature at PMA 24 weeks but reaches maturity by the first year of life. UGT has isoforms maturing at different rates (see Figure 1 showing clearance maturation profiles of drugs mainly metabolised by UGT).[5] Lack of understanding of UGT maturity led to gray baby syndrome with chloramphenicol in the 1960s.

Maturation processes can also be affected by illnesses. Morphine clearance is reduced in the very sick neonate and propofol clearance is lower in children after cardiac surgery. Concomitant drug use also affects metabolism. Ketamine's sedative effects are less in children on long term phenobarbitone (CYP3A4 induction).

Renal clearance: Renal elimination is reflected by diuresis, GFR and renal tubular activity. At PMA of 25, GFR is only 10% of the mature value, 35% at term, and by one year it is 90% of the adult value.[4] Renal inefficiency in the neonate is due to low perfusion pressure, incomplete glomerular development and inadequate osmotic load for the counter-current mechanisms. Drugs almost exclusively cleared by GFR (cephalosporins, aminoglycosides, D-tubocurarine) have lower maintenance dose which is predicted by PMA. PMA is used because it more accurately estimates the time course of renal maturation. Immaturity of clearance has some therapeutic use in the management of apnoea. When using theophylline, N7-methylation development to produce caffeine is well developed. However, oxidative demethylation (CPY1A2) is deficient. The produced caffeine is effective in controlling apnoea.[20]

Pulmonary elimination: In the lungs, anaesthetic absorption is determined by alveolar ventilation, FRC, blood-gas solubility and cardiac output. These also have a bearing on elimination kinetics. Washout will be more rapid due to reduced distribution to fat and muscle.

Some agents undergo hepatic metabolism (halothane much more than isoflurane and sevoflurane). However, hepatic elimination is very small at typical anaesthetic concentrations.[5]

Table II summarises some PK considerations in neonates.[4]

Table II. Illustrations of the impact of neonatal physiology on the pharmacokinetics (absorption, distribution, metabolism, elimination) of specific drugs commonly administered to neonates[8]

Compound	Pharmacokinetics	Relevance
Iodine disinfectant	Skin more permeable, skin surface per kg weight higher (a)	Higher absorption may suppress thyroid function
Inhalational gases	Higher alveolar ventilation/FRC ratio (a)	Faster wash-in
Cefazolin	Lower protein-binding capacity results in higher distribution volume (d) and higher free plasma fraction (e) Lower GFR (e)	Peak concentration is lower Bactericid effect relates to free concentration Lower clearance, prolonged duration of bactericid effect
Bupivacaine	Lower protein-binding capacity (d) Lower clearance (e)	Free concentration related to adverse effects Accumulation during continuous administration
Propofol	Lipophilic compound, lower distribution volume (d) Glucuronidation for metabolic clearance (m)	Peak concentration is lower, redistribution more limited Accumulation during continuous or repeated administration More profound hypotension due to immature (para) sympathetic balance
Paracetamol	Water soluble compound, higher distribution volume (d) Glucuronidation for metabolic clearance (m)	Peak concentration is lower, less effective analgesia likely Accumulation during repeated administration possible
Midazolum	Clearance to metabolite (1-hydroxy) is low (m) Elimination clearance of (1-hydroxy) midazolam is low (e)	Metabolite is also sedative Lower clearance results in prolonged sedation
EMLA cream	Skin more permeable, skin surface/kg higher (a)	Higher absorption, may induce local anaesthetic related seizures Increased risk of methaemoglobinaemia
Codeine	Clearance to metabolite (morphine) is low (m) Elimination of codeine and metabolite is low (e)	Shorter or reduced analgesic effect Accumulation of codeine or metabolite more likely, prolonged or more pronounced analgesia
NMBD	Increased distribution volume (d) Lower clearance (m)	Lower concentration at end plate, compensated by lower acetylcholine Prolonged effect

Reproduced with permission. Key: absorption (a), distribution (d), metabolism (m), and elimination (e)

Table III. Inhaled anaesthetic agents' pharmacology[1]

	Halothane		Enflurane		Isoflurane		Sevoflurane		Desflurane	
	A*	N†	A	N	A	N	A	N	A	N
MAC	0.75	0.87	1.7	–	1.2	1.6	2.05	3.2	7.0	9.2
Solubility: Blood-gas	2.4	2.14	1.9	1.78	1.4	1.19	0.66	0.66	0.42	–
Solubility: Brain-blood	1.9	1.5	1.3	0.9	1.6	1.3	1.7	–	1.2	2.7

*adult †neonate

Pharmacodynamics (PD) and the neonate: "What the drug does to the body"

Pharmacodynamics is the study of the drug effects (therapeutic and adverse) on patients. Despite there being significant differences in this population, drug responses in children have some commonalities with adults once developmental PK characteristics are considered.[21]

MAC for volatile anaesthetics is generally less in neonates than infants. Peak is at six months and then decreases to adult values by adolescence (see Table III). The variability in drug responses among the different volatile agents is influenced by the change in number of $GABA_A$ receptors and developmental shifts in the regulation of chloride transporters in the brain.[2]

Response to vasoactive drugs is also age-dependent. PD differences can be attributed to developmental changes in myocardial structure, cardiac function, and receptor function.

Table IV highlights some of the PD differences in neonates.

Components of ideal general anaesthesia include unconsciousness, analgesia and muscle relaxation. Measuring these pharmacodynamic outcomes in neonates is harder compared to children or adults. For example, unconsciousness is assessed by monitoring the anaesthesia depth with

Table IV. Pharmacodynamic differences of common drugs used in anaesthesia[5,23-26]

Drug	PD difference	Reason	Comments
Propofol	Profound hypotension of about 20 minutes in neonates given 3 mg/kg	Unclear	Needs further PD and PK investigation
Morphine	Increased sensitivity	Functional expression of mu receptors is developmentally regulated	–
Local anaesthetics	Amide agents induce shorter block duration Need higher dose for subarachnoid block (see text)	Myelination, spacing of nodes of Ranvier and length of nerve exposed	–
NMBD	Increased sensitivity to effects Succinylcholine induces bradycardia	Immature neuromuscular junction	–
Inotropes	Dopamine can be used in the presence of pulmonary hypertension Signs of α-receptor stimulation may occur at lower doses than β-receptor stimulation	Fewer dopamine receptors in pulmonary vs systemic vasculature β receptor maturation lags behind α maturation	Dopamine popular in the neonatal population compared to adults
Sedatives	Bolus midazolam associated with hypotension (especially if given with fentanyl)	–	–
Thiopentone	Dose 3.4 mg/kg (compared with 6.3 mg/kg in infants and 4-7 mg/kg in adults)	Uncertain PK and PD Uncertain cause ? immature cerebral cortical function ? rudimentary dendritic abnormalities ? relatively few synapses	–
Paracetamol	Poorly defined PD Early exposure may be related to later development of atopy-related syndromes ? early PDA closure	Unknown link	–
Prokinetics	Not very useful in very preterm neonates but useful at full term	Age-dependent expression of intestinal motilin Modulation of antral contractions in the neonate	–
Bronchodilators	Ineffective	Paucity of bronchial smooth muscle that can cause bronchospasm	–
Calcium channel blockers	Can cause life-threatening bradycardia and hypotension	Cardiac calcium stores in the endoplasmic reticulum are lower because of immaturity	Exogenous calcium has greater impact on contractility

electroencephalogram (EEG) or bi-spectral index in adults. However, use of these devices cannot yet be supported in children and EEGs are different in the various categories of paediatric patients.[22]

Adverse drug effects (ADE): Drug dosage errors are more common in children with the problem being further aggravated by narrow error margins in delivery and dilution.[27] Off-label drug administration in neonates is still common with limited evidence-based pharmacotherapy. Therefore, it is requisite to design and participate in trials in the PK and PD of compounds commonly used by paediatric anaesthetists using suitable formulations and assessment methods.

In addition to the potential ADE that can occur in adults, neonates are potentially prone to particular effects because of immaturity of their physiology. Exposure to stimuli at a sensitive point of development may result in permanent effects. There are concerns that exposure of neonates to anaesthesia may cause increased neuronal apoptosis and long-term memory deficits. Implicated drugs are N-methyl D-aspartate antagonists (ketamine and nitrous oxide) and $GABA_A$ agonists (benzodiazepines, propofol, all volatile anaesthetic agents and barbiturates).[28] Translating these observations to humans has proven difficult. The FDA issued a warning on drugs used for anaesthesia in 2016 raising concerns among parents of children undergoing anaesthesia. The General Anaesthesia Spinal (GAS) study indicated that a sevoflurane-based anaesthetic of less than an hour does not increase the danger of adverse neurological outcome at two years of age.[29] The Paediatric Anaesthesia Neuro-Development Assessment (PANDA) study showed no significant differences in full-scale IQ at 10 years of age between exposed (general anaesthesia) and unexposed siblings. Scores assessed memory, language, attention, motor processing speed and behaviour among other things.[30] The area of long-term effects of anaesthesia in children is one of ongoing research and debate.

Conclusion

Neonates have significant pharmacological differences compared to adults due to rapidly maturing physiological systems. Paediatric anaesthetists have to be knowledgeable in the PK and PD of neonates through studying available literature and participating in ongoing research in this area.

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PACSA SUPPLEMENT

Difficult airway management in children

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It is fortunate that the majority of children will have airways that are simple to manage. However, in a small number of cases difficulty may be encountered. The focus of any airway management technique is to provide adequate oxygenation and ventilation. In a cooperative adult, this can be achieved by performing awake intubation techniques, however in children it is often impossible to manage them without performing anaesthesia or deep sedation. In this situation, there are three main ways that airway management is accomplished:

- Face mask ventilation
- Supraglottic airway device ventilation
- Endotracheal intubation

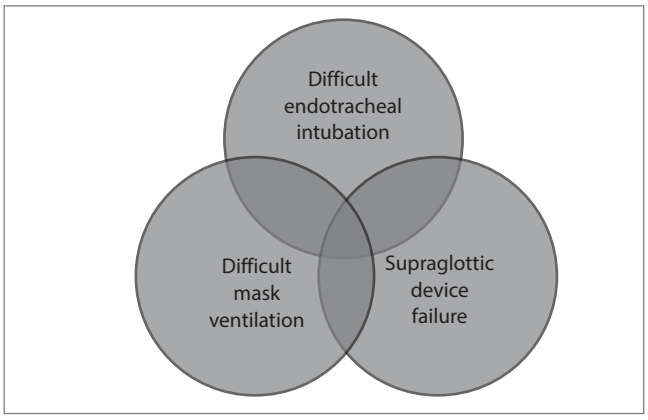

Figure 1. What makes an airway difficult?

There is no formal definition of what constitutes a difficult airway, but from a practical perspective it should be thought of as difficulty with any of the techniques used to provide oxygenation and ventilation. The area of difficulty where all three of the main techniques used to oxygenate a patient converge is the most worrying situation (Figure 1). The incidence of children who are difficult to intubate also experiencing failure of supraglottic device and mask ventilation is unknown, but it can rapidly lead to a 'can't intubate, can't oxygenate' (CICO) event with immediate life-threatening consequences. Multiple guidelines have been produced to aid anaesthetists in the management of the paediatric difficult airway (e.g. https://www.das.uk.com/guidelines/paediatric-difficult-airway-guidelines and http://www.anzca.edu.au/documents/ps56-2012-guidelines-on-equipment-to-manage-a-diff.pdf).

This review will discuss each aspect of airway management and the existing evidence that should be used when deciding how to approach a child with a difficult airway.

Pre-anaesthetic assessment and preparation

Before initiating anaesthesia a thorough medical history and physical examination should be performed. There are several factors that may point to a child being at risk for having a difficult airway.[1] These are summarised in Table I. Additionally, it is important to ask about previous anaesthetics and if possible, interrogate previous anaesthetic records for a formal description of previous airway management techniques. It should be noted that approximately 20% of difficult intubations in children are unanticipated,[2] so every anaesthetic plan should include back-up contingencies to cope with unexpected difficulty with airway management. Children who weigh less than 10 kg are also more likely to experience complications related to airway management.[2] When difficulty is anticipated, planning should take into account the location where the airway management will occur, the equipment required, and personnel needed to minimise complications. The safest place to manage an anticipated difficult airway is in the operating room.[3] The equipment required will vary depending on the circumstances. Advanced airway equipment from the anaesthetic team (e.g. flexible bronchoscopes, videolaryngoscopes) can be supplemented by the presence of our ENT surgical colleagues

Table I. Factors that may predict a difficult airway in children[1]

Soft tissue pathology	Tumour
	Abscess
	Scars
	Previous radiotherapy
	Burns
Maxillofacial malformations	Mandibular hypoplasia
	Micro/retrognathia
	Asymmetrical facies
	Reduced mouth opening
Intraoral anomalies	Microstomia
	Macroglossia
	Large overbite
C-spine pathology	Decreased mobility
	Instability
Airway obstruction	Stridor
	Obstructive sleep apnoea

and their equipment (e.g. rigid bronchoscopes, tracheostomy). Another essential feature of the management of the difficult airway is clear communication between all those involved, particularly if the airway needs to be shared with a surgical team. Any plan should be fully discussed with the nursing and surgical staff, and if needed, explicit recognition of everyone's role, and when roles may be exchanged (e.g. when the surgical team should take over attempts at intubation if the anaesthetic team have been unsuccessful).

Difficult mask ventilation

Difficulties ventilating children with a face mask occur in approximately 6% of cases.[4] Physical features that should be observed during the physical examination that may be associated with difficult mask ventilation include:

- Micro/retrognathia
- Craniofacial abnormalities
- Cervical spine abnormalities
- Obesity
- Obstructive sleep apnoea (OSA)

Positioning the patient 'head up' at approximately 30 degrees and the use of airway adjuncts such as oral or nasopharyngeal airways may improve the ability to ventilate via a face mask. If the patient has significant anatomical abnormalities, such as a base of tongue tumour or a neck mass, that make it difficult to bypass the obstruction with an airway adjunct, maintaining spontaneous breathing may be safer than a technique reliant on positive pressure ventilation.

Infants and neonates who experience difficult mask ventilation are at risk of developing significant gastric distension. This can impact on the ability to oxygenate, cause rapid oxygen desaturation through atelectasis and decreased functional residual capacity, resulting in less time available to attempt definitive airway management.

If difficult mask ventilation occurs there are several strategies that can be used to try to improve it:

- Early use of airway adjuncts such as oral/nasopharyngeal airways
- Two-person technique with a two-handed jaw thrust and a second person manually ventilating
- Change of head and/or patient position
- Early decompression of the stomach
- Early use of alternative technique, particularly a supraglottic airway

Difficult supraglottic device ventilation

Supraglottic devices were first described for use in adults in 1983.[5] Over the intervening decades many different supraglottic devices have been created for use in children. At the time of writing these include[6,7]:

- AirQ and AirQ SP
- Ambu AuraGain, Ambu Aura-i and Ambu AuraOnce
- Cobra
- I-gel
- Laryngeal tube
- LMA Classic, Flexible, ProSeal, Supreme and Unique
- PRO-Breathe
- SLIPA
- Softseal

When considering their use in children with difficult airways, the main concern is the risk that a device will fail to provide adequate oxygenation and ventilation. The available evidence examining the failure rates of different devices in children with normal airways is summarised in Table II. The rate of failure depends on the type of device and the individual child. Anatomical features associated with the presence of a difficult airway will tend to increase the risk of a supraglottic device failing.

Table II. Failure rates of supraglottic devices in children[7]

Device	Failures/total cases	% (95% CI)
AirQ	0/126	0 (0-3.0)%
AirQ SP	1/69	1.4 (0.26–7.8)%
Ambu AuraGain	0/50	0 (0–7.1)%
Ambu Aura-i	0/32	0 (0–10.7)%
Ambu AuraOnce	2/132	1.5 (0.42–5.4)%
Cobra	4/301	1.3 (0.52–3.4)%
I-gel	37/1 079	3.4 (2.5–4.7)%
Laryngeal tube	2/108	1.9 (0.51–6.5)%
LMA Classic	4/1 118	0.36 (0.14–0.92)%
LMA Flexible	0/69	0 (0–5.3%)%
LMA ProSeal	6/1 211	0.50 (0.23–1.1)%
LMA Supreme	9/488	1.8 (0.97–3.5)%
LMA Unique	2/410	0.49 (0.1–1.8)%
PRO-Breathe	6/100	6.0 (2.8–12.5)%
SLIPA	0/50	0 (0–7.1)%
Softseal	0/36	0 (0-9.6)%
Total	75/5 379	1.4 (1.1–1.7)%

It is not possible to choose a single supraglottic device to recommend over others for use in children. In general, second-generation devices (those with oesophageal and laryngeal outlets) are considered superior to the original supraglottic devices as they demonstrate:

- Higher seal pressures
- Increased ease of insertion
- Oesophageal lumens allow access to the stomach to help prevent aspiration and enabling decompression of the stomach whilst continuing to ventilate

The correct choice of device will be influenced by the patient, and the reason for using the device. For example, a recent network

meta-analysis by Mihara et al. in 2017 compared the current supraglottic devices available for use in children.[7] In this study, the authors concluded that the LMA-ProSeal may overall be the best supraglottic airway device for use in children. However, if the intent is to use the supraglottic device as a conduit to facilitate tracheal intubation, the LMA-ProSeal could be considered a poor choice when compared to the AirQ laryngeal airway, or the i-Gel.

It is also important to emphasise the early use of supraglottic devices when confronted by an unanticipated difficult airway in children. They may be life-saving when used to facilitate oxygenation during airway management and, as mentioned above, have been used as a conduit to facilitate tracheal intubation when used in combination with flexible bronchoscopy.[8]

Difficult tracheal intubation

Difficult tracheal intubation in the paediatric population is estimated to occur in 0.28–1.35%[2,9] of patients. Predictors of difficult intubation in children include extremes of weight, younger age, increased illness severity as measured by the American Society of Anesthesia (ASA) classifications, and types of surgery such as cardiac or oromaxillofacial surgery that may also serve as a surrogate for associated congenital abnormalities.[1,2] Nearly 20% of difficult intubations are not anticipated.[3] Common physical examination findings associated with difficult intubation include micrognathia, limited mouth opening and cervical spine immobility.[3] In 2012 the Pediatric Difficult Intubation Registry (PeDIR) was formed under the auspices of the Society for Pediatric Anesthesia in the USA. This registry is a multinational database that, at the time of writing, contains over 4 000 cases of difficult paediatric intubation, that has been used to gather data on this vulnerable population. The registry revealed that severe hypoxia occurred in 9% of these children, with cardiac arrest occurring in nearly 2%.[2] Every cardiac arrest was preceded by hypoxia. This demonstrated that during difficult tracheal intubation, maintenance of oxygen saturations should be our first priority.

Tracheal intubation can be accomplished by many different techniques.

Direct laryngoscopy (DL)

DL remains the most commonly chosen technique for tracheal intubation in children. It was used in 98% of cases in the Apricot study examining over 31 000 anaesthetics in 261 institutions in Europe,[9] and was the first choice technique in nearly half of the patients in the PeDIR.[2] Unfortunately, DL has a low success rate in children who are difficult to intubate, with first attempt success rates of 4% and eventual success rates of only 21%.[10] Given these poor success rates, DL has a limited role in the management of anticipated difficult intubation. If used as a first choice, it is imperative that back-up plans are in place to ensure a rapid progression to more advanced techniques. However, complications associated with intubation are related to the number of attempts at intubation,[10,11] so choosing a technique with higher first pass success rates is sensible (Table III).

Table III. Success rates of different intubation techniques from the Pediatric Difficult Intubation Registry[2,8,10]

Technique	First attempt success	Eventual success
Direct laryngoscopy	4%	21%
Flexible bronchoscope	Not reported	53%
Hyperangulated VL (GlideScope)	53%	82%
Intubation through an SGA	59%	89%

Videolaryngoscopy (VL)

Videolaryngoscopes use video cameras embedded within the laryngoscope blade to obtain a view of the larynx. They can be thought of as two distinct types:

1. Hyperangulated videolaryngoscopes
2. Standard bladed videolaryngoscopes

Hyperangulated devices cannot be used to directly visualise the larynx because they do not allow alignment of the oral, pharyngeal and laryngeal axes in the same fashion as standard laryngoscopy blades. Hyperangulated VLs look around the curve of the airway and rely solely on the view provided by the video camera. Hyperangulated blades include the GlideScope, Airtraq, Pentax AWS, Truview and the Storz C-Mac D-Blade.

Standard blade videolaryngoscopes are identical to traditional DL blades, but have a camera mounted distally within the blade. This allows DL to be performed, but also provides a second point of view (video-assisted DL–VADL) that may give a better view of the larynx, and allow others to view the endotracheal tube passing through the vocal cords. Standard laryngoscope VL systems include the Storz C-Mac Macintosh and Miller blades, McGrath Mac blades and the UE Scope. VL has been shown to achieve better views of the larynx when compared to DL,[12,13] but there has been a suggestion that it may increase the time taken to intubate by approximately five seconds.[14] This has not been shown to increase complications, and in particular there is no evidence that VL use is associated with a greater incidence of hypoxia.

In the PeDIR database, the hyperangulated GlideScope (GVL) was the most frequently used video system, accounting for 76% of all VL use. Park et al. compared GVL with DL use in children in the PeDIR and found that GVL had much higher initial and eventual success rates. The initial success rate with the GVL was 53%, with an eventual success rate of 82%, compared to just 4% and 21% with DL.[10] Interestingly, the success rates of GVL were significantly lower in children weighing less than 10 kg with initial success rates of 39% and eventual success in 73%. In adults, the success rate of GVL following failed DL is greater than 90%,[15] so the success rate of GVL in children and particularly infants, is significantly lower. Possible reasons for the lower success with GVL in children compared with adults include the more rapid oxygen desaturation seen in children, increased technical difficulties when using smaller equipment, and possibly inappropriate blade size selection. This study also showed no difference in the rates of hypoxia or trauma when

using GVL or DL. This was confirmed in a prospective study comparing videolaryngoscopy and direct laryngoscopy in patients predicted to be difficult intubations, which also showed no difference in rates of airway trauma or desaturation.[16]

One of the drawbacks of hyperangulated VL is that even if the larynx is clearly visualised, it may not be possible to pass the ETT into the trachea due to the angulation of the larynx with respect to the laryngoscope blade. Different methods to combat this have been described, including using stylets in different configurations to pre-shape the ETT,[17-19] or using a flexible bronchoscope as a manipulatable stylet to enter the trachea.[20]

Flexible bronchoscopic intubation (FBI)

Awake flexible bronchoscopic intubation has been shown to be a safe and effective method of securing potential difficult airways in adults, with a failure rate of ~1%.[21] Most children will not tolerate awake or even sedated airway management, so FBI is most commonly performed after induction of general anaesthesia. Despite advances in videolaryngoscopy, FBI remains an essential technique for difficult airway management in children. It may be the only option (aside from tracheostomy) for patients with limited or no mouth opening that precludes laryngoscopy or supraglottic airway placement. FBI was the choice for initial airway management in ~1/3 of the patients in the PeDIR.[2]

There are limited data assessing the safety and effectiveness of FBI in children who are difficult to intubate. Within the PeDIR, FBI had a first pass success rate of 38% in patients weighing less than 10 kg and 54% in those more than 10 kg. In a mannequin study simulating a difficult airway in a child with Robin sequence, Fiadjoe et al. compared first attempt intubation success between Glidescope and FBI amongst attending anaesthesiologists at two major paediatric centres. They found no difference in intubation success rates.[22] FBI has also been described as a successful technique in real infants with Robin sequence,[23,24] but it should also be considered an important part of combined techniques such as intubation via a supraglottic airway, or when used with VL.

Supraglottic airway as a conduit to flexible bronchoscopic intubation

A supraglottic airway can often bypass the causes of upper airway obstruction and in most cases provides direct access to the larynx. It is possible to perform FBI through a supraglottic device by passing a flexible bronchoscope through the lumen of the device and into the trachea. An endotracheal tube can then be railroaded over the flexible bronchoscope into the trachea. This technique has the advantage of allowing continuous oxygenation to occur via the SGA, and may even allow continuous ventilation depending on the size of the ETT and FBI used.[25] In neonates and young infants, awake supraglottic airway placement is generally well-tolerated and allows for assessment of adequate placement prior to induction.[24-26] Among the FBI-SGA patients entered into the PeDIR, rates of hypoxia were significantly lower when continuous ventilation was used during intubation (7% vs. 25%, p = 0.04).[8] The AirQ laryngeal airway was the most commonly used SGA to facilitate FBI in children. In a study comparing the AirQ assisted technique with a 'free-hand' approach in children younger than two years of age, no differences were found in the number of attempts needed to intubate, or the time taken. However, there were less adjustments needed to optimise the view of the larynx if the AirQ was used.[27]

Other combined techniques

There are numerous case reports describing techniques combining different airway management techniques. As an example, laryngeal visualisation is often possible with hyperangulated videolaryngoscopes, but navigating the endotracheal tube into the trachea can be problematic. Flexible bronchoscopic intubation combined with hyperangulated VL allows for two vantage points to view the airway and the flexible bronchoscope can be used as a movable stylet to guide the ETT into the trachea.[20,28] The ability to view the glottis with the GVL whilst advancing the ETT over the flexible scope can help identify and solve problems that may occur, with the aim of decreasing potential trauma from blind, forceful ETT advancement.

Other combined techniques described include both hyperangulated videolaryngoscopy and video-enhanced direct laryngoscopy in combination with an optical stylet, light wand, or flexible bronchoscope.[29-31]

Supplemental oxygen administration during airway management

Children can experience rapid oxygen desaturation during airway management. This occurs because of their high rate of oxygen consumption coupled with a lower functional residual capacity. The use of supplemental oxygen during routine airway management is not currently recommended, however in the setting of a difficult airway, it should be used. When supplemental oxygen is administered during intubation, a significant increase in the time to oxygen desaturation has been demonstrated.[32-34] Techniques have included administering oxygen via nasal cannula,[35] through the laryngoscope[32,34] and through specific equipment designed to deliver high flow, humidified oxygen (e.g. Transnasal Humidified Rapid Insufflation Ventilatory Exchange [THRIVE]).[33,36] The THRIVE system has been shown to maintain oxygen saturations for at least twice as long as the expected age-dependent apnoea times in healthy children.[33]

Steiner et al. examined the use of 'deep' oxygen insufflation via a PCD Truview videolaryngoscope, through its side-port attached to an oxygen supply, and a modified traditional direct laryngoscope blade. They compared the time to oxygen desaturation using these devices compared to traditional direct laryngoscopy without oxygen supplementation, in apnoeic children.[34] The graph below illustrates their results, showing that children without supplemental oxygen desaturated much more rapidly:

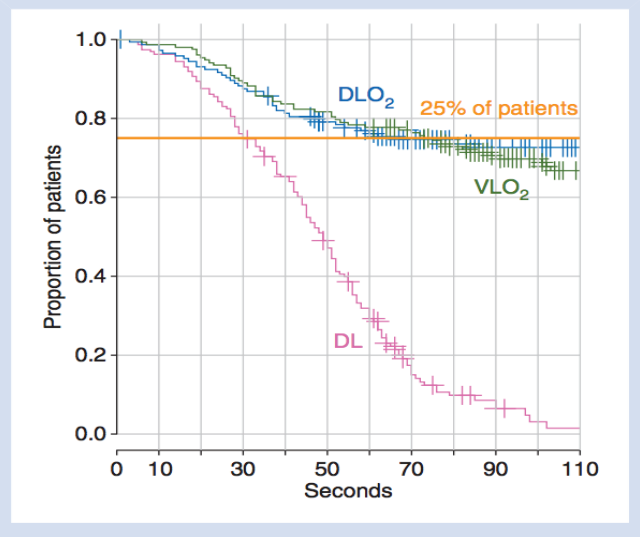

Figure 2. Kaplan-Meier curves of time to 1% reduction in saturation from the baseline. Time to 1% reduction in saturation was censored at the end of intubation.[34]

Riva et al. also studied the effect of oxygen administration via standard nasal cannula versus the use of the THRIVE system in children. They studied apnoeic children receiving 100% inspired oxygen using THRIVE or via low-flow nasal cannula (0.2 litre kg^{-1}) and 30% oxygen using THRIVE.[37] Their results demonstrated an increase in apnoea times in both groups given 100% oxygen, but not in the 30% group. These studies support the use of supplemental oxygen administration during intubation attempts to increase the time to desaturation and increase the time available for practitioners to secure the airway.

There is clear evidence that the use of supplemental oxygen can increase the time to oxygen desaturation during airway management. It should be used whenever a difficult airway is encountered. A recent editorial by Fiadjoe and Litman also addressed this issue,[38] concluding that oxygen supplementation should be used on all expectedly difficult or prolonged intubation attempts in children. The benefit-to-risk ratio is too great to ignore.

Muscle relaxation

Compared with the adult literature, there is less evidence in children to support the use of neuromuscular blockade (NMB) to optimise intubating conditions. A recent Cochrane review included 34 studies evaluating the influence of neuromuscular blockade on outcomes in tracheal intubation in adolescents and adult patients. Avoidance of NMB was statistically significantly associated with difficult direct laryngoscopy (RR 13.27, 95% CI 8.19–21.49, P = 0.00001).[39] There is more limited evidence in children that neuromuscular blockade improves intubating conditions. In contrast to the adult reviews on this topic, only seven studies met criteria for inclusion for a recent meta-analysis evaluating NMBA use and intubating conditions in children.[40] This study concluded that muscle relaxants may be recommended for intubation over opioids to improve intubation conditions. Of note, all the included studies in this meta-analysis compared intubating conditions between patients receiving muscle relaxant to those receiving a combination of opioids and volatile anaesthetics. The doses of opioids administered in these studies could be expected to render patients apnoeic, therefore the conclusions from these studies may not be applicable in answering questions concerning safety and effectiveness in spontaneously breathing patients. The characteristics of the trials included in the meta-analysis are outlined in Table IV.

There is no evidence that maintaining spontaneous breathing decreases the risk of complications and hypoxia during airway management. Indeed, the opposite may be true, in that complications such as laryngospasm and hypotension from the higher doses of anaesthesia required may occur when neuromuscular blockade is avoided.

The most recent study using data from the PeDIR examined the differences in complications in patients who were breathing spontaneously versus those who underwent controlled ventilation with and without muscle relaxation. The initial hypothesis was that those breathing spontaneously would experience less complications than those who were rendered apnoeic, however, the opposite was found to be true. The spontaneously breathing group was more than twice as likely to experience complications than the apnoeic group. Interestingly there were no differences in complications between the group that was paralysed and those rendered apnoeic without neuromuscular blocking agents, so it is possible that the complications seen in the spontaneously breathing group relate to inadequate depth of anaesthesia, although it is not possible to confirm this with a retrospective review.

Table IV. Characteristics of the trials included in the meta-analysis[40]

Paper	Patient age	Anaesthetic agent and dose	Opioid and dose	Muscle relaxant and dose
Blair et al.[41]	3–12 years	Propofol (3 mg kg^{-1})	Alfentanil (10 mcg kg^{-1})	Succinylcholine (1 mg kg^{-1})
Blair et al.[42]	3–12 years	Propofol (3 mg kg^{-1})	Remifentanil (1–3 mcg kg^{-1})	Mivacurium (0.2 mg kg^{-1})
Crawford et al.[43]	2–12 months	Propofol (4 mg kg^{-1})	Remifentanil (2 mcg kg^{-1})	Succinylcholine (2 mg kg^{-1})
Devys et al.[44]	1–24 months	Sevoflurane (8% inspired)	Alfentanil (20 mcg kg^{-1})	Rocuronium (0.3 mg kg^{-1})
Morgan et al.[45]	2–16 years	Propofol (4 mg kg^{-1})	Remifentanil (1.25 mcg kg^{-1})	Succinylcholine (1 mg kg^{-1})
Ng and Wang.[46]	2–10 years	Halothane (3% inspired)	Alfentanil (20 mcg kg^{-1})	Succinylcholine (2 mg kg^{-1})
Steyn et al.[47]	2–14 years	Propofol (3–4 mg kg^{-1})	Alfentanil (15 mcg kg^{-1})	Succinylcholine (1.5 mg kg^{-1})

Our current practice is to recommend the use of neuromuscular blockade in the majority of patients and to maintain spontaneous respiration in patients who have anatomically obstructing lesions that are not possible to bypass with airway adjuncts (e.g. large neck masses causing tracheal deviation, large mediastinal masses compressing the airway, etc.). In patients where controlled ventilation has been established with a mask or supraglottic device, we consider it safe to administer neuromuscular blockade and recommend it to ensure optimal intubating conditions are achieved for the first attempt at intubation.

Front of neck access (FONA)

In the rare, but potentially catastrophic 'Cannot Intubate, Cannot Oxygenate' (CICO) scenario, emergency front of neck access (eFONA) will be the technique of last resort to restore the ability to oxygenate the patient. Options to accomplish eFONA include surgical approaches via a cricothyrotomy or tracheostomy, or utilising a Seldinger approach with needle cricothyrotomy. Once the trachea is accessed, oxygenation can be supplied using jet-ventilation through the cannula or from an alternate oxygenation source.

The Difficult Airway Society has released guidelines recommending a surgical approach for eFONA using a 'scalpel, twist, bougie, tube (STBT)' technique. The steps for this technique involve a scalpel incision through the cricothyroid membrane, followed by a twist to widen the tract. A bougie is inserted into the trachea, then an endotracheal tube railroaded over the bougie. This technique has been demonstrated to be successful, even in the most adverse conditions. Using this technique, Lockey et al. reported a 100% success rate in 98 pre-hospital STBT cricothyrotomies. Mabry also described an 85% success rate of cricothyrotomy using the STBT technique when utilised by battlefield physicians in Afghanistan.

Infants and neonates in particular pose a challenge to performing an STBT approach due to their smaller airway dimensions. In this population, even a neonatal size endotracheal tube may have a larger outer diameter than the size of the average neonatal cricothyroid membrane, complicating the ability to utilise an STBT technique. As an alternative, a cannula-based approach that relies on a smaller catheter placed into the trachea, either through the cricothyroid membrane or trachea itself, can be used. This may prove less traumatic. A study from 2015 performed in rabbits, compared needle cricothyrotomy with surgical techniques for eFONA.[48] In this study, the animals chosen weighed approximately 4 kg in order to simulate procedural conditions in neonates/infants. While the study noted difficulty with both techniques, needle cricothyrotomy had 100% success while surgical techniques, a 75% success rate.

There is currently insufficient evidence to recommend a given technique for eFONA in children. While anaesthetists may have greater comfort with needle-based techniques, STBT may be more effective in older children and adolescents. Newer emergency oxygenation and ventilation devices such as the Ventrain,[49] that allow for both oxygenation and ventilation via a small lumen catheter may be beneficial, though at this time there is minimal evidence on its use in children[50,51] and it is not licensed for use in children by the FDA in the USA.

Conclusion

Though airway management is children is generally uncomplicated, children who prove to be difficult to intubate can be susceptible to significant complications. In particular, when difficulty is encountered, there is a risk of hypoxia and hypoxia-related cardiac arrest. Complications are associated with increased intubation attempts therefore strategies to best minimise risk in this patient population include:

- Mitigating risk of hypoxia through adequate preoxygenation and providing supplemental oxygen throughout airway management.
- Optimising conditions for successful first attempt at intubation by considering advanced airway techniques rather than direct laryngoscopy if difficulty is anticipated.
- Utilising muscle relaxation to provide the best possible conditions for intubation provided there is assurance that the patient can be safely ventilated.
- In the setting of failed intubation, there should be rapid progression to alternate techniques and to the most experienced provider.

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PACSA SUPPLEMENT

The physiologically difficult airway

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Introduction

The difficult airway has traditionally referred to anatomical characteristics which made visualisation of the glottic opening or placement of the endotracheal tube through the vocal cords difficult. In this paper we discuss how physiological derangements of the patient may place them at increased risk of cardiorespiratory collapse from airway management.[1] There are several predictable anatomical and physiological differences in children which places them at greater risk during the intubation process. These are briefly summarised in Table I.

The **anatomically difficult airway** is defined as a clinical situation in which a conventionally trained anaesthesiologist experiences difficulties with facemask ventilation, tracheal intubation or both.[3] With the expansion of devices available for airway management, contextual factors such as operator experience, time pressures, the clinical setting, and the patient's underlying physiological alterations still often result in difficulty with optimisation of gas exchange, which is the primary goal. The **physiologically difficult airway** is one where pre-existing physiological derangements (e.g. cardiopulmonary pathology, anaemia, low cardiac output, VQ mismatch and hypermetabolic states) place the patient at higher risk of cardiovascular collapse with intubation and conversion to positive pressure ventilation.[1,4] These factors should be accounted for in the intubation plan.[1]

The high risk nature of these airways is accentuated by the fact that 'waking up' the patient is often not an option, and reversing the effects of drugs does not reverse the mechanical or physiological cause of airway difficulty. Anatomically normal airways become physiologically difficult due to rapid deterioration, decreased reserve and urgency.[5]

Pathophysiology

The physiologically difficult airway is not well described and there is very limited data available on management methods particularly in the paediatric population. Most of the published literature is from Emergency Medicine and Critical Care units with predominantly experience-based recommendations, and where available, evidence-based recommendations.[1,5-8] Four clinically relevant physiologically difficult airway scenarios that the anaesthesiologist may commonly encounter include hypoxaemia, hypotension, severe metabolic acidosis, and right ventricular dysfunction or failure.

Hypoxaemia

Hypoxaemic respiratory failure (Type 1) commonly occurs due to an aetiology that disrupts optimal alveolar-capillary gas exchange e.g. pneumonia, paediatric acute respiratory distress syndrome (PARDS), and cardiogenic or non-cardiogenic pulmonary oedema, resulting in a ventilation/perfusion (VQ) mismatch.

There is increased risk of atelectasis with apnoea e.g. increased abdominal load, decreased muscle tone with reduced functional residual capacity. These patients are at high risk for rapid desaturation, resulting in bradycardia, haemodynamic instability, cardiopulmonary arrest and hypoxic brain injury. It is thus necessary to identify these patients with limited reserve, and to utilise all techniques available to prolong time to desaturation or 'safe apnoea time'.

Table I. Anatomical and physiological differences in children and strategies to address them[2]

Anatomical/physiological differences	Strategy to address
Large occiput	Position patient appropriately to align external auditory meatus with sternal notch. Infants may need shoulder roll, toddlers and school age children usually well aligned without support, older children and adolescents frequently benefit from elevation of the head similar to adults
Anterior, cephalad airway	Videolaryngoscopy and/or fibre-optic bronchoscopy, rescue device being supraglottic device
Large floppy epiglottis	Straight blade, engaging hypo-epiglottic ligament
Elliptical shaped airway	Appropriate cuffed endotracheal tubes
Smaller lung volume	
↓FRC, ↑closing capacity →rapid desaturation ↑ metabolic rate, ↑O_2 consumption →↓reserve Short apnoea time	Preoxygenation Apnoeic oxygenation

Recommendations

1. Preoxygenation

Preoxygenation depends on spontaneously breathing 100% oxygen. This denitrogenates the functional residual capacity (FRC) of the lungs and hence increases the FRC oxygen store and delays the onset of arterial desaturation and hypoxaemia.[9] The current standard of oxygenation involves the use of a tight fitting face mask (that prevents air leak from the anaesthetic circuit) with tidal breathing for 3–5 minutes with the aim of achieving FeO2 > 90%.[10] Safe apnoeic time is prolonged with preoxygenation, but variable with device seal, patient agitation/movement, factors that change the rate of oxygen consumption or functional residual capacity.

Non-invasive positive pressure ventilation (NIPPV) has been shown to improve oxygenation beyond usual preoxygenation methods, particularly in patients with obesity and shunt physiology. NIPPV increases mean airway pressure with the benefit of alveolar recruitment, temporarily decreasing the shunt fraction and improving oxygenation.[1] Nasal NIPPV has been shown to be well tolerated amongst the paediatric population. Positive pressure can be applied via standalone disposable continuous positive airway pressure (CPAP) masks connected to non-invasive machines or standard ventilators; or by closing the adjustable pressure limiting (APL) valve on the anaesthetic circuit and maintaining a tight seal as the patient breathes spontaneously or using a positive end-expiratory pressure (PEEP) valve on a standard bag mask.[11] NIPPV settings of inspiratory pressure 5–15 cm H_20, PEEP 5 cm H_20 and target tidal volumes of 6–8 ml/kg are usually used.

When NIPPV is deemed inadequate due to anatomic characteristics that make obtaining and maintaining an adequate mask seal difficult, supraglottic airways may be an option for preoxygenation.[1] Supraglottic airway devices have been inserted successfully in awake children after adequate local anaesthesia for the mouth and pharynx (e.g. LMA insertion in awake neonate with Pierre Robin syndrome after application of 2% lignocaine gel to airway).[12] Once inserted, it can be used as a conduit for tracheal intubation with a fibre-optic scope.[13]

Pharmacological assistance to decrease anxiety or induce sedation, without compromising airway tone, may be useful in improving patient tolerance during these manoeuvres. **Delayed sequence intubation (DSI)** is a technique in which ketamine (0.5–2 mg/kg) will dissociate the patient but allow them to maintain their protective airway reflexes while preoxygenating.[5,13,14]

Dexmedetomidine is an alternative.[7] This can be thought of as procedural sedation in which the procedure being performed is preoxygenation.

2. Apnoeic oxygenation

Apnoeic oxygenation is the passive flow of oxygen into the alveoli during apnoea. This can be achieved by oxygen insufflation through the nasopharynx (e.g. nasal prong oxygen, high-flow positive pressure humidified nasal prong oxygenation[15] or modified Trumpet manoeuvre[16]) or oropharyngeal passages, or through a needle inserted in the cricothyroid membrane,[10] or while intubating with a fibre-optic bronchoscope (FOB) through a supraglottic airway device[17] or even via an endotracheal tube attached to a laryngoscope e.g. Truview PCD videolaryngoscope.[18]

Transnasal humidified rapid insufflation ventilatory exchange (THRIVE) which is the same as high-flow positive pressure humidified nasal prong oxygenation ($HFNPO_2$), combines the benefits of apnoeic oxygenation and CPAP with some reduction in CO_2 levels through gaseous mixing and flushing of the dead space.[1,10] This can be used in preoxygenation and during apnoeic oxygenation.[15] Recommendations on flowrates are noted in Table II.

On average $PaCO_2$ increases 8 to 16 mm Hg in the first minute of apnoea, and then approximately 3–4.2 mm Hg per minute.[11,19] It is rare that the $PaCO_2$ increase and pH decrease are clinically significant. An exception is in profound metabolic acidosis (patients compensate for acidosis via tachypnoea and hyperpnoea) in patients with elevated intracranial pressure (CO_2 can lead to cerebral vasodilation) and pulmonary hypertension (where the hypercarbia and acidosis can precipitate a pulmonary hypertensive crisis).[11] Under these

Table II. Nasal cannula and $HFNPO_2$ flow rates

Proposed recommendations for nasal cannula flow rates during apnoeic oxygenation in children[2]			
	Adjusted per year of age	**Stepwise approach**	**Infant/child versus adolescent**
General Recommendations	1–2 L/min per year of age (max 15 L/min)	< 3 y: 2 L/min 3–8 y: 4 L/min > 8 y: 6 L/min	Infants/children: 5 L/min Adolescent: 15 L/min
Applying each recommendation across sample ages			
1-y-old	1–2 L/min	2 L/min	5 L/min
5-y-old	5–10 L/min	4 L/min	5 L/min
16-y-old	15 L/min	6 L/min	15 L/min
Recommendations for high flow humidified nasal prongs oxygen flow rates			
≤ 12 kg	2 L/kg/min		
> 12 kg	2 L/kg/min (for the first 12 kg) + 0.5 L/kg/min for each kg thereafter (max flow of 50 L/min)		

circumstances the patient should be actively hyperventilated prior to any airway intervention.

3. Recruitment

Anaesthesia and intubation attempts worsen pulmonary mechanics and gas exchange in the critically ill. Provided haemodynamic stability is maintained, recruitment manoeuvres are beneficial in hypoxaemic patients following intubation. Various techniques have been suggested, one of which is using inspiratory pressure of 30–40 cm H_20 for 25–30 s to increase lung volume and oxygenation, and decrease atelectasis without adverse effects.[5]

Hypotension

When managing the airway of a sick child, there needs to be an awareness of normal cardiopulmonary interactions. The reduced left ventricular afterload that results from positive pressure ventilation (PPV) may be beneficial when myocardial contractility is poor. However, securing the airway of these patients carries risk. Positive pressure ventilation reduces preload, potentially reducing cardiac output. Small infants can have augmented vagal response to PPV, leading to bradycardia and further reduction in cardiac output. These changes with PPV can be exacerbated by hypovolaemia, sepsis, acidosis, reduced cardiac contractility, attenuation of catecholamine surge with resolution of hypoxia and hypercarbia, vasodilatory and myocardial depressing effects of induction agents.[20] It is thus necessary to predict or mitigate peri-intubation hypotension.

Recommendations

1. Fluid resuscitation

Increase in circulating volume will increase mean systemic pressure and venous return. If the right heart can accommodate the increased venous return, the patient will be volume responsive and the cardiac output will increase. Volume responsive is typically defined as an increase in cardiac output by > 15% in response to a fluid challenge.[1] Those patients who are not fluid responsive will require inotropic support. See Figure 1.

2. Inotropic support

Inotropic support may need to be considered before commencing with airway management. Adrenalin and/or dobutamine infusions may be helpful in maintaining vascular tone and perfusion pressure. They are useful for ameliorating the decrease in vascular tone induced by anaesthetic agents and maintaining systemic vascular resistance and diastolic perfusion of the coronary arteries until the transient hypotension resolves or fluid resuscitation is optimised. When given for a short period of time, diluted peripherally administered vasopressors have been shown to be low risk.[9]

3. Haemodynamically neutral induction agents

There needs to be careful consideration and selection of induction agents as they are often associated with haemodynamic effects. No drug is risk free. Ketamine is often an attractive choice due to its sympathomimetic properties. Etomidate maintains blood pressure during intubation but has potential adrenal suppressive effects, especially in septic patients; these effects can worsen haemodynamic instability.

Severe metabolic acidosis

When acidemia develops from metabolic acidosis, mechanism of acid base homeostasis depends on a compensatory respiratory alkalosis from alveolar hyperventilation.[1] When hypocapnia is already present due to respiratory alkalosis, further hyperventilation results in incrementally smaller decreases in $PaCO_2$ and eventually reaches a plateau at which point there is no effect of further increasing alveolar ventilation (Figure 2). Thus in severe metabolic acidosis as occurs with salicylate toxicity or severe lactic acidosis, the acid production demands on alveolar

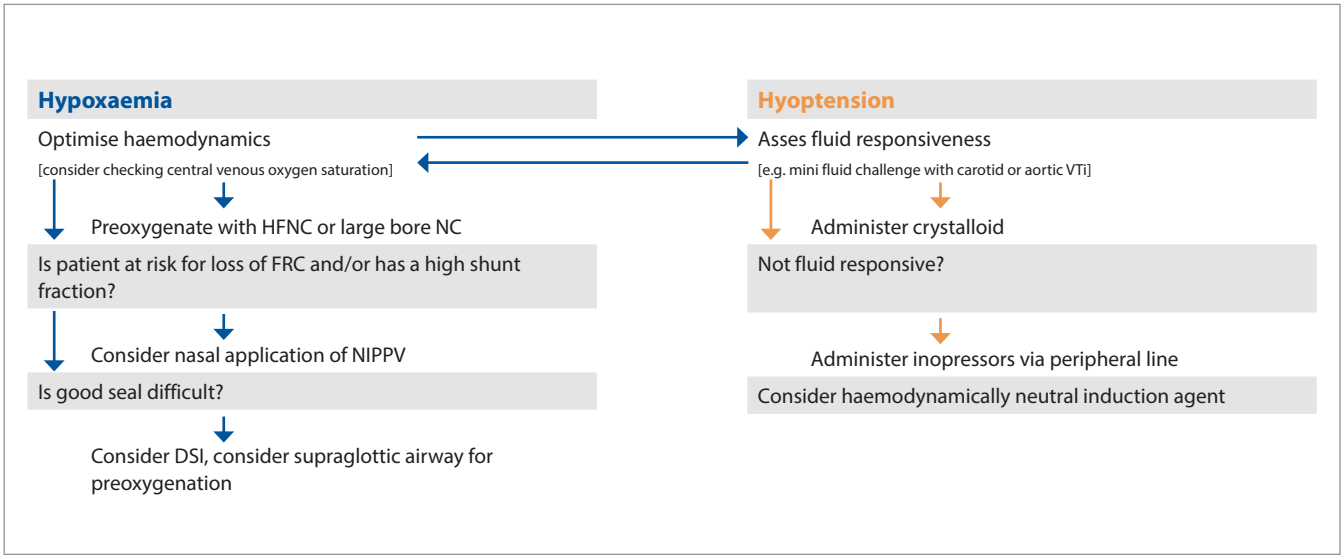


Figure 1. Summary of the management strategies in hypoxaemia and hypotension

NIPPV - non-invasive positive pressure ventilation, DSI - delayed sequence intubation, HFNC - high flow nasal cannula, VTi - velocity time integral, FRC functional residual capacity[6]

ventilation cannot be met and subsequently a profound acidemia develops. In this event should the patient require intubation, even a brief period of apnoea can lead to a precipitous drop in the pH. Furthermore, the pre-intubation ventilation cannot be matched by the mechanical ventilator. Consequently lung protective strategies may need to be abandoned.[1,21]

Recommendations

1. Intubation should be avoided if possible; instead the underlying metabolic derangement should be corrected.
2. Where intubation is necessary, use short-acting agents, so that there is rapid return of spontaneous respiratory drive. This will allow the patient to maintain their own high minute ventilation.
3. Once intubated, choose ventilation mode that allows better patient synchrony and comfort in order to maintain their respiratory compensation e.g. pressure support or pressure control modes.

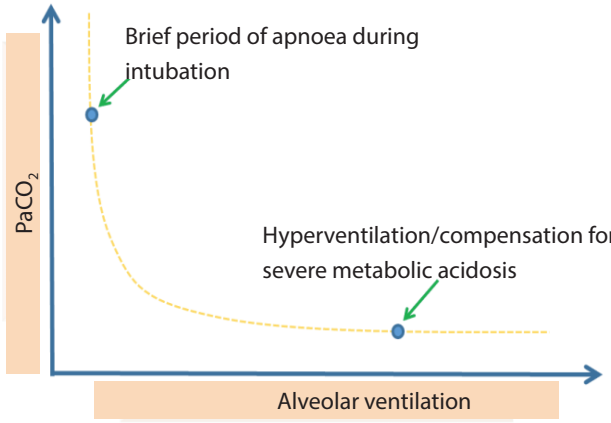


Figure 2. The relationship between alveolar ventilation and $PaCO_2$. A brief fall in alveolar ventilation (e.g. with intubation) can result in dramatic increases in $PaCO_2$ and acidemia which may be fatal in pulmonary hypertension[21]

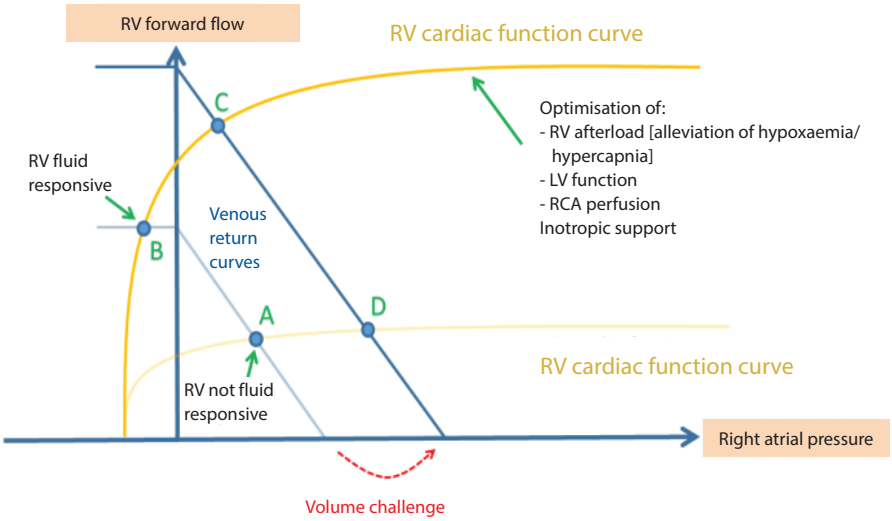


Figure 3. Optimising RV function first will move the operating point from A to B. Provision of fluids at point B will shift the venous return curve and RV forward flow will rise from point Bb to C. If volume is given prior to optimisation of RV function, the operating point will move from A to D. This will raise right atrial pressure without augmenting flow.

RV - right ventricle, LV - left ventricle, RCA - right coronary artery[21]

Right ventricular failure

The right ventricle (RV) is a low-pressure, high-compliance, flow-based chamber geared to propel venous blood returning to the heart into the pulmonary circulation.[1] It is important to differentiate RV dysfunction (some reserve retained) from RV failure, where there is an inability to meet increased demands with ensuing RV dilatation, retrograde flow and ultimately systemic hypotension and cardiovascular collapse.[1] Positive pressure ventilation which causes an increase in intrathoracic pressure, increased RV afterload and decreased preload often leads to cardiovascular collapse in patients with pre-existing RV pathology. Elevations in pulmonary vascular resistance e.g. hypoxaemia, hypercarbia, acidosis and sympathetic stimulation such as intubation, also have the potential to further increase RV afterload.

Recommendations

1. Bedside echocardiographic assessment of RV function should be performed to differentiate RV dysfunction from RV failure. If there is still some contractile reserve (RV dysfunction), cautious fluid resuscitation is possible.[1]
   Preoxygenation and apnoeic oxygenation should be performed.
2. Haemodynamically stable drugs should be used.
3. Continous dobutamine infusion should be started prior to induction in the hypotensive patient with the goal of increasing mean arterial pressure higher than pulmonary artery pressure.
4. Goals of ventilation should be to keep low mean airway pressure to prevent excessive right ventricle overload, hyperventilation with high FiO_2 and moderate PEEP with the aim of decreasing RV afterload.

General management principles

It is imperative to have appropriate airway assessment, planning and preparation for the difficult intubation. Rescue techniques including front of neck access should be readily available. The double approach is encouraged. Furthermore, key factors in making problem solving and crisis management successful are teamwork and communication to ensure a shared mental model, and situational monitoring.[5,22]

Standard **monitoring** must include pulse-oximetry, waveform capnography, blood pressure, electrocardiogram and, where available, end-tidal oxygen concentration.[5] If clinically indicated, a preintubation focused echocardiography to assess RV function can be performed. After haemodynamic assessment of the

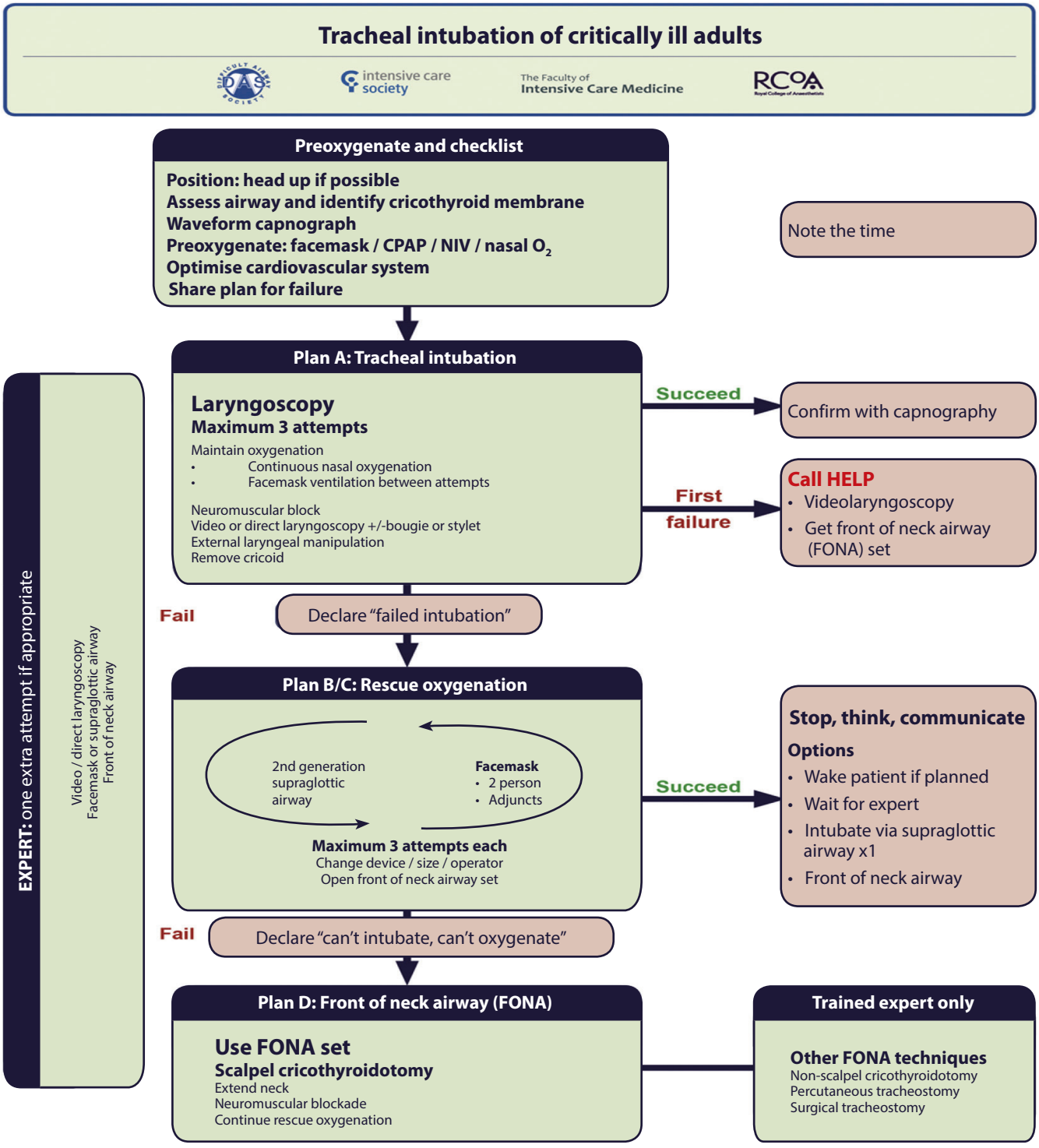
patient, consideration of fluid resuscitation and/or vasoactive agents takes place. Thereafter haemodynamically neutral induction agents may be used.

In the **preoxygenation** period the following should take place:

- Position patient in the ear to sternal notch position.
- Risk categorise patient and apply appropriate preoxygenation assisted by DSI where necessary
- Low risk identified by SpO_2 96–100% receive a tight-fitting face mask, high risk identified by SpO_2 9–95% should get a tight-fitting face mask or CPAP or bag mask device with PEEP 5–15 cm.
- Aim to achieve SpO_2 > 98%.
- Consider slight hyperventilation in patients with PHT, ↑ICP and severe metabolic acidosis.

During the apnoeic period:

- Remove face mask and apply nasal cannulae at high flow, THRIVE or nasal CPAP (or other alternatives of **apnoeic oxygenation**) throughout the intubation attempt.



This flowchart forms part of the DAS, ICS, FICM, RCoA guideline for tracheal intubation in critically ill adults and should be used in conjunction with the text.

Figure 4. Algorithm for tracheal intubation of critically ill adults[5]

- Limit lengths of laryngoscopic attempts until oxygen saturations falls lower than a predetermined level (often 90–92%) or length of time (e.g. 30–45 seconds) to decrease the frequency of hypoxia without affecting success rates.

If visualisation of the glottis is poor, the provider should reassess the patient's position to improve the alignment of the oral-pharyngeal-laryngeal axes. **Optimal external laryngeal manipulation** (BURP – backwards, upward and rightward pressure on the larynx[23]) can be used to bring the larynx into view. Direct or indirect laryngoscopy techniques performed by an experienced provider should be used, failing which the provider should consider the usage of a supraglottic airway device and/or fibre-optic device. The double setup approach, a strategy of preparing for two airway approaches simultaneously in patients with anticipated difficult airway, is advocated.[7] The cricothyroid membrane may be identified by ultrasound or clinically before inducing the patient.

Every attempt should be made to establish institutionally relevant modifications of the **difficult paediatric airway guidelines.** Figure 4 represents an algorithm suggested by the Difficult Airway Society in 2017 for tracheal intubation in the critically ill adult. This encompasses the principles of having a maximum of 3 laryngoscopy attempts, with rapid progression to simple techniques of oxygenation and ventilation, failing which a surgical airway is recommended.[24-26]

Conclusion

There is no substitute for good clinical judgement, and first attempt success is the goal for airway management in patients with physiological derangements. Clinicians should thus optimise all critically ill patients prior to intubation as the physiological airway is a high-risk procedure requiring significant expertise in airway handling as well as understanding of pathophysiology of the disease process. There is minimal margin of error. Many of the recommendations are based on clinical experience and physiological principles in the adult patient, thus presenting an opportunity for formal investigation in the paediatric patient.

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PACSA SUPPLEMENT

Clearing the air: Medical marijuana in adolescents with chronic pain

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Introduction

In 2012, the American Academy of Child and Adolescent Psychiatry (AACAP) reported concerns about the negative impact of cannabis in adolescents.[1] In 2019, the AACAP concerns further grew due to legalisation of cannabis and its usage, especially amongst adolescents.[2] One in five Canadian adolescents (aged between 15 to 19 years of age) uses cannabis.[3] There is a global awareness of cannabis usage in adolescents, both medicinally and recreationally. However this research is in its infancy and scanty. This review aims to shed some light on cannabis, its botany, pharmacology and its suitability for adolescents with non-malignant chronic pain.

Cannabis botany

The cannabis plant, also known as marijuana, belongs to the genus Cannabaceae. Cannabis is a genus of flowering plants within the hemp family. A native of Asia, cannabis has been naturalised and cultivated worldwide over thousands of years. Traditionally, three major classes have been recognised: Cannabis sativa, Cannabis indica and Cannabis ruderalis.[4] Cannabis sativa is found worldwide and has very potent psychoactive effects. Cannabis indica is found in India and the Middle East and is also known as Hashish. It has moderate psychoactive properties and Cannabis ruderalis is found in Central Asia and has minimal psychoactive properties. Currently the cannabis plant is being cultivated and engineered as hybrid species where the different species are mixed together to obtain different potencies.

Cannabis plants usually have one of two types of flowers, male or female. Some plants have both. Male flowers grow in elongated clumps along the leaves. They turn yellow and die after blossoming. Female flowers grow in spike-like clusters and remain dark green for a month after blossoming, until the seed ripens. Hashish, more potent than marijuana, is made from the resin of the cannabis flowers.[5]

Marijuana is that part of the plant that consists of dried leaves, flowers, stems and seeds. Medical marijuana or medical cannabis refers to the physician-recommended usage of the cannabis plant and its compounds to treat disease or improve symptoms.[5] Medical cannabis is an all-encompassing term that includes products consumed as smoke, vapours, oils and tablets. Botanical and medical cannabis overlap with no clear cut boundaries for prescription.

Cannabis through time

As of November 2016, marijuana has been legalised in over 40 American states.[6] Some of the earliest records of cannabis usage date back to as early as 3000 BC where traces have been identified in Egyptian mummies. The earliest Chinese records date back to Emperor Shen Nung in 2727 BC In 1000 AD the Arabs used it to treat epilepsy. In 1798 Napoleon took cannabis back to Europe from the Egyptians. In the 1800s cannabis was part of the United States pharmacopoeia where it was a staple in cough syrups and infant diarrhoea medication. In 1941 it was removed from the pharmacopoeia (due to the marijuana tax act) and in the 1960s and 1970s cannabis became highly stigmatised. Currently, research input is being directed to find new uses for an age old drug.[7]

Cannabinoids

The cannabis plant has over 421 chemicals. Sixty-one of these chemicals make up a group of substances known as cannabinoids. A cannabinoid is one of a class of diverse chemical compounds that act on cannabinoid receptors. It is the cannabinoids that give cannabis its properties.[8,9]

Currently two cannabinoid receptors have been identified. These are Cannabinoid 1 (CB1) and Cannabinoid 2 receptors (CB2). CB1 receptors are found in neurons of the brain, spinal cord, peripheral nervous system and in organs and tissues including endocrine glands, spleen, heart and parts of the reproductive, urinary and gastrointestinal tracts. They are also highly expressed in the cerebellum, hippocampus and the basal ganglia thus reflecting their importance in motor control, memory processing and pain modulation.The CB2 receptors are mainly found in immune cells, leukocytes, spleen and tonsils. Its functions include modulation of cytokine release in the immune system.[6,8,9]

Activation of CB1 receptors produces marijuana-like effects on psyche and circulation whereas CB2 activation does not. Thus CB2 is being investigated for therapeutic uses like analgesia, chemotherapy and anti-inflammatory effects.

Ligands for the cannabinoid receptor proteins include phytocannabinoids which are cannabinoids found within the cannabis plant, endocannabinoids which are produced within the body and synthetic cannabinoids, which are synthetically manufactured.[9]

Phytocannabinoids are produced by the cannabis plant. Δ-9-tetrahydrocannabinol (THC) is the most psychoactive cannabinoid and most extensively studied. It contributes to the behavioural toxicity and unique pharmacological characteristics of cannabis.[6] Cannabis has been highly stigmatised due to the psychological effects like euphoria, paranoia, distorted perceptions and anxiety.

The mechanism of action of cannabinoids is best demonstrated through THC. THC binds to and is a partial agonist at CB1 and CB2 receptors. When THC binds to CB1 receptors, presynaptic dopamine is released resulting in the psychoactive effects of cannabis.[6] Other phytocannabinoids include cannabinol (which is less powerful than THC), cannibidiol (CBD) and cannabigerol (CBG). These have little or no psychoactive potential and are being isolated from the plant and investigated for potential uses. CBD is being investigated for its analgesic, anti-inflammatory, anti-depressant, anti-epileptic and anti-insomnia effects.[6] The main side-effect is somnolence and due to its lack of neuropsychiatric effects, it looks appealing as a medical drug.

Endocannabinoids refer to a complex, lipid signaling network of neurotransmitters with receptors within the nervous system, organ tissue, connective tissue, glands and immune cells.[6] The two main endocannabinoids are anandamide and 2-arachidonylglycerol (2-AG). Their receptors are CB1 and CB2 receptors. Endocannabinoids play a role in maintaining homeostasis in cognitive processes, fertility, appetite, pain sensation, mood and memory and newer research is focused on its role in psycho-neuro-immunology and mind-body medicine.[6]

Synthetic cannabinoids are available in some countries. Examples include dronabinol, nabilone and nabiximol. Uses include treatment of chemotherapy-induced nausea and vomiting, appetite stimulation in immunocompromised patients, relief of spasticity from multiple sclerosis and childhood epilepsy.[6]

Pharmacology of cannabis and implications in adolescence

Most data on the pharmacology of cannabis is related to THC in adults. Little is known about the pharmacology of THC and other cannabinoids in the paediatric and adolescent population.[7]

In the absence of paediatric and adolescent pharmacokinetic data, adult data becomes a reference point. Adolescents differ not only in body weight but also show changes in body composition, organ size and maturation. This has to be taken into consideration in the pharmacology of cannabis.[7]

Absorption

Administration of cannabis is mainly through smoking, inhalation, vaporisation and ingestion of edible products. Smoked and vaporised cannabis has a rapid absorption with THC detectable in the plasma within seconds and peak concentrations within three to ten minutes.[6] This route provides rapid onset of action and intense effects. Oral ingestion of cannabis allows for a much slower absorption, with peak plasma concentration of THC reached within one to four hours; thus allowing for slower absorption and less intense effects.

Age-related differences in bio-availability and time to maximum concentration will affect absorption in adolescents.[7]

Distribution

THC is highly lipophilic and is initially taken up by highly perfused tissues like the lung, heart, brain and liver and then slowly released from adipose tissue. Age-related differences in the extent of volume of distribution will impact intensity and duration of cannabinoid activity.[7]

Metabolism

Hepatic hydroxylation of Δ-9-THC generates the psychoactive compound 11-hydroxy Δ9 tetra hydrocannibinol (11-OH-THC) and further oxidation leads to the inactive metabolite 11-nor-9-carboxy- Δ 9- tetrahydrocannibinol. Adolescents have similar values to adults for hepatic metabolism. Metabolism occurs via the cytochrome P-450 system. Extra hepatic metabolism occurs in the brain, intestine, tissues and lungs.[6,7,8]

Elimination

Sixty-five percent of THC is excreted in the faeces and 20% in the urine. Anatomical and functional immaturity of the kidney and the discordance in the maturation of glomerular and tubule function can contribute to considerable inter-individual variability in renal elimination in paediatric patients. However, by adolescence the kidney has reached adult maturity.[6,7]

Effects of cannabis on the adolescent brain and behaviour

It has been traditionally known that brain development takes place in utero mainly. Due to the large explosion in neuroscience, it is now evident that brain maturation continues through adolescence and into the mid-twenties.[10] Therefore the adolescent brain is still undergoing development and is considered immature and vulnerable.

The World Health Organization's definition of adolescence is that it begins with the onset of physiologically normal puberty and ends when an adult identity and behaviour appears. This is around the ages of 10 to 19 years of age.[11] During this time of maturation, cognitive functions such as working memory, decision-making and impulsivity control occur.[8]

The adolescent brain is vulnerable and undergoes strong remodelling. Physiological activity at this point includes active development of the endocannabinoid system and changes in cortical volume, grey matter and white matter of the brain.[9] Cannabis usage at this age disrupts brain development by impairing cognitive function and decreasing executive brain function.[10,11] Neuroimaging studies of cannabis users at adolescence has shown a decrease in cortical and subcortical volumes and a decrease in white matter.[12]

Acute cannabis usage in adolescence results in dizziness, deficits in attention, lack of co-ordination, euphoria, abnormal perceptions, anxiety, irritability and paranoia.[12] Chronic usage tends to cause poor school performance with deficits in verbal learning and memory, early school leaving, intellectual disabilities, poor socialisation and even aggressive behaviour. It also has a 1:6 chance of adolescents developing a recognised cannabis use disorder by the age of seventeen. Chronic cannabis usage can even act as a gateway to concurrent substance abuse.[9,10,11]

Medical marijuana and chronic pain

Paediatric and adolescent chronic pain are both under-recognised and under-treated and have an incidence of between 20–35% worldwide.[11,12] The generally accepted definition of chronic pain in adults is pain lasting longer than three months. However in the paediatric and adolescent population it has been redefined to "pain that extends beyond the expected period of healing and therefore lacks the acute physiological signs".[13]

The American Pain Society mentions chronic pain in paediatrics and adolescence as multifactorial. Some of these factors include biological, psychological and socio-cultural factors.[13,14] Chronic non-malignant pain usually presents with abdominal pain, headaches or musculoskeletal pain. The symptoms may vary from anxiety, fatigue, sleep disturbances, depression, learning difficulties, early school leaving and socialisation issues.[14]

When multimodal chronic pain regimens of adjuvant analgesics such as anti-epileptics, anti-depressants and nonsteroidals have proven to be unsuccessful, adolescents turn to cannabis as a possible form of pain relief.

Adolescents who smoke cannabis have a "high" with each use. This "high" is then confused with temporary pain relief.[12]

Currently most of the literature on the use of medical marijuana for chronic non-malignant pain is adult based. There is a paucity of data for the paediatric and adolescent population. A review by Wong et al. looked at one case report of two adolescent patients being treated with dronabinol for pain.[14] They concluded that there was an improvement in pain scores but it was not statistically significant. Harrison et al. examined three case reports on adolescents who use medical marijuana for chronic non-malignant pain and despite smoking medical marijuana, the patients' pain persisted and furthermore these patients experienced difficulties in socialisation and schooling.[12]

The treatment of chronic pain in the adolescent population requires thorough evaluation, adequate management, compliance of adjuvant analgesics and even non-pharmacological management aimed at restorative programmes to improve daily function. It should also involve parents and family members as the entire household's dynamic is affected.[10,11,12] Parenting styles may require modification and schooling options like homeschooling or online schooling may need to be entertained.[10,11,12]

Challenges with medical cannabis

The European Pain Federation has just released literature on how to use medical cannabis in adults.[15] They conclude that therapy with medical-based cannabis should only be considered by experienced clinicians as part of a multidisciplinary team and in conjunction with adjuvant analgesia.[15]All patients must be closely surveyed and if the patient is burdened with any adverse effects, medical marijuana treatment should be terminated.[16] These principles can be extrapolated to the adolescent population until proper adolescent guidelines are formulated.

Despite advances in medical marijuana use in adolescents for epilepsy (Dravet Syndrome), spasticity associated with multiple sclerosis, autism and chemotherapy-induced nausea and vomiting, prescribing medical cannabis has its limitations.[16] These include:

- Delivery method and quality control – The easiest and commonest route of delivery of cannabis remains smoking. It is difficult for practitioners to regulate the actual amount of beneficial cannabinoids being inhaled and the actual amount of THC being ingested contributing to neuropsychiatric symptoms.[16]
- Surveillance for addiction potential – Different individuals have varying adverse effects and addiction potential. Practitioners who start adolescents on medical cannabis need to be trained in constant surveillance for addiction and adverse effects.[16]
- Contaminants – Studies have reported alarming levels of contaminants in cannabis, including bacteria and the fungus Aspergillus. Other contaminants identified include aluminium, cadmium and organophosphates. Glass beads and sand have also been found in street cannabis to increase its value by weight.[16]

Cannabis and the law

South African laws regarding cannabis and its usage are still under scrutiny. As of 18 September 2018, private citizens can no longer be penalised for the possession of cannabis for private use. Based on a person's constitutional right to privacy, Deputy Chief Justice Raymond Zondo of the South African Constitutional Court effectively decriminalised:

a. the use or possession of cannabis by an adult in private for that adult person's personal consumption in private; and
b. the cultivation of cannabis by an adult in a private place for that adult's personal use.[17]

The Constitutional Court ordered the Parliament of South Africa to amend any legislation that did not comply with the above within 24 months.[17]

The South African Health Products Regulatory Authority (SAHPRA) is responsible for regulating all medicines and medical devices in South Africa by ensuring that they meet standards of efficacy, safety and quality. In terms of Sections 21 and 22A(9)(a)(i) of the Medicines and Related Substances Act, authorised practitioners can apply to the SAHPRA for permission to access

and prescribe unregistered medicines when intended to treat individual patients. The Minister of Health has moved CBD from a Schedule 7 drug to a Schedule 4 drug.[18] Furthermore, in light of the uncertainty regarding the way forward on the regulation of cannabis and its usage in South Africa, the Minister of Health has suspended scheduling for a 12-month period for CBD preparations containing a maximum dose of 20 mg of CBD, or raw cannabis products containing not more than 0.001% of THC and 0.0075 mg of CBD. Stakeholders need to consult and decide what to do during this time.[18]

The legislation has not specifically dealt with the paediatric and adolescent population. The government is currently engaging with all stakeholders to develop South Africa's laws regarding cannabis usage, regardless of the motive, and hopefully such engagements don't only deal with usage by adults.[17,18]

In a nutshell:

1. Private usage by adults is allowed.
2. If practitioners want to prescribe cannabis as medicine or to cultivate it, they need to apply to SAHPRA.

As research and data emerge these laws will have to be revisited and the paediatric and adolescent population will have to be considered.

Conclusion

Despite advances in medical cannabis usage and the ability to isolate THC from non-THC or less potent THC compounds, there is still controversy that shrouds the use of medical cannabis for chronic pain in adolescents. The paucity of data available currently does not seem promising but opens up avenues for new research especially with CBD. Legislation also needs to consider the paediatric and adolescent patient population and practitioners need to weigh up the risks versus the benefits when prescribing to an already vulnerable population.

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"*There's a child with a heart problem on my orthopaedic list*": An approach to anaesthesia for children with congenital heart disease presenting for non-cardiac surgery

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Congenital heart disease is the most commonly occurring congenital anomaly. 95% of patients with mild to moderate lesions will now survive to adulthood, as will 69% of patients with critical disease. These patients are likely to present for non-cardiac surgery. Assessing risk of anaesthesia in these patients is important as they are at increased risk for perioperative morbidity and mortality. New physiological classifications of congenital heart disease are discussed, as are factors associated with increased risk in these patients. Patients with high and moderate risk should ideally be referred to a unit familiar with congenital heart disease.

Keywords: congenital heart disease, children, non-cardiac surgery, anaesthesia, risk assessment

Introduction

Children with congenital heart lesions are no longer uncommon in clinical anaesthetic practice.

Congenital heart disease (CHD) is the most commonly occurring congenital anomaly, occurring in about eight per 1 000 live births. It is associated with a high incidence (15–30%) of extra-cardiac defects and recognisable genetic syndromes (particularly Trisomy 21).[1] There is a suggestion that the global incidence of CHD is rising; whether this reflects a true increase in the condition or improvement in diagnostic modalities, is uncertain. The reported incidence of CHD in Africa of 2.3 per 1 000 live births is almost certainly a significant under-representation of the situation.[2]

Survival rates for patients with CHD have improved markedly. Where paediatric cardiology and surgery facilities are available, 97% of babies with non-critical CHD will survive to one year, and 95% will survive to adulthood. 69% of babies with critical CHD will also survive to adulthood.[3] For probably the first time in human history, there are now more adults with CHD alive than there are children with CHD.

When presenting for non-cardiac surgery, it is well recognised that these patients have increased morbidity and mortality perioperatively, although the actual incidence is difficult to define accurately. The evidence for risk assessment and the best perioperative management is likewise limited and likely to remain so in the near future because of the enormous variation in pathology seen and the rapidly changing cardiac treatment modalities.[3]

Physiological classifications of congenital heart disease

Anaesthetists often use a physiologically-based classification, as opposed to the anatomically-based classifications used by cardiologists and surgeons, because they provide some guidelines into the perioperative management of these patients. The original physiological classification divided CHD patients into those who were cyanotic and those who were not. This was adequate when very few patients with complex lesions survived but given the variety and complexity of lesions and treatments currently seen, newer classifications have been proposed.

1. Circulation-based physiological classification of CHD

(i) Those patients with normal or 'series' type circulation

In a normal or series type circulation, there is separation of the pulmonary and systemic circulations, which work together in series. Most patients with repaired CHD who have two ventricles will be in this category, as are some types of unrepaired CHD, such as coarctation of the aorta and valvular stenoses or regurgitations.

One sub-group of these patients are those with smaller, unrepaired atrial and ventricular septal defects and patent ductus arteriosus (ASD, VSD, PDA). The blood flow, or shunt, across such a defect depends upon the pressure gradient across the two circulations.

When the pulmonary vascular resistance is lower than the systemic vascular resistance, the shunt is from the systemic (left) to the pulmonary (right) circulation – the 'left-to-right shunt' of acyanotic CHD.

Another subset of these patients have lesions that result from obstruction to the pulmonary circulation, (Tetralogy of Fallot, isolated pulmonary stenosis with a VSD). The resulting shunt is usually from the right side of the heart to the systemic circulation – the 'right-to-left shunt' of cyanotic congenital heart disease.

(ii) Patients with parallel or 'balanced' circulation

In a parallel or balanced circulation, the systemic and pulmonary circulations are in full communication with each other and function in parallel. The blood flow to each circulation depends upon the balance of the systemic vascular resistance to the pulmonary vascular resistance, with the shunt from left-to-right or from right-to-left, depending on alterations of the resistances.

An example of a balanced circulation would be a child with an atrio-ventricular septal defect (AVSD). Patients with artificial defects such as a modified Blalock-Taussig (BT) shunt or an atrial septostomy in uncorrected transposition of the great vessels (TGV) can have balanced circulations.

(iii) Single ventricle circulation

In patients with only one functioning ventricle, palliation by way of conversion to a Fontan circulation usually requires a three stage procedure. Patients may present for non-cardiac surgery after any one of these stages.

The first procedure, usually performed as a neonate or infant, is to provide a reliable, low pressure circulation to the lungs by way of a modified BT (aorto-pulmonary) shunt; a Sano (ventriculo-pulmonary) shunt or by banding of the pulmonary artery.

These patients are then palliated to a bi-directional Glenn shunt. This produces a cavo-pulmonary connection supplying the left and right pulmonary artery with blood directly from the superior vena cava (SVC). The BT shunt or other shunts from the heart to the lungs are taken down and the lungs are supplied passively by the SVC.

Full conversion to a Fontan circulation is best done before the age of five years to preserve ventricular function. The inferior vena cava is anastomosed to the pulmonary circulation, resulting in a passive pulmonary circulation with the ventricle providing the systemic cardiac output.

2. Classification of CHD as severe, moderate and mild[4]

Severe CHD presents in the neonatal period or during infancy and usually requires early cardiac surgery. Examples of this type of disease include Tetralogy of Fallot, other cyanotic heart disease, transposition of the great vessels, hypoplasia of the right or left ventricle, critical pulmonary or aortic stenosis, symptomatic coarctation of the aorta, large VSDs, PDAs and AVSDs.

Moderate CHD is amenable to medical treatment until the child grows to a larger size, when corrective cardiac surgery or catheter laboratory corrections may be indicated. Lesions include moderate aortic or pulmonary stenosis or regurgitation, other septal defects and non-critical aortic coarctation.

Patients with *mild CHD* constitute the largest group of patients and often present with minimal symptoms or a cardiac murmur. They may or may not require correction.

Perioperative risk classification of CHD[5,6,7,8]

The following classification of risk is a suggested guideline for assessing children with CHD presenting for non-cardiac surgery.

High risk	Intermediate risk	Low risk
Severity of lesion		
Complex lesions – Tetralogy of Fallot with pulmonary regurgitation, large septal defects, valvular lesions, single ventricles, balanced circulations, cardiomyopathy	Simple lesions – Restrictive ventricular septal defects, small atrial septal defects, repaired defects with normal series circulation	Simple lesions
Physiological compensation		
Poor physiological compensation – cardiac failure, pulmonary hypertension, arrythmias, cyanosis	Good compensation – normal physiology and cardiac function or well-compensated parameters of cardiac functioning – good effort tolerance, satisfactory physical and cognitive development	Good physiological compensation, normal physiology
Type of surgery		
Major surgery – intra-peritoneal, intra-thoracic, major orthopaedic surgery, procedures with significant blood loss likely to require transfusion	Major surgery including procedures that will require blood transfusion	Minor (surface type) surgery
Emergency surgery	Emergency surgery	Elective surgery
Length of hospital stay prior to surgery > 10 days	Length of hospital stay prior to surgery > 10 days	Length of hospital stay prior to surgery < 10 days
Age < 2 years	Age < 2 years	Age > 2 years

Ideally, children with CHD who have a high or moderate risk of complications during anaesthesia should be referred to a unit familiar with CHD.

Physiological compensation of CHD[9]

Physiological compensation in this context refers primarily to good cardio-respiratory function. Correction of CHD does not always result in good cardio-respiratory function, conversely, patients with uncorrected cardiac lesions can be well compensated. An example of a poorly compensated corrected patient could be a child after correction of AVSD with residual pulmonary hypertension and atrio-ventricular valve regurgitation. An example of a well-compensated non-corrected defect would be a child with a restrictive ventricular septal defect and normal pulmonary artery pressures.

Cardiac failure in CHD may be due to volume overload (for example, in defects causing left-to-right shunts); pressure overload (for example, in pulmonary or aortic stenosis) or cardiomyopathy (genetic; due to a single ventricle or acquired,

or after a Jatene switch with poor left ventricular function). Cardiac failure is associated with a high perioperative morbidity and mortality – in one study, there was a 10% risk of cardiac arrest and 96% of the patients required perioperative inotropic support.

Cyanosis is a common feature of patients with right-sided obstructive lesions, such as Tetralogy of Fallot and in those patients who have been palliated with a modified BT or bi-directional Glenn shunt. These patients often have an arterial saturation of between 75 and 85%.

Cyanotic patients are at high risk of complications, because of their cardiac pathology, including 'tet spells' and because of the associated polycythaemia. A low platelet count, the physiological response to polycythaemia, can predispose to coagulation disorders. Hyperviscosity syndromes can be a problem in children under the age of five years, with the risk of cerebral vein and cerebral sinus thrombosis, particularly in the presence of dehydration, fever and starvation.

All children with CHD presenting for surgery should have an electrocardiogram (ECG) as the incidence of arrythmias is high and increases with increasing age. Right-bundle branch block is common but unlikely to lead to heart block. Ventricular ectopic beats in children are more sinister – these patients are at a high risk of sudden death.

Pulmonary arterial hypertension is another clear predictor of perioperative morbidity, with an 8% increase in the risk of perioperative complications.

Management of children with CHD

There are no clinically validated regimens for perioperative management of anaesthesia for non-cardiac surgery for patients with CHD. Given the variety of CHD seen and the individual physiological responses to the conditions and to treatment, these will be difficult to produce.[7,10]

Case study

A three-year-old child presents for correction of a club foot.

A history of an uncorrected VSD, diagnosed at the age of nine months after a lower respiratory tract infection, is noted. The child is taking furosemide and digoxin. He has no current symptoms related to his chest or heart. He weighs fifteen kilograms, is active and developing normally. Clinical examination reveals a healthy child with no cyanosis. A loud systolic murmur is heard over the heart. Mild cardiomegaly is present on the chest x-ray. The patient's ECG is normal.

Assessment

This patient has one of the commonest types of CHD (32% of all CHD). He is classified as having a normal, series circulation with a left-to-right shunt. The lesion is in the moderate category, not having required early correction.

There are no signs of cardiac failure (failure to thrive, tachycardia, tachypnoea, repeated lower respiratory tract infections) or pulmonary hypertension, so the child is physiologically well compensated.

There is a possibility of pulmonary hypertension associated with this type of lesion and therefore an echocardiogram would be useful prior to surgery. In this case, the echo reveals a restrictive ventricular septal defect with a left-to-right shunt, mild right ventricular hypertrophy and dilation, and normal pulmonary arterial pressures.

The patient is older than two years of age. The surgery is elective and superficial.

The risk assessment therefore suggests that this patient is at low risk for complications perioperatively.

Suggested management of a patient with well-compensated moderate or mild CHD and a left-to-right shunt

Preoperative considerations

1. Avoid prolonged starvation in children with cardiomegaly who may require higher filling volumes to maintain cardiac output.
2. Sympathetic stimulation caused by crying can increase pulmonary arterial pressure, as can hypoxia or hypercarbia caused by excessive sedation. Judicious use of premedication under close supervision may be warranted.

Intraoperative considerations

1. Standard 'ASA' monitoring is sufficient for minor procedures.
2. There is no evidence to suggest that intravenous induction of anaesthesia is superior or inferior to gas induction. It is acceptable to gain venous access after gas induction in these patients. Avoid using prolonged, high doses of sevoflurane which are vasodilatory and negatively inotropic. Propofol reduces systemic vascular resistance but has little effect on pulmonary vascular resistance. Ketamine is widely used and considered safe.
3. There is a risk of paradoxical air embolism from the right ventricle to the systemic circulation so that meticulous attention must be paid to de-airing intravenous lines and when injecting drugs.
4. Good analgesia is required to avoid sympathetic stimulation. Regional techniques work well.
5. Antibiotic prophylaxis for bacterial endocarditis is not required in this case.

   Antibiotic prophylaxis is required for patients with the following[7]:

   - Gums, teeth, oral mucosal surgery.
   - Patients who have prosthetic material inserted as part of the repair (patches for VSD repairs, BT shunts) within six months of their placement.

- Unrepaired congenital cyanotic conditions and repairs with residual defects.
- Prosthetic heart valves.
- Previous episodes of infective endocarditis.

6. Haemodynamic goals of anaesthesia management:
   - Maintain sinus rhythm.
   - For patients with left-to-right shunts, maintain the ratio of pulmonary to systemic blood flow.
   - Increasing pulmonary blood flow by reducing pulmonary vascular resistance, (high inspired oxygen concentrations, hyperventilation) will result in increased shunt, decreased lung compliance, increased work of breathing and systemic hypotension.
   - Increasing pulmonary vascular resistance (hypoxia, hypercarbia, acidosis, hyperthermia) can result in sudden increases in pulmonary artery pressure and acute right ventricular failure – a pulmonary hypertensive crisis.
   - Vaso-active drugs tend to act on both the systemic and pulmonary circulation.
   - Patients with large hearts and increased resting cardiac output tolerate hypovolaemia poorly but are also susceptible to fluid overload.

Postoperative concerns

Most patients with CHD should be nursed in a high-care environment postoperatively, particularly if they have reactive pulmonary arteries. Avoidance of hypoxaemia, hypercarbia, acidosis, hyperthermia, hypothermia and sympathetic stimulation will avoid cardiac complications.

Summary

Children with CHD are at increased perioperative risk when presenting for non-cardiac surgery. A risk assessment may be useful in deciding whether the child should be referred to a specialised facility.

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PACSA SUPPLEMENT

Approach to blood conservation strategies

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Introduction

Surgery for congenital heart defects is often performed on cardiopulmonary bypass (CPB). The prime volumes on CPB may lead to as much as 300% haemodilution.[1] The haemodilution effects may lead to severe anaemia associated with increased morbidity and mortality.[2] Use of blood products is therefore often unavoidable. Use of allogenic blood transfusion has been shown to lead to adverse events, such as: increased infections; lung injury; cardiac complications; and poor short- and long-term outcomes.[2] Societies have developed guidelines to reduce the use of allogenic blood transfusion. Hessel and Levy,[3] in their study, showed that fewer than half of the institutions they investigated did not follow their STS/SCA guidelines. Confusion over indications and risks of transfusion and concern of litigation were seen as reasons for failure to implement these guidelines.[4]

Risks of blood transfusion

Infections have been the biggest risk of blood transfusion over time. The introduction of the nucleic acid test (NAT) over two decades ago has reduced this risk.[5] However, this has not safeguarded patients from newer ever-evolving infection risks. Non-infectious risks of blood product transfusion have a great impact on clinical outcomes. These include: transfusion-related lung injury; transfusion-related circulatory overload; haemolytic and non-haemolytic transfusion reactions; alloimmunisation; and immunomodulation.[5]

Clinical impact of transfusion-related complications

Transfusion-related complications have been reported to lead to mortality, albeit at a reduced rate due to recent improvements in transfusion-related practices. Transfusion-related lung injury (TRALI), haemolytic transfusion reactions (HTR), sepsis, and transfusion-associated circulatory overload (TACO) are reported to have had mortality rates of 48%, 26%, 12% and 11% respectively in the USA in a five-year span from 2005.[5] Viral infections such as Human Immunodeficiency Virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV) have been on the decline due to improvements in testing such as the NAT system.[6]

TRALI is particularly common after transfusion of FFP, mostly from multiparous female donors due to alloimmunisation. Preferential donation of FFP and single donor platelets from males have reduced this rate.[7] In the 2009 Serious Hazards of Transfusion (SHOT) report, TACO was associated with a mortality rate of 12%.[8] Literature reports allude to an increase in cancer rates and metastatic disease related to transfusion-related immunomodulation (TRIM).[9]

Complications of transfusion in the paediatric population were mostly related to human error in the SHOT trial. These were reported to be related to over-transfusion and lack of knowledge of special requirements for blood product transfusion in the neonatal group such as irradiation and extensive screening for infectious causes.[5]

Challenges for blood conservation in paediatric age group

Paediatric cardiac patients are unique in that they often present with cyanosis, which is accompanied by coagulopathy. They have small blood volumes, require higher haematocrit on bypass, have an immature immune system, and often undergo a hypothermic

Table I. Perioperative blood conservation strategies

Preoperative	Intraoperative	Postoperative
Autologous blood transfusion	Target haematocrit	Point-of-care tests
Erythropoietin therapy	Monitoring of oxygen delivery	Antifibrinolytics
	Reduced Volumes of lines	Prothrombin Complex Concentrates
	Acute normo-volaemic haemodilution	Activated Factor VII
	Retrograde autologous priming	FDP
	Antifibrinolytics	Reduced blood sampling
	Miniature circuits	
	Vacuum assisted venous drainage	
	Surface modified circuits	
	Cell salvage devices	
	Other procoagulant agents	
	Topical haemostatic agents	
	Ultrafiltration	

cardiopulmonary bypass. They may have congenital deficiencies of clotting factors such as factor VII, VIII and vWF. Due to shunts and abnormal flow patterns, they also present with qualitative and quantitative platelet abnormalities.[10]

Strategies

Preoperative

Preoperative erythropoietin and iron supplements have been used to increase haematocrit, often to 35–40%. This strategy may be used together with autologous blood donation, which can be performed a few times preoperatively, with the last donation ideally one week before surgery. The process of preoperative donation can, however, be cumbersome and expensive, and may have complications.[10] Supplemental folic acid and vitamins A, C, and K are also often used.[10]

Intraoperative

The target haematocrit on bypass is a subject of debate. Following the Boston Hematocrit Trial, extrapolations and conclusions have been made that a Hct of ≥ 23.5% on bypass, especially low-flow bypass, confers benefit.[11,12] Oxygen delivery has to be maintained with adequate haemoglobin, optimum pump flow rates and monitoring with near infrared spectroscopy (NIRS) trends.[13]

CPB prime volumes are often 200–300% that of the patient's blood volume, particularly in neonates.[14] This leads to massive haemodilution. Use of low prime oxygenators, integrated arterial line filters, shorter tubing with small internal diameter can mitigate this effect. Ging et al.[15] used a total prime volume circuit of 220 ml in a case of a seven-month-old, 5.9 kg, 69 cm Jehovah's Witness infant for a ventricular septal defect (VSD). They primed their pump with 121 ml Plasmalyte A, 15 ml NaBic, 3 ml heparin, 1 ml calcium chloride, 18 ml Trasylol, 50 ml 25% albumin and 12 ml 20% mannitol.[15]

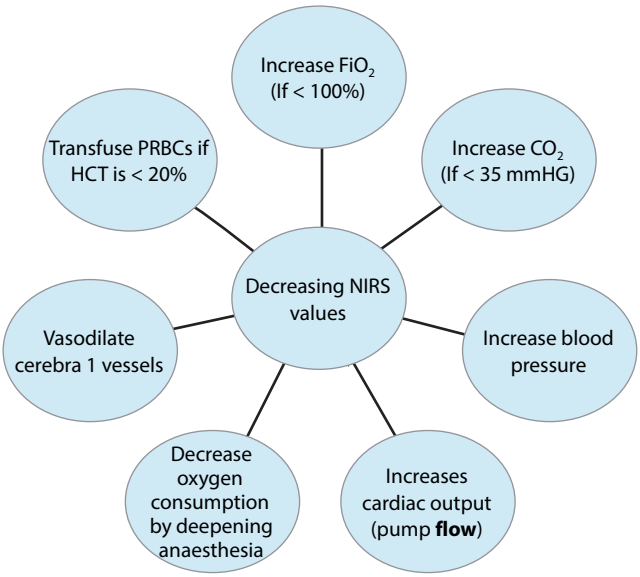

Figure 1. Strategies to optimise NIRS values[15]

Using acute normovolaemic haemodilution (ANH) they saved approximately 10 ml/kg of the patient's blood at the time of invasive line insertion. This group, using retrograde autologous priming, which removed 140 ml of the clear prime, together with vacuum assisted venous drainage, infusion of cardioplegia by syringe directly into the aorta and continuous ultrafiltration and cell salvage; managed to have a haematocrit (Hct) decrease from 35.5– 28.9% on admission to ICU. Erythropoeitin (EPO) and iron supplements were used to increase Hct preoperatively.[15]

Common strategies utilised to mitigate for a low NIRS value were: increasing blood pressure; increasing carbon dioxide if < 35 mmHg; increasing FiO2 if < 100%; transfusing blood if Hct < 20% with blood saved during ANH; vasodilating cerebral vessels; decrease oxygen consumption by deepening anaesthesia; and increasing cardiac output (pump flow).[15]

Use of ultrafiltration, conventional and modified, is extensively reported on in paediatric cardiac surgery. Conventional ultrafiltration removes excess water, electrolytes and substances with a molecular size smaller than the membrane pore size.[16] Modified ultrafiltration (MUF) is performed at the end of bypass to reduce haemodilution and oedema. There is evidence of improved coagulopathy and reduced blood transfusions. The technique, however, is not devoid of complications.[17]

Ultrafiltration has been shown to significantly reduce duration of mechanical ventilation and inotrope requirements 48-hours after surgery. Appropriate use of MUF circuits can improve the patient's Hct and whole blood compared to cell salvage which leads to losses of plasma, factors and platelets.[13]

In a study by Avgerinos et al.,[2] where they instituted a smaller volume circuit together with an intraoperative autologous donation (IAD) strategy using the DeBois nomogram (Table II), there was a significant reduction in percentage change of intraoperative haematocrit, transfusion of red blood cells, FFP and platelets, and better 30-day mortality rates in the intervention group. The nomogram uses weight and preoperative Hct to estimate volume that can be taken off during IAD.[2]

Good surgical haemostasis during surgery is paramount. The STS Blood Conservation Guideline Task Force Guidelines recommend (Class IIb) use of topical agents in their multimodal blood management programme.[18] Use of fibrin sealants in paediatric cardiac surgery, in the presence of coagulopathy, may be effective.[19,20]

Microplegia employs syringe pumps to deliver a non-diluted cardioplegia solution. Its advantages are a higher myocardial oxygen supply, with a higher haemoglobin content; a negligible fluid balance of cardioplegia; reduced tendency for tissue oedema, and reduced risk of fluid overload with associated dilution of clotting factors.[17]

Point-of-care devices such as thromboelastography and ROTEM may be useful in assessing clot firmness and lysis. Point-of-care platelet function assays allow assessment of maximum clot firmness.[21] Galas et al.[22] in their prospective study, suggested

Table II. The DeBois nomogram used to calculate IAD

Weight (kg)	30%	32%	34%	36%	38%	40%	42%	44%	46%	48%	50%
40	355	379	403	426	450	474	497	521	545	568	592
45	437	446	495	525	554	583	612	641	670	699	729
50	498	531	564	598	631	664	697	730	796	830	865
55	578	616	655	693	732	801	841	881	921	961	1002
60	658	701	745	819	865	910	956	1001	1047	1092	1138
65	737	816	867	918	969	1020	1071	1122	1173	1224	1275
70	847	903	959	1016	1072	1129	1185	1242	1298	1355	1411
75	929	990	1052	1114	1176	1238	1300	1362	1424	1486	1548
80	1010	1078	1145	1212	1280	1347	1415	1482	1549	1617	1684
85	1092	1165	1238	1311	1384	1456	1529	1602	1675	1748	1821
90	1174	1252	1331	1409	1487	1566	1644	1722	1800	1879	1957
95	1256	1340	1424	1507	1591	1675	1759	1842	1926	2000	2000
100	1338	1427	1516	1606	1695	1784	1873	1962	2000	2000	2000
105	1420	1515	1609	1704	1799	1893	1988	2000	2000	2000	2000
110	1502	1602	1702	1802	1902	2000	2000	2000	2000	2000	2000
115	1584	1689	1795	1900	2000	2000	2000	2000	2000	2000	2000
120	1666	1777	1888	1999	2000	2000	2000	2000	2000	2000	2000
125	1748	1864	1981	2000	2000	2000	2000	2000	2000	2000	2000
130	1829	1951	2000	2000	2000	2000	2000	2000	2000	2000	2000
135	1911	2000	2000	2000	2000	2000	2000	2000	2000	2000	2000
140	1993	2000	2000	2000	2000	2000	2000	2000	2000	2000	2000
145	2000	2000	2000	2000	2000	2000	2000	2000	2000	2000	2000
150	2000	2000	2000	2000	2000	2000	2000	2000	2000	2000	2000

that fibrinogen concentrate was as efficient as an alternative to cryoprecipitate and FFP. Recombinant factor VIIa in extreme clinical cases where bleeding continues despite use of standard blood products, can be useful.[23] There is, however, paucity of quality data on this.

During reversal of heparin, care should be taken not to use an overdose of protamine as excess protamine inhibits platelet and serine protease and leads to an increase in bleeding.[24] Use of heparin concentration instead of ACT may be of benefit.[24]

Cell salvage, despite its reported benefits, has its disadvantages. In small children with a body weight of < 10 kg, blood collected may be insufficient for processing even when the bowl is 100 ml. The process may lead to the cost of collection of shed blood being higher than savings from reductions of homologous blood transfusion.[25] Cell saved blood is devoid of factors and platelets. In contrast, pump blood, collected at cessation of pump, has the same quality of the patient's blood at this point. This blood can be collected in a bag and re-transfused to the patient, with heparin reversed using protamine. The blood will contain platelets and plasma proteins.[17]

Postoperative

Reducing blood sampling and excessive flushing of lines reduces transfusion rates. Chollete et al.[26] showed that children with single ventricle physiology who undergo cavopulmonary anastomosis, did not benefit from a liberal transfusion strategy 9 vs 13 g/dl. However, there is a suggestion that children with cyanosis should have a higher Hct.[10] Antifibrinolytics can be used in the postoperative period. In the post aprotinin era, refractory postoperative bleeding has been treated with FVIIa 72–87 μg/kg, reducing chest tube drainage and blood product transfusion. Post-of-care testing guides transfusion of blood products where necessary.[10]

Conclusion

The success of a blood conservation strategy is depended on a multidisciplinary effort, with a concerted effort at every point to reduce haemodilution, blood product wastage and meticulous surgical haemostasis and use of haemostatic agents. Care should be taken in paediatric patients, as their blood volume is small and those with cardiac lesions may not have a normal coagulation system.

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PACSA SUPPLEMENT

Point-of-care ultrasound in neonatal anaesthesia – current applications and future practice

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Point-of-care ultrasound (POCUS) is a widely accepted and used modality across many fields of medicine, particularly in anaesthesia. Ultrasound devices with improved image quality and mobility as well as reduced cost and size have made POCUS widely available, even in resource-poor settings. Many adult protocols have been adapted for neonatal use, as ultrasound is easily able to visualise neonatal organs and vessels. Functional or focused echocardiography is routinely performed in many institutions, with many bedside applications including central line placement, peripheral and arterial line placement, lung ultrasound and endotracheal tube localisation.

Introduction

Point-of-care ultrasound (POCUS) is an accepted standard of care imaging modality that is used across many fields of medicine, in fact, any specialisation where time-sensitive information is required for patient care.[1-3] Neonatology and paediatrics no less so, and paediatric anaesthetists are using POCUS in day-to-day practice at an ever increasing rate. Due to decreasing costs, increased imaging power and portability of various devices on the market, the newly fledged paediatric anaesthetist needs to rapidly become expert with evidence-based application of POCUS in their practice. Particular use may be found during central line placement, peripheral line placement, cardiac function assessment, diagnosis of pneumothoraces and endotracheal tube localisation, amongst others.

Figure 1. High frequency linear probe – A small footprint aids handling and visualisation in small neonates

Central venous access

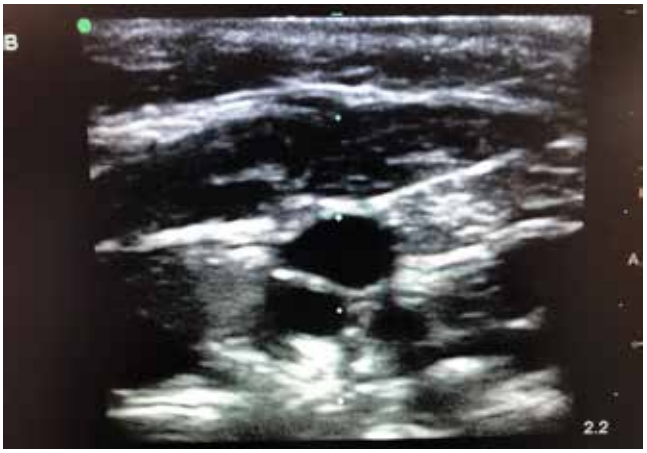

Figure 2. Internal jugular vein above smaller artery. Abnormal anatomy is often visualised on routine scans.

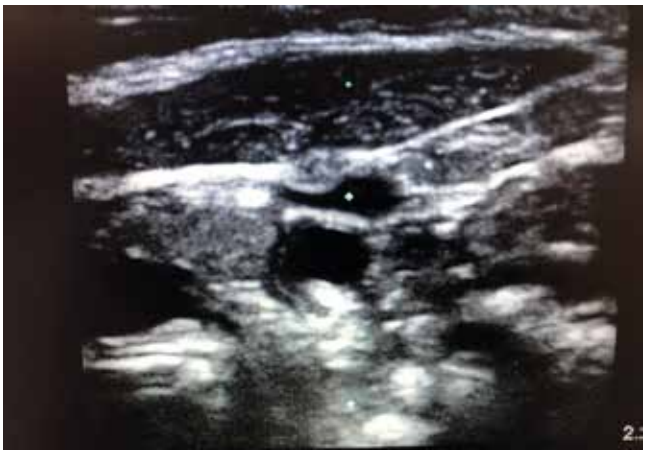

Figure 3. With pressure applied by the probe, the internal jugular vein collapses easily. The nearby artery remains patent, and in some circumstances may become more prominently pulsatile.

A variety of central vascular catheters may be placed in neonates, including umbilical artery catheters, umbilical venous catheters, peripherally inserted central catheters and central venous catheters. Besides facilitating placement, ultrasound (US) may

be used to confirm correct tip placement. Tip placement by standard chest radiography may be imprecise due to the doming of the diaphragm. One study in very low-birth-weight newborns showed that when the catheter tip was interpreted by X-ray as located in the vena cava-right atrium junction, 8/29 (28%) were in fact in the left atrium by echocardiogram.[1] US allows direct visualisation of umbilical, peripherally inserted central catheters (PICC) and central venous catheters, more accurately confirms correct placement and without the risks of ionising radiation.[2,3] Doppler also allows identification of vessels and associated anatomy.

The best insertion and maintenance technique of central venous catheters in small babies is a debatable subject, as smaller vessel and catheter diameters imply increased technical difficulties. Although space when operating is limited, US does allow the identification and use of vessels not normally identified by landmark techniques alone. US is useful for identifying the internal jugular vein (IJV) in neonates, but there are no large studies showing any significant advantage.[4] It may be useful to still use US to mark the position of the vein, but when doing a real-time cannulation, the operator must be aware of the effect of the probe on the collapsibility of the IJV (compare Figures 2 and 3), especially in the shocked premature neonate. The needle may be advanced under the probe either out-of-plane (where the needle crosses the US beam perpendicularly) or in-plane, where the entire needle remains in view at all times (see Figures 4 and 5).[5]

The brachiocephalic in-plane US guided technique used by Breschan is useful, as the targeted vessel tends to maintain its diameter in hypovolaemic and shocked patients.[6] During a seven-year period, the technique described in their 2018 paper resulted in successful cannulation of the brachiocephalic in 94% of patients (weights between 590 g and 2 500 g), with only one attempt necessary in 70% (100/142). The left brachiocephalic appears easier to cannulate due to its more horizontal appearance and allows an in-plane needling technique, as demonstrated in Figures 6 and 7.

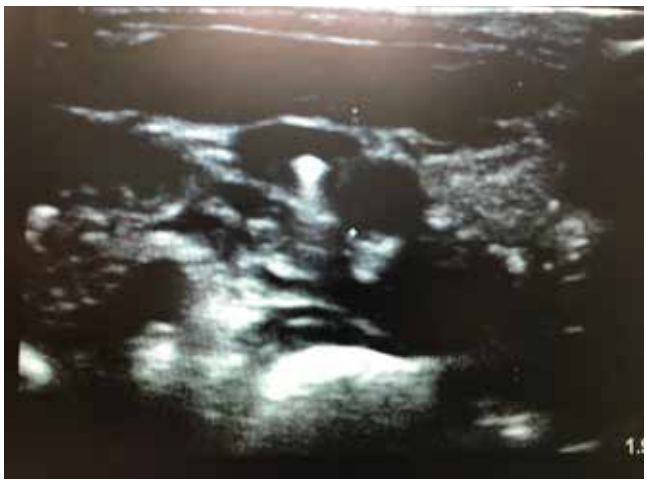

Figure 4. Out-of-plane approach revealing guidewire in-situ

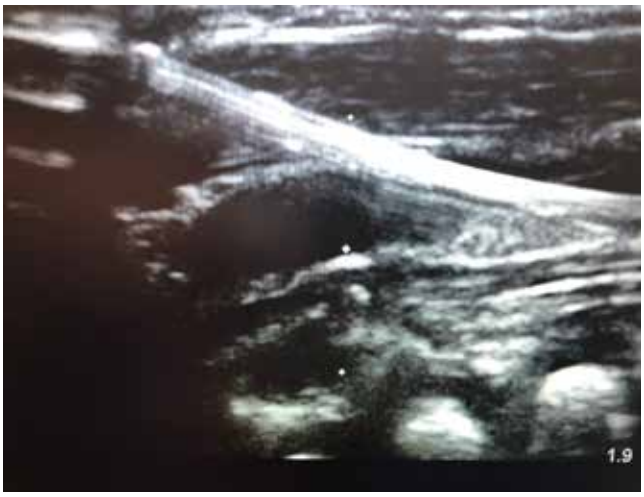

Figure 5. In-plane approach, guidewire correctly positioned in a vessel

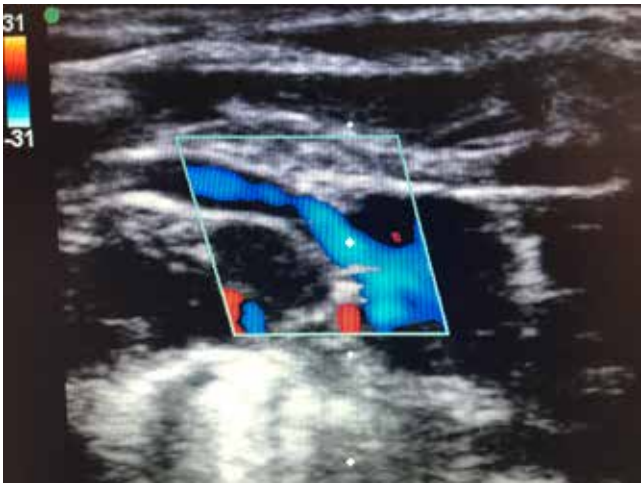

Figure 6. Left brachiocephalic vein with doppler

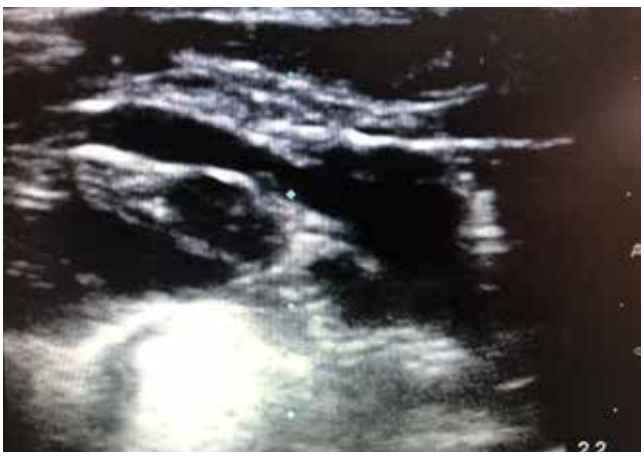

Figure 7. Left brachiocephalic vein

Arterial access

No matter how experienced an anaesthetist is, arterial cannulation in neonates can be dishearteningly challenging. The target, even in larger infants is depressingly small: even at one year of age, the average short axis diameter is 1.7 mm, 1.6 mm and 1.2 mm for the posterior tibial, radial and dorsalis pedis arteries respectively.[7] US has revolutionised the placement of arterial lines, in both adults and children. For arterial line placement in adults, US has been shown to improve first pass

success rates (RR 1.55; 95% CI, 1.02–2.35).[8] A meta-analysis of four randomised controlled trials (345 patients) in small children and infants demonstrated a significantly increased first-attempt success rate (RR 1.94, 95% CI, 1.31 to 2.88, P = 0.001) when using ultrasound to guide arterial access.[8]

Cardiac

Cardiac point-of-care US is an extension of a standard physical assessment and seeks to be brief, and address a specific clinical question, usually binary in nature. It is not a replacement for a cardiology assessment or detailed structural echocardiogram. It is one of the more common applications of POCUS and allows for frequent serial assessments of haemodynamics during the perioperative period. It is well established in adult medicine,[9] the accuracy of non-cardiologist evaluation of myocardial function and haemodynamics is high[10] and has now become an accepted part of the armamentarium of the neonatologist.[11]

Rather than looking at a detailed anatomical analysis, neonatal cardiac POCUS concentrates on helpful real-time measures of haemodynamics such as ventricular function, volume assessment and cardiac filling. The presence of a patent ductus arteriosus may also be sought. Qualitative measures of contractility along with quantitative fractional shortening measurements may be quickly determined in a deteriorating patient. Good views are usually simple to achieve due to thin thoracic walls.

When cardiologists are not available on site or after hours, targeted cardiac ultrasound may be critical to the management of the unstable neonate, especially as serial evaluations of an evolving illness may be made. There is limited data on the overall effect of functional cardiac ultrasound on neonatal outcomes, but there is certainly much anecdotal reporting of benefit in the setting of acute cardiorespiratory collapse.[12] A retrospective study of 199 neonates in a Canadian neonatal intensive care unit who underwent 512 targeted neonatal echocardiograms showed a change in clinical management in 212 cases (41%) and avoidance of a planned intervention in 112 cases (22%).[13] Extending targeted echocardiography to the perioperative phase by anaesthetists is logical but there is a need for standardisation of training and quality assurance.[14] The anatomical assessment of the complex congenital heart lesion should remain the domain of the cardiologist but it is equally important to recognise normal patterns to know when to suspect the presence of a congenital heart lesion.

Lung

Lung US has been well established in adult medicine and is a proven aid in diagnosis and management of critically ill patients.[15–17] It can be performed quickly, with virtually any probe available and has a higher diagnostic accuracy than physical examination and chest radiography combined.[18] It is relatively easy to learn and appropriate for use in all perioperative areas. Other advantages include a reduction in the cost of image acquisition and exposure to ionising radiation as well as decreased time to interpretation of images and appropriate therapy. Given the large change in acoustic impedance as US waves penetrate the air/tissue interfaces of the lung, most waves are reflected back to the probe, meaning that only artifacts may be seen. It is the interpretation of these artifacts and recognition of particular patterns that allows the appropriate diagnosis to be made. A recent publication by Neethling et al. provides a more detailed explanation of how to incorporate lung US in the South African context.[17]

In neonates, the thin chest wall and shallow chest cavity as well as a cartilaginous sternum allow very detailed views to be made with high resolution linear probes (10–15 MHz). Alternatively, a micro-convex probe may also be used, and can be easily applied between the ribs. There are no pathophysiological reasons for different signs in neonates, and the standard signs can all be defined in the critically ill neonate: A-lines, lung sliding, pleural effusions, B-line artifacts and the lung point indicating a pneumothorax.[19] Table I briefly summarises the normal and abnormal signs that may be identified. A number of lung US protocols exist, allowing a standardised approach to lung pathology, such as the Bedside Lung Ultrasound in Emergency (BLUE) protocol. In the adult, it can help diagnose six major pathologies seen in 97% of patients within three minutes.[18] This may be adapted for neonatal use. There are characteristic patterns associated with pneumonia, transient tachypnoea of the newborn and respiratory distress syndrome.[20]

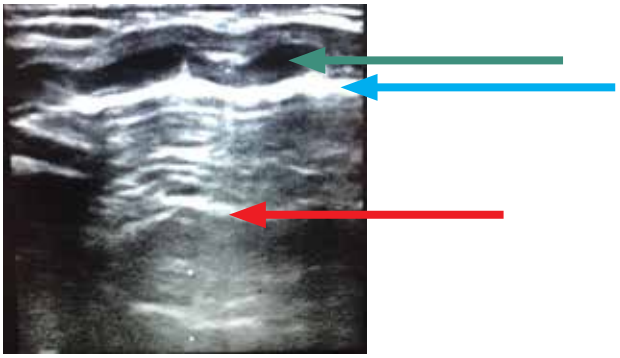

Figure 8. Lung ultrasound: Green arrow: ribs; Blue: pleura; Red: A-lines

As in adults, all neonatal lung ultrasound signs arise from the pleural line, which can be recognised as a hyperechoic line between the rib shadows. This is usually referred to as the 'bat' sign. Six standardised points of analysis are sufficient for use in point-of-care protocols: two anterior and one semi-posterior/lateral bilaterally. The operator must be able to recognise normal lung tissue using certain standardised artefacts or signs. Regular horizontal lines, usually equal to the skin-pleural line distance, are referred to as 'A-lines' and represent normal lung tissue (see Figure 8). Because the lung is constantly moving, lung 'sliding' may be seen: this is the shimmering appearance of the visceral and parietal pleurae as they rub over each other, also known as the 'line-of-ants' (see supplementary materials video 1). M-mode is a powerful addition to the examination, with the recognition of the 'seashore' sign. A regular pattern appears above the obvious pleural line (skin/fat/muscle tissue has no dynamic movement

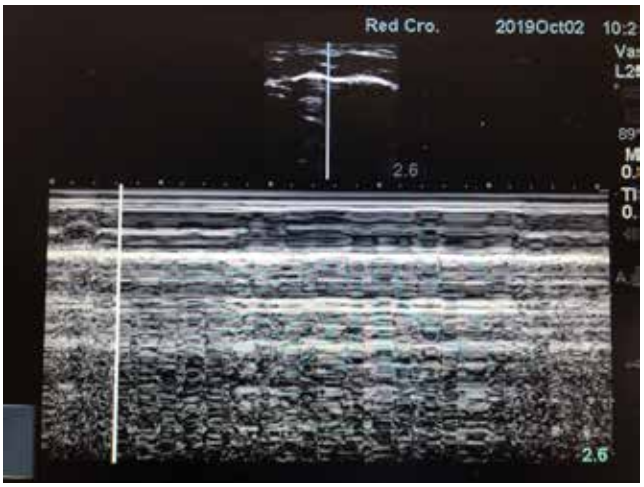

Figure 9. Lung US M-mode: Sandy beach sign

during the respiratory cycle) with a 'sandy beach' appearance below the pleural line, as there is permanent movement of the pleura and lung tissue (see Figure 9).[21]

The timeous recognition of a pneumothorax, either spontaneously, during surgery or after central line placement, is key to instituting treatment. Lung US is well suited to this as a sliding sign rules out a pneumothorax, whereas if a 'lung point' is identified, it is 100% specific for the presence thereof.[22] A lung point is the specific area where the visceral and parietal pleural surfaces separate when a pneumothorax forms. This point is dynamic and shifts during the respiratory cycle and may be seen alternating between the 'sandy beach' and 'stratosphere' or 'bar-code' signs.

Pleural effusions are easy to identify and as little as 50 millilitres of fluid may be identified. It is important to recognise interstitial syndrome in the critically ill neonate. B-lines, also known as comet-tail artefacts, are artefacts that are generated by the juxtaposition of alveolar air and septal thickening (usually from fluid or fibrosis) and indicate either pulmonary oedema (either cardiac failure or acute lung injury), interstitial pneumonia or lung fibrosis. These long, vertical hyperechoic lines diagnostically continue to the edge of the ultrasound screen, arise from the pleural line, erase A-lines and move with lung sliding.

Table I. Normal and abnormal lung ultrasound signs

Normal	Abnormal
Lung sliding or 'line of ants'	Absence of lung sliding
Lung pulse: If the pleural layers are still adjacent, cardiac pulsation will be transmitted to the pleura by the lung	Lack of lung pulse
A-lines	B-lines/comet-tail artefact Indicative of interstitial syndrome
M-mode: Seashore sign 'Sandy' pattern below pleural line Regular pattern above pleural line	M-mode: Stratosphere sign/ Bar-code sign Regular pattern above and below pleural line No movement at the level of the pleura
	Lung point Alternating stratosphere and seashore signs Change of pattern during respiratory cycle as lung moves in and out of field
	Pleural effusion – hypoechoic fluid above the diaphragm; the tip of lung may also be seen

Lung US has additionally been used to predict surfactant need in preterm and extremely preterm neonates.[23] In a study of 133 infants (mean weight 1 043 g), a simplified lung ultrasound score (LUS) adapted from adult critical care guidelines significantly correlated with oxygenation index ($\rho = 0.6$; $P < .0001$) could be used to accurately predict the need for the first surfactant dose (area under the curve = 0.94; 95% confidence interval: 0.90–0.98; $P < .0001$).[24] This LUS was calculated after scanning with a high-resolution linear probe in upper anterior, lower anterior and lateral chest area bilaterally. Each area was scored from 0 to 3: 0 indicated an A pattern (only normal A-lines present), 1 a B pattern with alveolar-interstitial pattern and ≥ 3 well-spaced B-lines, 2 a severe B pattern (crowded B-lines) and 3 an extended consolidation (size > 1 cm). An overall score of 8 increased the probability of surfactant replacement to 92%. Each lung US took on average three minutes to perform.

Lung US has also been used to differentiate between transient tachypnoea of the newborn, meconium aspiration syndrome, pneumonia and respiratory distress syndrome.[25] Lung US may not completely replace chest radiographs but it offers significant time-sensitive information and may be of particular use to the perioperative physician during resuscitation where the early detection and management of pneumothoraces and pleural effusions may be life-saving. Ongoing research and the requisite training are required to further delineate the role of point-of-care lung ultrasound in neonatal anaesthesia.

Intubation

Neonatal intubation remains a challenge even with the advent of videolaryngoscopy. The rate of erroneous mainstem intubations can be as high as 30% in older children and 7% in the neonatal population.[26] The standard confirmation of endotracheal (ETT) intubation remains the chest X-ray, which is limited by availability, ionising radiation exposure and repositioning. However, determining intra-tracheal versus intra-oesophageal placement can be readily discerned with US. More than 80% of ETT tips may be visualised by ultrasound alone. A prospective study from 1986 in 16 infants, showed an ultrasound visualisation rate of 86%, and a close correlation between the distance of the ETT tip to the aortic arch on US and the distance of the tip to the carina on XR ($r = 0.8$).[27]

In neonates, a midsagittal suprasternal view is most useful for endotracheal tube verification and appears comparable to X-ray and capnography in determining ETT position in this population. Sagittal and axial images were obtained in a local setting in Bloemfontein, where a feasibility study was performed demonstrating the use of ultrasound in intubated neonates.[28] If positioning is not satisfactory at the time of US examination,

adjustments can be made in real time and subsequently confirmed by bedside US. If a direct view of the ETT tip is not possible (usually due to a poor midsagittal suprasternal window), then examining for bilateral lung sliding using a probe bilaterally in the midaxillary or midclavicular lines can be useful.[29] By defining a 'deep' ETT as less than one centimetre above the apex of the aortic arch by US, a paired trial by Chowdhry et al. using 56 US and XR image pairs from 29 neonates had a sensitivity of 86% and specificity of 96% for identifying deeply positioned ETTs. There is also evidence that US visualisation of a saline-filled ETT cuff may increase sensitivity and specificity.[30] A transverse substernal/subxiphoid view can also be used to evaluate bilateral diaphragm motion – however this view only assumes intubation has been successful.

Old technology, new applications

Cranial sonography is widely used in the point-of-care evaluation of infants. A recent prospective observational study of thirty infants undergoing cardiac surgery examined whether transfontanelle ultrasound could predict fluid responsiveness.[31] The authors hypothesised that the respiratory variation of internal carotid artery blood flow peak velocity could predict response to a 10 ml.kg-1 bolus of crystalloid. A single experienced operator performed transfontanelle ultrasound using a high-frequency transducer (5 to 8 MHz), examining the internal carotid artery as well as aorta blood flow peak velocity and stroke volume index. Fluid responders (57% of patients: as measured by an increase in stroke volume index of > 15%) had an internal carotid artery variation of 12.6 ± 3.3% prior to the bolus, and the resultant receiver operative characteristic (ROC) curve was 0.828 ($P < 0.0001$; 95% CI, 0.647 to 0.940). A measure of pulse pressure variation and central venous pressure, however, had ROC curve values of 0.52 ($P = 0.854$; 95% CI, 0.33 to 0.71) and 0.66 ($P = 0.140$; 95% CI, 0.47 to 0.82) respectively.

Other perioperative uses of neonatal POCUS also include the diagnosis of necrotising enterocolitis (NEC)[32] and the placement of caudal needles and catheters.[33,34]

Conclusion

The presence of a point-of-care ultrasound device has become ubiquitous in many theatre suites and has many applications in the perioperative management of the sick neonate. There is urgent need for expanded standardised training as well as adequate quality assurance and the support of local paediatric cardiologists and echo technicians is imperative.[14]

Anaesthetists must still be aware of the limitations of their skills and the technology that they use; use it as an extension of their own clinical skills and refer to other specialists as necessary. However, as the evidence base increases, and clinicians become more familiar with ultrasound, widespread adoption of POCUS in neonatal anaesthesia will inevitably occur.

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2019 PACSA Congress Abstracts

A case report of cardiac echinococcosis in a child with disseminated hydatid cystic disease

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Background: A 3-year 4-month-old child presented with a one-month history of non-productive cough, post-tussive vomiting and fever. Test for IgG Echinococcus was positive. CXR showed multiple cystic lesions and chest CT showed multiple hydatid cysts in the lungs, liver and pericardium. The child was transferred to Red Cross War Memorial Children's Hospital and managed medically for 5 weeks whilst awaiting surgery.

Echocardiography: The TTE showed an hydatid cyst measuring 2 x 3 cm in the anterior myocardium of the LV with no other abnormalities.

Perioperative management: Intravenous midazolam and fentanyl were followed by gas induction and pressure-controlled ventilation in the operating theatre. Invasive lines were placed before surgery. The major anaesthetic concerns were: high alert for an anaphylactic reaction due to rupture of cyst during intra-operative period; maintaining sinus rhythm, adequate cardiac output and perfusion pressure during the perioperative period. Surgery was via a median sternotomy. The patient was supported on CPB and a core temperature of 27°C was reached. The myocardium around the cyst at the base of the left ventricle was dissected and the ruptured/complicated cyst was removed under circulatory arrest. The patient came off bypass uneventfully on Adrenaline 0.04 mcg/kg/min which was stopped 3 hours later in PICU. The child was discharged from PICU the following day. TTE was done on day 3 and at 6 weeks post-surgery.

Conclusion: Cardiac echinococcosis is rare, comprising 0.01 – 2% of all registered cases. Hydatid cyst of the left ventricle is usually localised sub-epicardially and rarely ruptures into the pericardial space.

A retrospective study to evaluate the anaesthetic choices and complications for patients with osteogenesis imperfecta at a quaternary referral hospital

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Background and aim: Osteogenesis imperfecta (OI) is an inherited genetic syndrome affecting connective tissue. Patients often undergo surgery due to an increased susceptibility to bone fractures. Anaesthesia is associated with many perioperative challenges. The study aimed to describe and evaluate the perioperative management of OI paediatric patients presenting for surgery at Inkosi Albert Luthuli Central Hospital.

Methods: A retrospective chart review of children under 18 years who had OI and underwent surgical procedures from 2000 to 2017 at a quaternary referral hospital was conducted. Patients were identified from the electronic hospital database. The following variables were extracted: demographic data, preoperative history, examination, investigations, chronic medications, intraoperative management, postoperative plan and perioperative complications. Simple descriptive statistics were performed using Excel.

Results: 38 patients who underwent 93 surgeries were included. The majority (72%) had severe type III OI and had elective orthopaedic surgery. Anaemia was identified in 64.5% of patients and 40% had a spinal deformity and respiratory abnormality. A supraglottic airway device (SGAD) was used in 91% of patients, with only three airway complications. 87% of cases had combined general (GA) and regional anaesthesia (RA). No children had documented signs suggestive of hypermetabolism or malignant hyperthermia.

Conclusions: Despite the majority of patients in our sample having severe OI, few of the complications and difficulties described in the literature were identified. Combined GA and RA technique with a SGAD was shown to be a safe anaesthesia technique. Improved perioperative investigation, especially full blood count, due to the high incidence of anaemia, should be encouraged to improve overall care.

Anaesthetists' knowledge of South African law pertaining to informed consent

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Background: Anaesthetists require knowledge of informed consent laws to mitigate the risk of litigation. The knowledge of South African anaesthetists regarding informed consent law is unknown.

Methods: Participants from an academic anaesthetic department anonymously completed a researcher-developed questionnaire with 23 questions. Factors affecting questionnaire performance were recorded: years after graduation from medical school (YGMS); professional designation (PD); years of anaesthetic

experience (YAE); and attendance at formal postgraduate training on informed consent (APGT).

Results: A subgroup analysis of data pertaining to the paediatric population (less than 18 years old) from 167 participants was conducted. The mean questionnaire score (SD) achieved was 60.08% (12.61%). Questions assessing The Children's Act No 38. of 2005 achieved the lowest mean score percentage overall, with a score of 51.82 ±17.84. Knowledge of the Children's Act correlated positively with PD (p=0.0004), YAE (p=0.0180) and APGT (p=0.0080). Mean questionnaire score improved with APGT (p=0.0161) and higher PD (p=0.0163). Of the 23 questions, question 7.1 was the best answered question, with 152 (91%) anaesthetists answering it correctly. It dealt with consent for medical and surgical treatment of a child. Question 6.1 was the most poorly answered question, with 32 (19%) anaesthetists answering it correctly. It dealt with gaining consent for blood transfusion for a child Jehovah's Witness.

Conclusions: Anaesthetists have suboptimal knowledge of informed consent laws. Anaesthetists should attend training and postgraduate education institutions should run these courses regularly. Comparative studies should be conducted in other anaesthetic academic departments countrywide and should include surgical staff.

Better safe than sorry; emergent intubation of a child with hereditary angioedema

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Background: Hereditary angioedema (HAE) is a rare autosomal dominant condition caused by a deficiency in the C1-esterase inhibitor. It has a reported incidence of 1:50 000 and it is estimated that there are approximately 800 affected individuals in South Africa. Acute attacks are potentially life-threatening if they involve the airway; in a case series of 60 patients in South Africa published in 2017, the incidence of airway involvement was 44.2% with a mortality rate of 4.7%.

Methods: We report on patient LN, who is known with HAE and is being managed by the Department of Allergology at the Red Cross War Memorial Children's Hospital. This was the patient's second acute attack: it involved the face and upper airways. On presentation to the paediatric emergency department, he was noted to have marked facial swelling but no evidence of airway obstruction.

Results: After administration of a bradykinin inhibitor called Icatibant, urticaria was noted at the injection site and the patient complained of difficulty breathing. It was decided to perform an emergent intubation in theatre and to ventilate him in ICU until the swelling subsided. The patient underwent a Sevoflurane gas induction and was kept breathing spontaneously. No significant airway oedema was noted on videolaryngoscopy and the patient was intubated uneventfully with a nasal endotracheal tube.

Conclusion: While HAE is a rare condition, it is one of the few potential causes of acute upper airway obstruction and anaesthetists should be aware of the risks involved and have a management plan thereof.

Case report: Anaesthetic management of a hypotonic, syndromic infant with pulmonary hypertension

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Background: A 16-month-old female patient with dysmorphic features, hypotonia (cause unknown) and delayed milestones had been admitted for pneumonia. She was found to have upper airway obstruction secondary to adenoid hypertrophy with pulmonary hypertension, cor pulmonale and a patent PDA: she needed an adenotonsillectomy.

Methods: A TIVA technique was used, intubation assisted with videolaryngoscopy.

Results: The anaesthetic was complicated by a pulmonary hypertensive crisis following a difficult intubation, which responded to treatment. The patient was extubated to high-flow nasal cannula after the procedure and discharged 3 days later, clinically much improved.

Conclusion: The undiagnosed hypotonic, syndromic child with significant pulmonary hypertension presents multiple anaesthetic concerns and considerations with a high risk for complications if not well managed.

Case report: Bilateral erector spinae catheter placement for bilateral nephrectomy in a paediatric patient

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Background and aims: The erector spinae plane (ESP) block is a novel regional anaesthetic technique with reported use in thoracic, abdominal and hip surgery. Increasing use is also reported in the paediatric surgical population. Placement of indwelling catheters in the fascial plane can provide prolonged analgesia and may be useful in supplementing postoperative analgesia.

Methods: We report a case with the use of continuous, bilateral ESP blocks with catheters for analgesia in an infant undergoing resection of bilateral Wilm's tumours in a resource-constrained environment and provide a review of the literature on the use of ESP blocks in children.

Results: ESP blocks are proposed to have a safer approach and reduced side effect profile as compared to other regional and neuraxial anaesthetic techniques.

Conclusions: The ESP block allows for the provision of good analgesia and opioid-sparing effects.

Case report: Management of the difficult airway in an infant

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Background: This case study details a 5-month-old baby with temporomandibular joint ankylosis and a unilateral hypomandible, requiring release of the pterygomandibular ankylosis. Airway manipulation and management of paediatric temporomandibular joint ankyloses has previously been fully described in the literature. What makes this case so unique is the age and size of the child, as well as unusual other anatomical abnormalities such as a significant fat pad around the neck and sinus below the chin.

Methods: The case was expedited by the surgeons as there was a concern regarding obstruction of the airway by the growing tongue. Due to the baby's extremely difficult airway, the only possible radiographic investigation was a CT scan and sonar done with gentle restraint. It was not possible to sedate this child for an MRI. The CT showed a severely abnormal airway with no epiglottis and abnormal vocal cords situated on the right lateral wall of the pharynx. A fat pad was situated over the anterior part of the neck extending from the chin to the sternal notch. The sinus did not appear to communicate with the interior of the mouth.

Results: As previously described in the literature, the airway was managed with a nasopharyngeal airway and flexible bronchoscopic intubation. The ENT surgeons were on standby for a surgical airway. Postoperatively the child was ventilated for 72 hours in ICU and brought back to theatre, via MRI, to be extubated.

Conclusion: A multidisciplinary approach for such a case is imperative.

Case report: Managing an unusual case of a threatened spinal cord in a child

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Background: A 20-month-old boy with Conradi-Hünermann syndrome presented for fusion of his cervical spine. He presented with asymptomatic complete atlantoaxial dislocation and dislocation of the dens tip with accompanying spinal cord stenosis and compromise. We performed an intravenous induction using propofol and rocuronium. Manual in-line stabilisation (MILS) of the c-spine was performed for intubation with the use of a videolaryngoscope (CMAC) with a D-blade. Surgeons placed Mayfield clamps on the patient whilst supine and maintained MILS during proning. The clamp was secured to the table in a neutral position. No spinal cord monitoring was used so isoflurane was used for maintenance of anaesthesia with multi-modal analgesia. Postoperatively the patient was extubated and admitted to the intensive care unit (ICU) where he had an uneventful stay.

Discussion: Conradi-Hünermann syndrome is a rare x-linked genetic disorder characterised by skeletal malformations, skin abnormalities, cataracts and short stature. It is a form of chondrodysplasia punctata which is characterised by the formation of small, hardened spots of calcium on the epiphyses of the long bones or inside other areas of cartilage in the body. Atlantoaxial instability presents some unique challenges to the anaesthetist. In children, cervical-spine instability is caused by ligamentous laxity, hypoplasia of the odontoid or inflammatory diseases.

Conclusion: Careful positioning of the patient and maintaining c-spine immobility during airway manipulation and positioning for surgery, particularly prevention of flexion, is essential to prevent further neurological fallout. These cases are especially dangerous in the asymptomatic child.

Effect of pre-warming on paediatric patients presenting for magnetic resonance imaging under general anaesthesia

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Background and aims: The combination of anaesthesia and environmental factors in the magnetic resonance imaging (MRI) suite increases patient susceptibility to hypothermia. This study aimed to determine whether pre-warming paediatric patients presenting for MRI under general anaesthetic prevented them from developing hypothermia.

Methods: A prospective, quasi-experimental research design was followed. A total of 102 patients were enrolled during the 4-month study period and were divided equally between pre-warmed and control groups. Inclusion criteria were patients aged 6 months to 6 years, ASA physical status I or II and with written informed consent from a caregiver. The pre-warmed group received 30 minutes of active warming with a forced-air warmer. The MRI examination was conducted using a volatile-based general anaesthetic. Tympanic temperatures were measured at baseline, pre-scan and post-scan.

Results: The pre-warmed group received an average (SD) of 34.8 (4.3) minutes of warming. The median (IQR) time spent inside the MRI unit was 60 (50 to 77) minutes. The incidence of hypothermia was 1.96%. There was a statistically significant change in CBT (core body temperature) between the pre-warmed and control groups (0.15°C; p = 0.0001). A weak negative correlation between patient weight and temperature change (r = -0.220, p = 0.026) and between length of time of pre-warming and temperature change (r = -0.268, p = 0.006) was found.

Conclusions: The effect of pre-warming to prevent hypothermia under general anaesthetic in the MRI unit could not be established due to the low incidence of hypothermia. Pre-warming patients for 30 minutes prevented a statistically significant decline in CBT, however, this finding was not clinically relevant.

Extracorporeal membrane oxygenation (ECMO) as a bridging therapy after ALCAPA repair: Red Cross War Memorial Children's Hospital's first success story

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Background: Anomalous left coronary artery (LCA) originating from the pulmonary artery (ALCAPA syndrome), also known as Bland-White-Garland syndrome, is a rare form of acyanotic congenital heart disease. It affects 1:300 000 live births and has a 90% mortality in the first year if left untreated. Patients usually present with left ventricular dilatation and failure, secondary to chronic ischaemia. Mitral incompetence is a common occurrence. Symptomatology and age of presentation depends on the degree of collateral flow between the right and left coronaries and stenosis of the proximal LCA.

Methods: This poster will discuss one such case seen at the Red Cross War Memorial Children's Hospital (RCWMCH) in September 2019. A 3-month-old female presented with ALCAPA syndrome, with mitral incompetence and left ventricular failure.

Results: Surgical repair was uneventful, with adequate coronary flow afterwards. However, after 3 unsuccessful attempts to wean from cardiopulmonary bypass (CPB), the patient was placed on venoarterial ECMO as a bridging therapy. After 3 days the patient was decannulated with good left ventricular function on adrenaline and milrinone infusions. Ventilatory parameters were acceptable.

Discussion: ALCAPA syndrome is a rare disease. At RCWMCH 4 ALCAPA cases were seen and operated on since January 2018. This was the second time ECMO was utilised at RCWMCH (a first for ALCAPA repair) and the first ECMO case with a favourable outcome. Future cases will benefit from the experience gained by all staff involved with this life-saving therapy.

Panendoscopy and anaesthesia for debulking of juvenile onset recurrent respiratory pappilomata (RRP) using target control infusion (TCI) and the Manujet III for high-pressure source ventilation (HPSV)

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Background: Laryngeal papillomata causes upper airway obstruction. Airway papilloma results from exposure to the human papillomavirus (HPV) at birth (HPV Types 6; 11), a history of genital warts and other immunological risk factors. Presenting features include respiratory difficulties and voice changes and diagnosis is often delayed as illnesses like asthma, croup and foreign body aspiration are excluded. Diagnosis requires laryngoscopy or fibre optic bronchoscopy. Debulking of airway papillomata has unique challenges and timely intervention is lifesaving. Issues relate to a shared airway, unimpeded surgical access, adequate depth of anaesthesia, maintaining ventilation and overall cardiovascular stability. Available best practice guidelines for HPSV ensures safe practice but hypoxia, laryngospasm and other complications may occur. Papillomata regresses around puberty, but dysplasia occurs in 3%. Adjuvant therapies (acyclovir, monoclonal antibodies) to increase the time between repeat surgical procedures is being evaluated. HPV vaccination with good sexual health education will reduce disease prevalence, as will the delivery practice of mothers with active genital warts. Parental education remains important due to the risk of complete airway obstruction.

Case study: A child of 6 years with known RRP was scheduled for elective surgery. Monitoring included (NIBP), (ECG) and (SaO_2). End-tidal ($ETCO_2$) is not possible in the open system used and transcutaneous CO_2 monitoring is not done. Blood gas measurement for arterial PH and PCO_2 is mandatory as hypercarbia and a respiratory acidosis can occur. Induction began with sevoflurane and 100% oxygen. Manual assistance is given, and chest movements observed to ensure an uncompromised airway. TCI Propofol (Kataria model) (Ce) (2-4) µg/ml was started and titrated. Muscle relaxation (mivacron 0.1 mg/kg) and a short-acting opiate (Rapifen, 10-20 µg/kg) given. Ketamine (0.5 mg/kg) is added for its analgesic and sedation benefits. The Manujet III is connected to a side arm of the surgeon's laryngoscope. Jet-ventilation is supraglottic and intermittent and pressure varies from 0.5-2.5 Barr for children. Chest movements are observed to ensure oxygenation. Ventilation is halted when the laser used to minimise fire hazards, but saturation remains above 90%. Decasone (0.1mg/kg) to reduce surgical swelling and perfalgan (15 mg/kg) given for pain relief. Post-surgery patients given 4-hourly nebulisation with adrenalin and pulmicort. Ward monitoring occurs over 24 hours.