Towards evidence based medicine for paediatricians

Edited by Bob Phillips

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 admissions—and balances the workload between the arms too—for example, winter versus spring admissions—and balances the workload between the arms—impossible to achieve for very large studies.

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.

Reference

1 Phillips R. Concealed, blinded or masked? Arch Dis Child 2001;85:431.

REFERENCES


Should steroids be used in children with meningococcal shock?

Report by

R G Branco, R R Russell, Addenbrooke’s Hospital, Hills Road, Cambridge CB2 2QQ, UK; brancori@terra.com.br
doi: 10.1136/adc.2005.077701

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 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 parameters5) 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 et al | 300 adults with | Randomised controlled | 28 day survival | 28 day mortality of | Very specific population; Large confidence intervals, upper limit close to 1; Do not report incidence of hyperglycaemia associated with steroids |
| (2002) | dopamine resistant | trial (hydrocortisone | Time to | (steroids v placebo) 60/114 v 73/115 in | |
| | septic shock | 200 mg/day + | vasopressor | the non-responders and 22/36 v | |
| | divided | fludrocortisone | withdraw | 18/34 for responders–adjusted | |
| | according to the increase | 50 µg/day v | | Odds ratios of 0.54 (0.31–0.97) and | |
| | in cortisol in response | placebo, for 7 days) | | 0.97) (0.32–2.97), respectively | |
| Bollaert et al | 41 adults with | Randomised controlled | 7 day | 7 day reversal of | Discontinued early because primary end point was achieved |
| (1998) | septic shock requiring | trial (300 mg/day | mortality | shock (15/22 v 4/19, p = 0.007) | Late inclusion of patients; Large confidence intervals (7 day | |
| | catecholamine for | hydrocortisone v | 7 day | Mortality (7/22 v 12/19, p = 0.45) | reversal of shock 17 to 77%) | |
| | more than 48 hours | placebo, for >5 days) | reversal of | Similar improve | Other clinical interventions were not described |
| | Response to corticortrophin | | shock | (7 d, 28 m) in responder and non-responder | |
| | stimulation test | | | | |
| | (increase >6 µg/dl) | | | | |
| Yildiz et al | 40 adults with | Randomised controlled | 28 day | 8/20 steroid and 12/20 | Only 9 (22%) shocked, Small sample; No power calculation; Trend for improve in survival, especially in the more severe group |
| (2002) | sepsis | trial (prednisolone | mortality | placebo (p = 0.34) | |
| | | 7.5 mg/day, for 10 days) | | Higher difference in APACHE II > 20 (not calculated) | |

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


shock. Of note, children with very severe disease had lower cortisol levels than children with a moderate presentation.\(^5\)\(^6\)\(^7\) 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.

### Table 2  Studies evaluating adrenal function in children with meningococcal disease

<table>
<thead>
<tr>
<th>Citation</th>
<th>Study group</th>
<th>Study type</th>
<th>Outcome</th>
<th>Key result</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone et al (2002)(^5)(^6)(^7)</td>
<td>65 children with meningococcal disease Divided according to the intensive management required: I = mild, II = moderate, III = extensive</td>
<td>Prospective cohort study</td>
<td>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</td>
<td>AI = 16.9% (11/65) (a = 8, b = 6)</td>
<td>Last 21 (24%) patients on enrolment 13 (35%) did not have LDST</td>
</tr>
<tr>
<td>De Kleijn et al (2002)(^6)</td>
<td>62 children with meningococcal sepsis Divided as: I = septic (12); II = shocked survivor (38); III = shocked non-survivor (12)</td>
<td>Prospective cohort study</td>
<td>Admission cortisol and adrenocorticotropic hormone (ACTH) levels AI defined as cortisol &lt; 138 nmol/l; partial AI defined as cortisol from 138 to 497 nmol/l</td>
<td>None had AI 7 (11.3%) children had partial AI</td>
<td>Didn’t test response to corticotrophin among shocked 12 children were non-shocked</td>
</tr>
<tr>
<td>Riordan et al (1999)(^7)</td>
<td>96 children with meningococcal disease Divided as: meningococcal sepsis (MS = 43); meningococcal meningitis + septicaemia (MM+MS = 46); meningococcal meningitis (MM = 7)</td>
<td>Prospective cohort study</td>
<td>Admission cortisol and mortality</td>
<td>Cortisol (nmol/l): MM 970 MM+MS 1268 MS 1183 Survivors &gt; non-survivors</td>
<td>Sepsis definition is not described. Do not specify previous steroid treatment</td>
</tr>
</tbody>
</table>

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

### 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)

### References


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

Report by M Haroon, Dept of Paediatrics, York District Hospital, UK; munibharoon@hotmail.com

do: 10.1136/adc.2005.077743

Hannah is a 7 year old girl with Henoch-Schönlein 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 Schönlein 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 Schönlein Purpura” AND “steroids” AND abdominal pain; 21 citations; 2 relevant.
“Henoch Schönlein Purpura” AND “abdominal pain”; 169 citations; no further relevant citations.
“Henoch schonlein purpura” AND “gastrointestinal”; 169 citations; 1 relevant.
“Henoch Schönlein Purpura” AND (“steroids” OR “prednisolone” OR “hydrocortisone” OR “dexamethasone”) AND “pain”; 26 citations; 5 relevant.
See table 3.

Commentary
Henoch-Schönlein 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

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

<table>
<thead>
<tr>
<th>Citation</th>
<th>Study group</th>
<th>Study type</th>
<th>Outcome</th>
<th>Key results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosenblum (1987)²</td>
<td>43 patients with HSP and abdominal pain</td>
<td>Cohort? 3b</td>
<td>Resolution of pain</td>
<td>Steroid treated v non treated</td>
<td>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, and steroid treatment. Age and sex distribution. Prednisone given at 1–2 mg/kg/day. Route? Daily? A retrospective study. No randomisation.</td>
</tr>
<tr>
<td>Leung (2001)²</td>
<td>Case reports of 2 patients (both aged 5) with HSP and abdominal pain treated with intravenous hydrocortisone</td>
<td>Case series 4</td>
<td>Resolution of pain</td>
<td>Rapid and complete relief of abdominal pain within 10 minutes</td>
<td>2 case reports Rapid relief but pain relapse at later date. Little mention of conventional analgesia.</td>
</tr>
<tr>
<td>Lin et al (1998)²</td>
<td>27 children (6.7 ± 0.5 y) with HSP and abdominal pain treated with corticosteroids</td>
<td>Retrospective study 4?</td>
<td>Resolution of pain</td>
<td>Resolution of pain in 2.4 ± 0.2 days</td>
<td>English abstract only. Limited data.</td>
</tr>
<tr>
<td>Reinehr et al (2000)⁷</td>
<td>101 children (mean 6 y) with HSP, 57 with severe pain or bleeding treated with steroids</td>
<td>Retrospective study</td>
<td>Resolution of pain</td>
<td>Steroid treated children: 77%—pain resolved in 24 h. Non-steroid treated children: 75%—pain resolved in 72 h.</td>
<td>No side effects observed. 1 patient treated with steroids and 2 not treated developed intussusception.</td>
</tr>
<tr>
<td>Gunasekaran et al (2000)⁴</td>
<td>4 children with confirmed duodenalulcer and clinical manifestations of HSP without the typical rash</td>
<td>Case series</td>
<td>Resolution of pain</td>
<td>Marked improvement in pain in 48 h</td>
<td>Patients followed up for 3 years.</td>
</tr>
<tr>
<td>Van den Broek et al (1995)⁷</td>
<td>4 year old with HSP treated with IV prednisone</td>
<td>Case report</td>
<td>Resolution of pain</td>
<td>Improvement in two days</td>
<td>Steroids started on day 7 of illness. Surgical complications diagnosed on day 25 at laparotomy after steroids stopped on day 19.</td>
</tr>
</tbody>
</table>
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)

**REFERENCES**


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**

C S Ashtekar, A Wardhaugh, University Hospital of Wales, Cardiff, UK; archetan@doctors.org.uk
doi: 10.1136/adc.2005.077651

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.

**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. Concerns regarding the use of cuffed ETTs originate from studies in adults and animals 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. Studies have documented a causal relation between the duration of intubation and the occurrence of laryngeal mucosal inflammation for cuffed and uncuffed ETTs. Subsequent studies 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, reduce the risk of aspiration, and improve end-tidal CO₂ monitoring. 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. 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?

<table>
<thead>
<tr>
<th>Citation</th>
<th>Study group</th>
<th>Study type (level of evidence)</th>
<th>Outcome</th>
<th>Key results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Khine et al (1997)</td>
<td>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.</td>
<td>RCT (1b)</td>
<td>1. Incidence of croup (post extubation stridor)</td>
<td>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 ($p&lt;0.001$).</td>
<td>Not blinded. Mallinkrodt lopro or Sheridan low-pressure cuffed endotracheal tubes were used and duration of intubation was 60 minutes.</td>
</tr>
<tr>
<td>Deakers et al (1994)</td>
<td>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.</td>
<td>Prospective Case control study (3b)</td>
<td>1. Incidence of post-extubation stridor</td>
<td>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.</td>
<td>Not randomised. Low pressure, high-volume cuffed endotracheal tubes were used.</td>
</tr>
<tr>
<td>Newth et al (2004)</td>
<td>597 children &lt;5 years of age, with 210 having cuffed tubes and 387 having uncuffed tubes were included. Setting was a paediatric intensive care unit.</td>
<td>Prospective case control study (3b)</td>
<td>Rate of post-extubation stridor</td>
<td>Racemic epinephrine use in children with cuffed tube: 7.4% in children &lt;1 month old, 9.5% in children 1–2 years of age, and 8.8% in children 2–5 years of age.</td>
<td>Not randomised.</td>
</tr>
</tbody>
</table>

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)

**REFERENCES**


This case is based on experience from several cases. Details have been altered to ensure patient anonymity.
Should steroids be used in children with meningococcal shock?

R G Branco and R R Russell

Arch Dis Child 2005 90: 1195-1196
doi: 10.1136/adc.2005.077701

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