

Towards evidence based medicine for paediatricians

Edited by Bob Phillips

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In order to give the best care to patients and families, paediatricians need to integrate the highest quality scientific evidence with clinical expertise and the opinions of the family.¹ *Archimedes* seeks to assist practising clinicians by providing “evidence based” answers to common questions which are not at the forefront of research but are at the core of practice. In doing this, we are adapting a format which has been successfully developed by Kevin Macaway-Jones and the group at the *Emergency Medicine Journal*—“BestBets”.

A word of warning. The topic summaries are not systematic reviews, through they are as exhaustive as a practising clinician can produce. They make no attempt to statistically aggregate the data, nor search the grey, unpublished literature. What *Archimedes* offers are practical, best evidence based answers to practical, clinical questions.

The format of *Archimedes* may be familiar. A description of the clinical setting is followed by a structured clinical question. (These aid in focusing the mind, assisting searching,² and gaining answers.³) A brief report of the search used follows—this has been performed in a hierarchical way, to search for the best quality evidence to answer the question.⁴ A table provides a summary of the evidence and key points of the critical appraisal. For further information on critical appraisal, and the measures of effect (such as number needed to treat, NNT) books by Sackett⁵ and Moyer⁶ may help. To pull the information together, a commentary is provided. But to make it all much more accessible, a box provides the clinical bottom lines.

The electronic edition of this journal contains extra information to each of the published *Archimedes* topics. The papers summarised in tables are linked, by an interactive table, to more detailed appraisals of the studies. Updates to previously published topics will be linked to the original article when they are available.

Electronic-only topics that have been published on the BestBets site (www.bestbets.org) and may be of interest to paediatricians include:

- Atropine: re-evaluating its use during paediatric RSI
- Absorbable sutures in paediatric lacerations

Readers wishing to submit their own questions—with best evidence answers—are encouraged to review those already proposed at www.bestbets.org. If your question still hasn't been answered, feel free to submit your summary according to the Instructions for Authors at www.archdischild.com. Three topics are covered in this issue of the journal.

- Should steroids be used in children with meningococcal shock?
- Should children with Henoch-Schonlein purpura and abdominal pain be treated with steroids?
- Do cuffed endotracheal tubes increase the risk of airway mucosal injury and post-extubation stridor in children?

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Randomisation

Randomisation is used within the context of therapeutic studies to try to reduce bias. It does this by using chance to spread, hopefully evenly, important prognostic factors across the groups within the study.

Randomisation can be performed in a number of ways; each variation can be used in different trial situations. To make life easier, for this article we'll assume there are just two arms, but the principles apply to studies with greater numbers of options too. Simple randomisation is as straightforward as tossing a coin for each individual entered. In small studies, doing this may run the risk of having an uneven number of participants in the trial arms, making interpretation more difficult. The simplest variation on this is to predetermine the number of individuals in the study, and (metaphorically) put the appropriate number of “A”s and “B”s in a bag and withdraw the letters. This gives an even spread of numbers across the study arms—but is impossible to achieve for very large studies.

Block randomisation is where a block of participants (typically 6–12 in size) is randomised into an even split between “A”s and “B”s. This lets “time” be balanced between the arms too—for example, winter versus spring admissions—and balances the workload between the arms—if the treatments are not drug therapies but physiotherapy, surgery, or a multidisciplinary team intervention. It also allows a study to stop with an even spread between the arms. However, if the blocks are of the same size it may be possible for investigators to start to guess what's coming next, upsetting the allocation concealment and jeopardising the trial.¹ One way around this is taking blocks of 6, 8, and 10 participants and randomising the order of these too.

Stratified randomisation is a method where the investigator doesn't leave the distribution of known or presumed prognostic variables entirely to chance; instead each major variable (for example, age, tumour stage, biological marker) is treated almost as a separate mini-trial, and participants within these strata are randomised independent of the other strata. (As a rule of thumb, you need at least 10 participants in each arm to make this valuable.) A similar type of process is used in minimisation allocation, which achieves similar results by a slightly different method.

Finally, cluster randomisation should be used when the unit randomised is not an individual child or family, but institution or group. For example, a trial of providing mosquito netting to prevent malaria may randomise villages, a study of a new computerised decision support system may randomise family practices.

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Additional information on each of the topics is available on the ADC website (www.archdischild.com/supplemental)

Should steroids be used in children with meningococcal shock?

Report by

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A 3 year old boy is admitted to a paediatric intensive care unit with a history of fever, non-blanching petechial rash, decreased conscious level, and grunting; capillary refill is poor. After screening for sepsis, antibiotics are started. He is intubated, receives fluid resuscitation (total of 100 ml/kg), and a central catheter is placed, showing a central venous pressure of 12 mm Hg. Despite dopamine infusion the attending physician is unable to stabilise his blood pressure, and he requires noradrenaline infusion to achieve and maintain his haemodynamic state.

Structured clinical question

In a child with meningococcal shock [patient group] does steroid replacement therapy [intervention] decrease mortality [outcome]?

Search strategy and outcome

Secondary (Cochrane library, 2004) and primary (Medline, Embase, Scielo) sources were included in the search. MeSH terms were used in Medline and Embase.

Search strategies: "meningococcal" AND "steroid replacement"; "meningococcal" AND "steroids" (limited to "all children" from 1984 to 2004); "shock, septic" AND "steroids" (limited to "randomised controlled trials" from 1992 to 2004).

Search outcome: 68 hits (3; 52; 13; each search respectively), of which 6 (0; 3; 3) studies were directly relevant to the question. See tables 1 and 2.

Commentary

The use of steroids in septic shock has been discussed for decades. The use of high dose steroids (30 mg/kg of methylprednisolone or equivalent) for a short period has been proven not to improve outcome.¹ However, the use of low doses (200–300 mg of hydrocortisone in adults; around 2–5 mg/kg/day in children) for longer periods (replacement therapy) has shown very promising results in adults.^{2–4} Table 1 summarises the main randomised controlled trials testing the use of steroids in low dose for septic shock. Although there is a discrepancy in the populations (and on the criteria for adrenal insufficiency), replacement therapy with steroids showed either significant reduction in the duration of inotrope requirement and 28 day mortality, or a tendency towards improvement. Although no studies have evaluated the use of steroids in paediatric septic shock, expert opinion (for example, the Society of Critical Care Medicine clinical practice parameters⁸) recommends the use of hydrocortisone in children with septic shock requiring catecholamines for blood pressure support and adrenal insufficiency, as evidenced by total cortisol lower than 18 mg/dl.

Meningococcal septic shock presents with an early, massive inflammatory response. Although absolute adrenal failure due to adrenal haemorrhage is rare, partial adrenal insufficiency has been described in these children even in the absence of adrenal haemorrhage.^{5–7} Table 2 summarises the main studies that have evaluated adrenal function in children with meningococcal disease. The incidence of adrenal insufficiency varied from 10.3% to 16.9% in children with

Table 1 Randomised controlled trials testing the use of steroids in low dose for septic shock

Citation	Study group	Study type	Outcome	Key results	Comments
Annane <i>et al</i> (2002) ²	300 adults with dopamine resistant septic shock divided according to the increase in cortisol in response to short corticotropin test (250 µg) as responders (>9 µg/dl) or non-responders (<9 µg/dl)	Randomised controlled trial (hydrocortisone 200 mg/day + fludrocortisone 50 µg/day v placebo, for 7 days)	28 day survival Time to vasopressor withdraw	28 day mortality of (steroids v placebo) 60/114 v 73/115 in the non-responders and 22/36 v 18/34 for responders—adjusted Odds ratios of 0.54 (0.31–0.97) and 0.97(0.32–2.97), respectively Time to withdraw vasopressor was (steroids v placebo) 7 v 10 days in non-responders (HR of 1.91 (1.29–2.84)) and 9 v 7 days in responders (p=0.49)	Very specific population Large confidence intervals, upper limit close to 1 Do not report incidence of hyperglycaemia associated with steroids Number of patients needed to treat to save 1 additional life is 7 (4–49)
Bollaert <i>et al</i> (1998) ⁴	41 adults with septic shock requiring catecholamine for more than 48 hours Response to corticotrophin stimulation test (increase >6 µg/dl)	Randomised controlled trial (300 mg/day hydrocortisone v placebo, for >5 days)	7 day reversal of shock 28 day mortality	7 day reversal of shock (15/22 v 4/19, p=0.007) Mortality (7/22 v 12/19, p=0.45) Similar improve (7 d, 28 m) in responder and non-responder	Discontinued early because primary end point was achieved Late inclusion of patients Large confidence intervals (7 day reversal of shock 17 to 77%) Other clinical interventions were not described
Yildiz <i>et al</i> (2002) ³	40 adults with sepsis	Randomised controlled trial (prednisolone 7.5 mg/day, for 10 days)	28 day mortality	8/20 steroid and 12/20 placebo (p=0.34) Higher difference in APACHE II>20 (not calculated)	Only 9 (22%) shocked Small sample No power calculation Trend for improve in survival, specially in the more severe group

Table 2 Studies evaluating adrenal function in children with meningococcal disease

Citation	Study group	Study type	Outcome	Key result	Comments
Bone <i>et al</i> (2002) ⁵	65 children with meningococcal disease Divided according to the intensive management required: I=mild, II=moderate, III=extensive	Prospective cohort study	Admission, 8 am and post-low dose Synacthen test (LDST) cortisol levels AI defined as (a) cortisol lower than 140 nmol/l; (b)LDST cortisol lower than 500 nmol/l	AI=16.9% (11/65) (a=8, b=6) 8am cortisol I<II (p<0.05) II>III (p=0.07) LDST cortisol I=II II>III (p<0.05)	Lost 21 (24%) patients on enrolment 13 (35%) did not have LDST Doesn't specify previous use steroids
De Kleijn <i>et al</i> (2002) ⁶	62 children with meningococcal sepsis Divided as: I=sepsis (12) II=shocked survivor (38) III=shocked non-survivor (12)	Prospective cohort study	Admission cortisol and adrenocorticotrophic hormone (ACTH) levels AI defined as cortisol <138 nmol/l, partial AI defined as cortisol from 138 to 497 nmol/l	None had AI 7 (11.3%) children had partial AI Cortisol (nmol/l): I(1158)>II (997)>III (654)	Didn't test response to corticotrophin 12 children were non-shocked Incidence of partial AI was 14%(7) among shocked
Riordan <i>et al</i> (1999) ⁷	96 children with meningococcal disease Divided as meningococcal sepsis (MS=43); meningococcal meningitis + septicaemia (MM+MS=46); meningococcal meningitis (MM=7)	Prospective cohort study	Admission cortisol and mortality	Cortisol (nmol/l): MM 970 MM+MS 1268 MS 1183 Survivors > non-survivors	Sepsis definition is not described. Do not specify previous steroid treatment Small group hypotensive (29), with 10.3%incidence of partial AI 10 referral had samples later, lower cortisol and higher mortality

shock. Of note, children with very severe disease had lower cortisol levels than children with a moderate presentation.⁵⁻⁷ Moreover, after a low dose Synacthen test, cortisol levels did not increase as much in the more severely affected children as they did in children with mild disease.⁵ These data support the hypothesis that children with meningococcal shock, particularly the more severely affected, can present with reduced adrenal response.

In summary, children with meningococcal shock have increased incidence of abnormal adrenal response, and extrapolation of data from adult septic shock and expert opinion supports the use of hydrocortisone replacement therapy in children with meningococcal shock dependent on catecholamines.

CLINICAL BOTTOM LINE

- Adrenal insufficiency is frequent in adults with septic shock, and there is good evidence to support steroid replacement therapy in this group. (Grade A)
- There is no direct evidence regarding the use of steroid replacement therapy in children with meningococcal shock.
- There is evidence of suppressed adrenal response (adrenal insufficiency) in children with meningococcal shock. (Grade B)
- Steroid replacement is a rational therapy that is likely to be of benefit in children with meningococcal shock. (Grade B)

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This case is based on experience from several cases. Details have been altered to ensure patient anonymity

Should children with Henoch-Schonlein purpura and abdominal pain be treated with steroids?

Report by

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Hannah is a 7 year old girl with Henoch-Schonlein purpura (HSP). She has a lot of abdominal pain which is not settling with simple analgesia. An ultrasound scan reveals that she does not have an intussusception. The SHO on-call tells you that her handbook of paediatrics says that such pain can be treated with steroids, but is there really any evidence to support this?

Structured clinical question

Do children with abdominal pain and HSP [population] treated with steroids [intervention] compared to children treated without steroids[comparison] show a more rapid resolution to their symptoms [outcome]?

Search strategy and outcome

Secondary sources

Best Bets: "Henoch Schonlein purpura"; match all/any words. No relevant citations.

"Steroids abdominal pain"; match all words. No relevant citations.

Match any words; 125 hits, no relevant citations.

Cochrane: "henoch schonlein purpura" (MeSH); 11 hits. None relevant.

"steroids" and "abdominal pain"; 43 hits. None relevant.

Primary source

Medline 1966–2004:

"Henoch Schonlein Purpura" AND "steroids" AND abdominal pain; 21 citations; 2 relevant.

"Henoch Schonlein Purpura" AND "abdominal pain"; 169 citations; no further relevant citations.

"Henoch schonlein purpura" AND "gastrointestinal"; 169 citations; 1 relevant.

"Henoch Schonlein Purpura" AND ("steroids" OR "prednisolone" OR "hydrocortisone" OR "dexamethasone") AND "pain"; 26 citations; 5 relevant.

See table 3.

Commentary

Henoch-Schonlein purpura is the most common vasculitic disease in childhood, most commonly affecting the skin, joints, gastrointestinal tract, and kidneys. Gastrointestinal involvement is said to occur in approximately 80% of patients, ranging from mild symptoms such as abdominal

pain, nausea, and vomiting, to more severe manifestations such as gastrointestinal bleeding and intussusception. Some textbooks suggest that the abdominal pain of HSP may respond to steroids, with some suggesting that there is a benefit in their use and describing a regimen.

No randomised controlled trials have ever been carried out to assess this problem and there have been no systematic reviews to date looking at the available data. The studies that are available include retrospective studies and case series. These studies show that children with HSP who are treated with steroids experience a quicker resolution of their pain than those not treated with steroids. This is seen within 24 hours of commencing treatment in the studies by Rosenblum and Reinehr *et al*.

Although the groups were similar for some characteristics, randomisation and blinding was not carried out—thus there is little to ensure that patients were equal in terms of factors such as severity of illness.

While steroids have been described in these studies as having a beneficial effect on abdominal pain, they are also known to have adverse effects, some of which have been noted in these studies—for instance, the masking of associated intra-abdominal pathology such as intussusceptions and bowel perforation.

A randomised controlled trial seems the natural next step in order to answer this question. If we assume that a trial looking at the effect of steroids for severe abdominal pain will have a power of 80% at a 5% significance level and assume 15% complete resolution of pain at 24 hours in placebo treated children and 25% resolution of pain in children

Table 3 Use of steroids in children with Henoch-Schonlein purpura and abdominal pain

Citation	Study group	Study type	Outcome	Key results	Comments
Rosenblum (1987) ²	43 patients with HSP and abdominal pain 25 (58%) given prednisone. 18 (42%) not given prednisone	Cohort? 3b	Resolution of pain at: 24 h 48 h 72 h	Steroid treated v non treated <24 h 44% v 14% p=0.02 <48 h 65% v 45% p=NS <72 h 75% v 75% p=NS	Similar groups but no mention of the use of analgesia in these groups. No mention of length of follow-up, discharge/re-admission for pain. Limited details of group. Age and sex distribution. Prednisone given at 1–2 mg/kg/day. Route? Daily? A retrospective study. No blinding/randomisation
Leung (2001) ³	Case reports of 2 patients (both aged 5) with HSP and abdominal pain treated with intravenous hydrocortisone	Case series 4	Resolution of pain	Rapid and complete relief of abdominal pain within 10 minutes	2 case reports. Rapid relief but pain relapse at later date. Little mention of conventional analgesia
Lin <i>et al</i> (1998) ⁴	27 children (6.7±0.5 y) with HSP and abdominal pain treated with corticosteroids	Retrospective study 4?	Resolution of pain	Resolution of pain in 2.4±0.2 days	English abstract only. Limited data
Reinehr <i>et al</i> (2000) ⁵	101 children (mean 6 y) with HSP. 57 with severe pain or bleeding treated with steroids	Retrospective study	Resolution of pain	<i>Steroid treated children:</i> 77%—pain resolved in 24 h <i>Non-steroid treated:</i> persistent pain for 5 days (median), range 1–28 days	No side effects observed. 1 patient treated with steroids and 2 not treated developed intussusception
Gunasekaran <i>et al</i> (2000) ⁶	4 children with confirmed duodenjejunitis and clinical manifestations of HSP without the typical rash	Case series	Resolution of pain Repeat endoscopic examination at 8–12 weeks	Marked improvement in pain in 48 h Normal	Patients followed up for 3 years
Van den Broek <i>et al</i> (1995) ⁷	4 year old with HSP treated with IV prednisone	Case report	Resolution of pain Surgical complications	Improvement in two days Entero-enteral fistula and abscess	Steroids started on day 7 of illness. Surgical complications diagnosed on day 25 at laparotomy after steroids stopped on day 19

treated with steroids, we would need 247 children in each group to complete this trial. Larger effects would be easier to detect, but even assuming a doubling of pain relief using steroids we would still need over 100 subjects per arm. A large district general hospital serving a population of 100 000 children would only see 18 children a year with HSP, of whom only six might have severe abdominal pain.

It is clear that this has affected why a prospective trial has not been carried out to date, as to do so would involve the detection of a small treatment effect, of an uncommon symptom (severe abdominal pain) in an uncommon condition. Ideally a large multicentre trial is needed, but an alternative approach may be a well designed large cohort study; one possibility may be to conduct it under the aegis of a body such as the British Paediatric Surveillance Unit.

CLINICAL BOTTOM LINE

- Case series and retrospective analyses show an improvement in pain when steroids are given to patients with HSP and abdominal pain. (Grade D)
- Further studies are needed to look at the magnitude of effects of steroids in alleviating abdominal pain in HSP and also to look at their possible adverse effects. (Grade D)
- Steroids should be used with caution to alleviate abdominal pain in HSP, particularly with regard to their effect in masking other intra-abdominal pathology. (Grade D)

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This case is based on experience from several cases. Details have been altered to ensure patient anonymity

Do cuffed endotracheal tubes increase the risk of airway mucosal injury and post-extubation stridor in children?

Report by

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You are a paediatric registrar on the children's intensive care unit. You are about to intubate a 2 year old child with severe meningococcal septicaemia. Your recent

experience in ventilating children with this condition is that they often develop acute respiratory distress syndrome, and require high pressures to maintain adequate oxygenation and ventilation. At these high pressures significant leaks occur around the endotracheal tube, impairing effective ventilation, and on occasion it is necessary to change to an endotracheal tube of greater diameter. Re-intubation under such circumstances carries a greater risk of hypoxia because of the inevitable loss of positive airway pressure during the procedure. You think it would be wise to insert a cuffed endotracheal tube, in which the cuff could be inflated if leak becomes a problem. It has been traditionally taught that only uncuffed endotracheal tubes should be used for intubation in children under the age of 8 years to decrease the risk of airway mucosal injury and post-extubation stridor. You wonder if there is any evidence to the above statement.

Structured clinical question

In children needing intubation [patients], are cuffed endotracheal tubes [intervention] associated with increased incidence of post-extubation stridor/increased risk of airway mucosal injury [outcome]?

Search strategy and outcome

Strategy

Cochrane and PubMed.

Cochrane—endotracheal tube.

Pubmed—cuffed endotracheal tube AND children.
Limits—RCT, English and child <18 years.

Outcome

Cochrane central register of controlled trials—1.

Pubmed—1 RCT (same study as in Cochrane register).
Limits excluding RCT—15 hits, of which 3 were relevant (1 review and 2 case control studies).

See table 4.

Commentary

Traditionally it has been taught that only uncuffed endotracheal tubes (ETT) should be used for children under the age of 8 years.^{4 5} Concerns regarding the use of cuffed ETTs originate from studies in adults^{6 7} and animals⁸ which indicate that cuffed tubes impair tracheal mucosal blood flow and are associated with higher incidence of post-extubation laryngeal oedema and tracheal stenosis. The pathological process of stenosis is thought to begin with tracheal tube pressure on the laryngotracheal mucosa, especially when the tube is too large or when the cuff is too inflated, causing mechanical oedema and ischaemic necrosis, followed by organisation into fibrotic tissue. However these data described the use of high-pressure, low-volume cuffed ETTs. Studies⁹ have documented a causal relation between the duration of intubation and the occurrence of laryngeal mucosal inflammation for cuffed and uncuffed ETTs. Subsequent studies^{1–3} using the modern high-volume, low-pressure cuffs have not shown any increase in the incidence of post-extubation stridor. In fact cuffed ETTs have been shown to decrease the number of laryngoscopies,¹ reduce the risk of aspiration, and improve end-tidal CO₂ monitoring.¹⁰ None of the studies were designed to compare incidence of subglottic stenosis between children intubated with cuffed or uncuffed endotracheal tubes. A cases series from France of five children with subglottic stenosis found that only one had immediate post-extubation stridor, with the others developing symptoms of dyspnoea 4–13 days after extubation.¹¹ For this reason, it cannot be assumed that the absence of immediate

Table 4 Do cuffed endotracheal tubes increase the risk of airway mucosal injury and post-extubation stridor in children?

Citation	Study group	Study type (level of evidence)	Outcome	Key results	Comments
Khine <i>et al</i> (1997) ¹	Children aged from term newborns to 8 y who required tracheal intubation as a part of anaesthetic care. 251 children with odd medical record numbers were assigned to the cuffed tube group, and 237 children with even numbers were assigned to the uncuffed tube group. Children with a history or physical evidence of intrinsic or extrinsic airway obstruction or severe pulmonary disease or those who required nasotracheal intubation were excluded	RCT (1b)	1. Incidence of croup (post extubation stridor) 2. Number of intubations required to achieve an appropriately sized tube. 3. Concentration of nitrous oxide in operating room 4. The need to use more than 21 min sup -1 fresh gas flow	6 (2.4%) patients in the cuffed tube group and 7 (2.9%) patients in the uncuffed tube group had signs or symptoms of croup and 3 patients in each group were treated with racemic epinephrine. None of them required reintubation 3 (0.01%) patients in the cuffed tube group required a second tube while 54 (22.7%) patients required a second tube in the uncuffed group Nitrous oxide concentration at 24 inches from patients mouth were greater when uncuffed tracheal tubes were used (p<0.001)	Not blinded. Mallinkrodt lo-pro or Sheridan low-pressure cuffed endotracheal tubes were used and duration of intubation was 60 minutes
Deakers <i>et al</i> (1994) ²	A total of 243 patients had 282 intubations in a paediatric intensive care unit setting. Of the 243 patients, 123 (49%) had cuffed endotracheal tubes. Analysis was performed for 188 (77%) of 243 patients. Patients who died, or had a history of upper airway obstruction or surgery to the upper airway were excluded	Prospective Case control study (3b)	1. Incidence of post-extubation stridor 2. Frequency of cuffed endotracheal tube use 3. Any increase risk of long-term post extubation complications	Incidence of stridor: (a) cuffed endotracheal tube, 15.1%; (b) uncuffed endotracheal tube, 14.7% [RR 1.02, CI (0.5, 2.34)] 2 patients from the cuffed endotracheal group and 4 from the uncuffed group required reintubation for post extubation stridor There was no significant difference in rates of stridor when the subgroups under 1 y and aged 1-5 y were compared 33 (17%) of the 188 patients required readmission to the hospital during the next 18 months. None of these had problems with upper airway	Not randomised. Low pressure, high-volume cuffed endotracheal tubes were used
Newth <i>et al</i> (2004) ³	597 children <5 years of age, with 210 having cuffed tubes and 387 having uncuffed tubes were included. Setting was a paediatric intensive care unit	Prospective case control study (3b)	Rate of post-extubation stridor	Racemic epinephrine use in children with uncuffed tube: 6.1% in children <1 month old, 6.7% in children 1-2 years of age, and 9.4% in children 2-5 years of age Racemic epinephrine use in children with cuffed tube: 7.4% in children <1 month old; 9.5% in children 1-2 years of age, and 8.8% in children 2-5 years of age	Not randomised

post-extubation stridor means that subglottic stenosis will not develop. Future studies should be designed with subglottic stenosis as an endpoint before routine use of cuffed endotracheal tubes could be recommended.

CLINICAL BOTTOM LINE

- The use of low-pressure, high-volume cuffed endotracheal tubes is not associated with increased incidence of post-extubation stridor in children. (Grade C)
- There are no studies which adequately assessed potential long term consequences such as subglottic stenosis. (Grade D)
- In selected cases in whom high airway pressures are anticipated during their intensive care stay, cuffed endotracheal tubes can be used to avoid the need for reintubation because of air leak around the ETT. (Grade C)

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This case is based on experience from several cases. Details have been altered to ensure patient anonymity