

# 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.<sup>1</sup> *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 They make no attempt to statistically aggregate the data, nor search the grey, unpublished literature.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,<sup>2</sup> and gaining answers.<sup>3</sup>) 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.<sup>4</sup> 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 Sackett<sup>5</sup> and Moyer<sup>6</sup> 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](http://www.bestbets.org)) and may be of interest to paediatricians include:

- Do we need to give steroids in children with Bell’s palsy?
- Is plain radiography indicated as 1st choice imaging modality in children with non-traumatic back pain?

Readers wishing to submit their own questions—with best evidence answers—are encouraged to review those already proposed at [www.bestbets.org](http://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](http://www.archdischild.com). Three topics are covered in this issue of the journal.

- Is nasogastric fluid therapy a safe alternative to the intravenous route in infants with bronchiolitis?
- Are methylxanthines effective in preventing or reducing apnoeic spells in infants with bronchiolitis?
- Are newer macrolides effective in eradicating carriage of pertussis?

## Bronchiolitis: evidence based challenge

It’s the end of winter in the northern hemisphere, and paediatricians at the clinical coalface may be a little bored with the unending stream of small children sounding like old smokers. Bronchiolitis provides those who are interested in practicing evidence based medicine a great challenge: it is a common problem, desperately miserable for the children and families affected, and asks a multitude of clinical questions. How should we diagnose this condition? Should we investigate the children affected? How should we intervene to improve their lot—both generally and specifically? What is the outcome over time—and in the long term?

*Archimedes* has frequently taken up the challenge of offering some aspects of bronchiolitis care to a review of their evidence.<sup>1–4</sup> We would like to take this time to point out some additional and pertinent evidence based resources. On the BestBets site you can read in more detail questions of the effectiveness of DNase, and monteleukast<sup>5 6</sup> (though we are still not aware of any research on the utility of dropping saline into a small child’s nostrils). An evidence based medicine journal contains a summary of a recent wide ranging systematic review of standard therapeutic options (bronchodilators and steroids).<sup>7</sup> An original review of the usefulness of diagnostic testing is also available (though not as readable).<sup>8</sup> We would also urge readers not to forget that all “snuffle and stop breathing” episodes are not bronchiolitis,<sup>9</sup> and offer some alternative approaches to the treatment of pertussis.<sup>10</sup>

And finally we’d like to offer a further challenge. Can we advance studies of bronchiolitis beyond enrolling only tens or hundreds of infants among the thousands that pour through our fingers, and achieve such numbers in therapeutic trials that we may truly be able to distinguish which therapies (if any) are helpful?

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**Bob Phillips**, Evidence-based On Call, Centre for Evidence-based Medicine, University Dept of Psychiatry, Warneford Hospital, Headington OX3 7JX, UK; bob.phillips@doctors.org.uk

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

# Is nasogastric fluid therapy a safe alternative to the intravenous route in infants with bronchiolitis?

Report by

**N Kennedy, N Flanagan, Royal Belfast Hospital for Sick Children, Falls Road, Belfast BT12 6BE, UK; neilsaraben@aol.com**

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It is mid-December. As a paediatric SHO working a busy evening shift in a district general hospital, you are called to re-site the intravenous cannula of an infant with bronchiolitis. This is the fifth time that day you have been asked to perform such a task, and you approach the distressed, chubby infant with a sense of dread. Of the 20 children on the ward, 15 have bronchiolitis and 10 are on intravenous fluids. You consider how much distress placement and regular replacement of the cannulae causes these infants, and wonder if fluids could be given safely by another route. Would rehydration using a nasogastric tube (NGT) be appropriate?

## Structured clinical question

In infants with bronchiolitis who need maintenance or replacement fluid therapy [subject], does administration by the nasogastric route [intervention] cause more respiratory difficulty or electrolyte disturbance [outcome] than intravenous infusion [comparison]?

## Search strategy and outcome

Cochrane Library: Nil relevant

PubMed: three searches:

- "bronchiolitis" AND "nasogastric"
- "nasogastric" AND "airway" OR "airway obstruction"
- "bronchiolitis" AND "fluid" OR "rehydration" Limits: birth-18 years, human.

Search outcome: 72 papers, of which seven were relevant (see table 1). (Editorial comment by Nicolai and Pohl<sup>4</sup> and Sporik,<sup>5</sup> and commentary of Milner<sup>5</sup> not included in table.)

Search date: March 2004.

## Commentary

Maintaining optimal hydration is an important component in the management of bronchiolitis. Practice varies between units as to the route of administration.

**Table 1** Nasogastric versus intravenous therapy in the treatment of bronchiolitis

Citation	Study group	Study type	Outcome	Key results	Comments
Sammartino <i>et al</i> (2002)	73 Australian infants admitted with bronchiolitis, 55 needing fluids. 37 given fluids by NGT. 18 infants needing fluids were excluded as <4 months or reduced level of consciousness or apnoea or GO reflux needing treatment	Uncontrolled cohort (level 4)	Respiratory and heart rate, SaO <sub>2</sub> Number going on to iv fluids	NGT "tolerated without incident" 2/37 deteriorated as illness progressed. Removal of NGT did not help	Uncontrolled case series Excluded children <4 months
Vogel <i>et al</i> (2003)	409 infants in 5 New Zealand hospitals	Uncontrolled cohort (level 4)	Percentage receiving i.v. or NGT fluids in each hospital	15-30% received iv fluids 1-39% received NGT fluids	Uncontrolled series. No comparison of outcome of NGT vs. i.v. Large variations in practice
Stocks (1980)	7 preterm infants (1.6-2.2 kg) measured with and without an NGT in-situ	Controlled physiological study (level 5)	Nasal resistance [Rn] (measured in 7) and total airway resistance [Raw] (measured in 4)	Increased Rn of 50-150% with NGT in situ. 30-50% increase in Raw with NGT	Study only of "well" preterm infants. No comment on clinical effects. Small study. Considerable measurement difficulties
Martin <i>et al</i> (1988)	8 preterm infants (1220-1740 g)	Controlled physiological study (level 5)	Change in oral/nasal airflow (measured as % total tidal volume [TV]) with and without NGT	Nasal TV decreased from 54% to 39% with NGT in place Total TV remained constant despite NGT	Small study of "well" neonates without significant lung disease
Greenspan <i>et al</i> (1990)	14 neonates <2 kg, 10 neonates >2 kg with either NG or orogastric tube (OGT)	Controlled physiological study (level 5)	Minute volume, pulmonary resistance	Reduced minute volume, increased pulmonary resistance in <2 kg group with NGT. No effect vs. OGT in babies >2 kg	Study only of "well" neonates, up to 3 kg without lung disease

There is some evidence<sup>1</sup> that a NGT increases airway resistance in small preterm neonates, but not in older heavier ones.<sup>2</sup> Total tidal volume in well neonates is not affected by an NGT.<sup>3</sup> However, it is difficult to extrapolate from these studies to the clinical significance of an NGT in older, larger children with bronchiolitis. Expert opinion varies. Nicolai and Pohl<sup>4</sup> and Sporik<sup>5</sup> argue “from first principles” that the nasogastric (NG) route be avoided because of the theoretical risk of increased airway resistance. However based on the same studies cited by Sporik, Milner came to the conclusion that the NG route is acceptable in infants over 2 kg.

The case series reported by Sammartino *et al* and Vogel *et al* show that there is widespread use of the NG route in many units.<sup>6,7</sup> However, no conclusions can be drawn from their data regarding the safety of NG fluids versus the intravenous route.

No studies were identified assessing the likelihood of electrolyte disturbance in children with bronchiolitis given intravenous rather than nasogastric fluids.

In infants with bronchiolitis, there is no good quality evidence that rehydration by the NG route is more or less safe than via the intravenous route. A randomised controlled trial is needed.

### CLINICAL BOTTOM LINE

- There is no good quality evidence for or against the use of nasogastric fluids in infants with bronchiolitis. (Grade D)
- Physiological studies would suggest that use of a nasogastric tube be limited to infants >2 kg. (Grade D)
- Until good quality evidence is available, local guidelines should be followed. (Grade D)

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## Are methylxanthines effective in preventing or reducing apnoeic spells in infants with bronchiolitis?

### Report by

P Ramesh, M Samuels, *University Hospital of North Staffordshire, Stoke on Trent, UK;*

*martin.samuels@uhns.nhs.uk*

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A 2 week old infant, born at 36 weeks gestation was admitted to the paediatric ward in November with a 24 hour history of runny nose, cough, and episodes of shallow breathing and apnoeas. This was thought to be due to bronchiolitis, and the consultant paediatrician suggested starting the baby on caffeine (theophylline derivative with less side effects). As the resident middle grade doctor, I knew that caffeine has been used widely in neonatal units for apnoea of prematurity, but I wondered if there was any evidence for its use in this clinical situation.

### Structured clinical question

In infants with bronchiolitis [patient] does caffeine [intervention] reduce or prevent apnoeas [outcome]?

### Search strategy and outcome

Cochrane database of systematic reviews: No directly relevant study found, but there was one systematic review on the efficacy of methylxanthines in reducing apnoea of prematurity<sup>1</sup> and another systematic review on the prophylactic use of caffeine to prevent postoperative apnoea following general anaesthesia in ex-preterm infants.<sup>2</sup>

Medline plus (no limits): Search terms: Infants *and* bronchiolitis/respiratory syncytial virus infections/virus/infection

**Table 2** Theophylline derivatives for bronchiolitis induced apnoea

Citation	Study group	Study type (level of evidence)	Outcome	Key results	Comments
Tobias (2000)	7 infants with RSV associated apnoea Gestational age 28–32 weeks Age at presentation 14–64 days	Retrospective review (level 4)	Prevention of mechanical ventilation	No infant had episodes of apnoea or bradycardia from 2 to 18 hours after the initial loading dose	Initial dose of caffeine base was 10 mg/kg and if further doses are needed, given as 5 mg/kg as second dose and 2.5 mg/kg as third dose
Johnston and Kuzemko (1992)	2 infants 1. RSV positive. Gestational age 33 weeks. Post conceptual age 40 weeks 2. Echo virus type 2. Gestational age 36 weeks. Post conceptual age 37 weeks	Case report (level 4)	Prevention of mechanical ventilation	Respiration became regular with disappearance of apnoea immediately after administration of aminophylline	5 mg/kg of iv aminophylline followed by 5–7 days of oral theophylline
DeBuse and Cartwright (1979)	1 infant with RSV positive bronchiolitis. Gestational age 29 weeks. Post conceptual age 38 weeks.	Case report (level 4)	Prevention of mechanical ventilation	No apnoeic episodes occurred 9 hours after administration of theophylline	Oral theophylline. Loading dose of 10 mg/kg in aliquots, then 4 mg/kg 6 hrly ×24 hours followed by 1 mg/kg

**Table 3** Theophylline derivatives and apnoea due to other causes

Citation	Study group	Study type (level of evidence)	Outcome	Key results	Comments
Henderson-Smart and Steer (2001)	192 preterm infants in 5 trials	Systematic review (level 1a)	Reduction in apnoea and use of IPPV	RRR for apnoea 0.45 (95% CI 0.31–0.60). RRR for IPPV 0.34 (95% CI 0.12–0.97)	3 studies used caffeine and 2 studies theophylline
Henderson-Smart and Steer (2001)	78 ex-preterm infants undergoing general anaesthesia for surgery. Gestational age 30–32 weeks. Post conceptual age 40–44 weeks	Systematic review (level 1a)	Reduction in the incidence of apnoea and bradycardia in the postoperative period	RRR 91% (95%CI 66 to 98). ARR 58%. No infant in either control or treatment group required intubation	Intravenous caffeine in a single dose during general anaesthesia. Dosage 5–10 mg/kg
Lim <i>et al</i> (2003)	42 term infants requiring PGE1 infusion for duct dependent congenital heart disease	RCT (level 1b)	Reduction in intubation for apnoea	6/21 required intubation in the placebo compared to 0/21 in the aminophylline group (p=0.02)	6 mg/kg iv aminophylline followed by 2 mg/kg iv 8 hourly for 72 hours

and apnoea/apnea and caffeine/xanthine/methylxanthine/phosphodiesterase inhibitors/theophylline

There was one retrospective review<sup>3</sup> and two case reports<sup>4 5</sup> (in the form of letters to the editor) directly addressing the problem (table 2). There was also one randomised controlled trial on the usefulness of aminophylline in reducing apnoeas and intubation in term infants during prostaglandin E1 infusion.<sup>6</sup>

Searches were performed in August 2004.

### Commentary

Recurrent apnoea is a common problem in otherwise well preterm infants. By term equivalent age, infants have usually “outgrown” their tendency to spontaneous apnoea. However, with an additional stress, such as infection (for example, bronchiolitis) or administration of drugs that depress the central nervous system (for example, general anaesthesia, prostaglandin), then apnoea and oxygen desaturations can recur.

Caffeine is recognised to reduce apnoea and the need for mechanical ventilation in preterm infants with apnoea of prematurity.<sup>1</sup> In addition caffeine prevents apnoea, bradycardia, and episodes of desaturation in growing preterm infants following general anaesthesia,<sup>2</sup> while aminophylline, which is another widely used theophylline derivative, was found to be effective for the prevention of apnoea and intubation during prostaglandin E1 infusion in term infants<sup>6</sup> (table 3). While these data are supportive, there may be significant differences in the mechanism of apnoea in general anaesthesia and viral induced apnoea.

We could only find three reports<sup>3–5</sup> involving a total of 10 infants, all of whom were born preterm and presented with bronchiolitis associated apnoeas approximately around term equivalent age. These reports have concluded that theophylline derivatives are effective in reducing the incidence of apnoeas and avoided the need for mechanical ventilation in this clinical situation (table 1).

Caffeine has a more favourable therapeutic index than aminophylline. No major adverse effects were reported from the studies included in the systematic reviews.<sup>1 2</sup> Jitteriness, tachycardia, and raised blood glucose are the common side effects, but routine drug level monitoring is not necessary at standard dosage.<sup>7</sup>

While these three reports claim that the use of caffeine helped avoid intubation in infants with viral infection induced apnoea, there are no data from randomised controlled trials confirming these benefits. As intubation for

apnoea in bronchiolitis is uncommon, a large multicentre trial would be needed.

### CLINICAL BOTTOM LINE

- In addition to its proven efficacy in apnoea of prematurity, caffeine has also been shown to reduce the incidence of apnoea in ex-preterm infants following general anaesthesia and in term infants following prostaglandin infusion.
- There is only limited evidence from case reports for the use of caffeine in infants presenting with bronchiolitis associated apnoeas.

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## Are newer macrolides effective in eradicating carriage of pertussis?

### Report by

R Srinivasan, T H Yeo, *Llandough Hospital, Cardiff, UK*; [ramsrniv@doctors.org.uk](mailto:ramsrniv@doctors.org.uk)  
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You are assessing a toddler who has presented with paroxysmal cough with a whoop and post-tussive vomiting. A clinical diagnosis of “whooping cough” is made and this is duly confirmed on pernasal swab cultures that reveal the growth of *Bordetella pertussis*.

From history, you note that he is allergic to penicillin and has been given erythromycin for a previous episode of

**Table 4** Use of newer macrolides in pertussis

Citation	Study group	Level of evidence	Outcome	Key results	Comments
Langley <i>et al</i> (2004)	477 children (6 mth–16 y) with clinical symptoms of pertussis were randomised to receive either azithromycin (10 mg/kg on day 1 followed by 5 mg/kg once a day for 4 more days) or erythromycin estolate (40 mg/kg/day in 3 divided doses for 10 days)	Multicentre randomised controlled trial (level 1b)	Bacteriologic eradication: Negative cultures at the end of treatment Relapse: Positive cultures a week after end of treatment Adverse GI events: (parent completed diary)	Azithromycin group: 53/53 v erythromycin group: 53/53 (eradication 100%. 95% CI 93.3–100) Azithromycin group: 0/51 (0%; 95% CI: 0–7.0) v erythromycin group: 0/53 (0%; 95% CI: 0–6.7) Azithromycin v erythromycin groups: Overall incidence of GI side effects was 18.8% v 41.2%, NNT= 4.46 Nausea (2.9% v 8.4%; 95% CI: –8.9% to –2.0%; NNT 18.1), vomiting (5.0% v 13.0%; 95% CI: –4.9% to –1.4%; NNT= 12.5) Diarrhoea (7.1% v 11.8%; 95% CI: –9.0% to –0.3%; NNT= 21.2) No serious adverse events were recorded in either group 90% in the azithromycin group v 55% in the erythromycin group	Group assignment not blinded after randomisation Positive Nasopharyngeal (NP) cultures for pertussis were found in 58/239 (azithromycin group) and in 56/238 (erythromycin group) Post treatment cultures not available on all subjects
Lebel and Mehra (2001)	153 children (<16 y) with clinical symptoms of pertussis received either clarithromycin 7.5 mg/kg/dose twice a day for 7 days (n=76) or erythromycin (13.3 mg/kg/dose three times a day for 14 days (n = 77)	Prospective randomised single blind trial. (level 1b)	Bacteriologic eradication: Negative post treatment cultures  Adverse GI events  Compliance: (inspection of medication containers)	Negative post treatment cultures recorded in 31/31 on clarithromycin (100%; 95% CI: 88.8–100) v 22/23 with erythromycin (96%; 95% CI: 78.1–99.9%) Seen in 45% of those on Clarithromycin Vs 62% of those on Erythromycin. (p=0.035; NNT = 5.8) Mean percent of drug taken by the Clarithromycin group was 98.5% Vs 88.8% by the Erythromycin group (p<0.001)	35/76 in the clarithromycin group and 27/77 in the erythromycin group had positive cultures of <i>B pertussis</i> 90% of subjects were appropriately immunised against pertussis  Post treatment cultures not available on all subjects
Pichichero <i>et al</i> (2003)	34 subjects (29 culture positive and 5 pcr positive) were all given azithromycin (10 mg/kg on day1 followed by 5 mg/kg once a day for 4 more days)	Prospective, open labelled, non comparative trial (level 2b)	Bacteriologic eradication: Negative cultures/PCR at days 2–3 of treatment and days 14–21 post treatment  Adverse events  Compliance	1/34 (3%) had positive cultures at 2–3 days on treatment Bacteriologic eradication 97% at 2–3 days and 100% by 14–21 days after starting treatment  No serious adverse events recorded 10% patients had GI side effects (nausea, loose stools, and abdominal discomfort) Reported 100%	Study group heterogeneous. No subset analysis available 5 of the 34 subjects were adults (parents of children), 12 were between 10–20 y of age and 17 were from the age of 6 mth to 10 y
Bace <i>et al</i> (1999)	37 subjects with culture proven pertussis. Mean age of patients 7.5 mth (range 2–18 mth). 60% of them were not immunised against pertussis. All received azithromycin. Dose: 10 mg/kg on day1 followed by 5 mg/kg once a day for 4 more days (n = 17) v 10 mg/kg once daily for 3 days only (n = 20)	Prospective, open labelled, non-comparative trial (level 2b)	Bacteriologic eradication: Negative cultures on day 7, 14 after commencement of treatment. Relapse: Positive cultures on day 21 after start of treatment Adverse events	Positive cultures on day 7: 2/19 in the 3 day group (10.5%) v 0/16 in the 5 day group. 100% bacterial eradication was seen on day 14 (0/16 v 0/16) in both groups 1/14 patients on the 3 day course (7.1%). None on the 5 day course Transient increase in liver enzyme ALT noted in up to 20.6% of all subjects	Allocation criteria to either regime unclear  Relationship of transaminitis to dose used unclear
Aoyama <i>et al</i> (1996)	17 patients (0– 13 y) with culture proven pertussis 8/17 received azithromycin (10 mg/kg once a day for 5 days) while 9/17 received clarithromycin (10 mg/kg/day in two divided doses for 7 days). Each study subject was matched with two historical controls treated with erythromycin (40–50 mg/kg/day in three divided doses for 14 days) 58.8% of subjects were not immunised against pertussis	Two separate open labelled trials using historical controls (level 4)	Bacterial eradication: negative culture on 1 week after treatment  Relapse: positive culture at 2 weeks after treatment	8/8 with azithromycin (100%, 95% CI: 68.8–100%) v 13/16 (81%, 95% CI: 54.4–96%) among controls given erythromycin 9/9 with clarithromycin (100%, 95% CI: 71.1–100%) v 16/18 (88.8%, 95% CI: 65.3–98.6%) among controls given erythromycin None in either study or control groups	Historical controls Allocation criteria to medications unclear Small study group

tonsillo-pharyngitis. His mother recalls that he suffered severe abdominal pain when taking it and did not complete the course. You wonder whether newer macrolides such as azithromycin or clarithromycin could be effective alternatives to erythromycin for the treatment of pertussis.

### Structured clinical question

In a child diagnosed with whooping cough [patient] are azithromycin or clarithromycin [intervention] compared with erythromycin [comparison] as effective in eradicating infection with fewer side effects [outcome]?

### Search strategy

Primary source: Medline via Pubmed using keywords Pertussis OR Whooping Cough and combining the search with Azithromycin, Clarithromycin separately. This was verified by an alternative search method using MeSH heading “Whooping Cough” and subheading “drug therapy” [MeSH]. Five relevant articles were found.

Secondary sources: Cochrane database and Best Bets. No further papers were identified.

See table 4.

### Commentary

Antimicrobials are usually administered when pertussis is suspected or confirmed. If the disease is already established (paroxysmal phase), antibiotics have little or no effect on the clinical course of the illness except to render the patient non-infectious to others. This is important, so as to limit the spread of infection especially to the unimmunised and young infants. A 10–14 day course of erythromycin is the long established treatment for whooping cough.<sup>1</sup> It is known to reduce transmission and hasten clearance of *B pertussis*.<sup>3</sup> However, gastrointestinal side effects seem quite limiting in a large proportion of patients treated with it.<sup>7</sup> This may have a bearing in ensuring compliance. Newer macrolides—clarithromycin and azithromycin—are superior to erythromycin in terms of absorption, acid stability, and tissue penetration. They have longer half-lives, enabling less frequent dosing and shorter treatment courses.<sup>5</sup> They are also known to have fewer side effects.

From the available evidence it can be seen that the newer macrolides are at least as effective as erythromycin in eradicating *B pertussis* infection. A significant reduction in adverse gastrointestinal side effects and a better compliance have been shown. No serious side effects have been observed

with these agents so far. Transient elevation in alanine aminotransferase (ALT) has been shown in one study.<sup>3</sup>

Regarding prophylaxis, the current UK guideline is to administer a seven day course of erythromycin, if a clinically suspected or confirmed case of pertussis is identified. The aim is to protect those at risk from pertussis: infants, especially neonates; all household contacts who are unimmunised; and contacts who are 5 years or older if they did not receive a pre-school pertussis booster. There is no evidence of any benefit from chemoprophylaxis given more than 21 days from the date of onset of the primary case. Unimmunised or partially immunised cases and contacts should complete their course of vaccine.<sup>8</sup> Clarithromycin and azithromycin are potential, but not proven alternatives to erythromycin for prophylaxis at present.

### CLINICAL BOTTOM LINE

- A five day course of azithromycin or a seven day course of clarithromycin is as effective as a 10–14 day course of erythromycin to eradicate *B pertussis* infection. (Grade A)
- Azithromycin and clarithromycin have fewer gastrointestinal side effects than erythromycin. (Grade A)
- Patient compliance is better on the newer macrolides compared to erythromycin. (Grade A)

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