

## PERSONAL PRACTICE

## Respiratory problems in children with neurological impairment

P C Seddon, Y Khan

Arch Dis Child 2003;88:75-78

Children with severe neurological impairment have a high incidence of respiratory problems which are multifactorial and may be related to or dependent on the underlying disability. In addition, common respiratory conditions such as asthma will be represented in this group as in the general paediatric population. In order to maximise quality of life and reduce morbidity and mortality, each child should be carefully assessed and treated, making adjustments where necessary in the treatment regime to take account of the disability.

Children with complex physical disabilities often have respiratory problems. This common clinical experience, while recognised in practice, is not well recorded in the literature and there are few clear guidelines for the practising clinician. Respiratory problems play a major role in the life quality and expectancy of these children. Among severely disabled children in three US institutions,<sup>1</sup> 77% of deaths were a result of pneumonia; in a large community survey of children and adults with learning disability,<sup>2</sup> 52% of deaths were caused by respiratory problems. The reasons are poorly understood and taught, with vague concepts such as "hypostatic pneumonia" being passed on uncritically.

We run a joint clinic with a neurodevelopmental paediatrician (YK) and a respiratory paediatrician (PS) and appropriate input from a multidisciplinary team. This paper presents the large spectrum of respiratory problems in children with complex disability and the variety of ways in which acute and chronic respiratory presentation can occur. The aim is to sketch out a logical approach to assessment and management of respiratory problems based on published literature and our own clinical experience.

#### WHY IS THERE A HIGH PREVALENCE OF RESPIRATORY DISEASE IN CHILDREN WITH SEVERE DISABILITIES?

A number of factors contribute to respiratory difficulties. In many severely handicapped children, several of these factors coexist and may interact with each other. Although these factors occur across a variety of primary handicapping diagnoses, the precise pattern and relative importance will vary between, for example, cerebral palsy (CP) and neuromuscular disease (NMD), and these differences will be discussed.

#### Recurrent aspiration

*Oropharyngeal motor problems.* Swallowing is a complex process involving a sequence of intricate timed manoeuvres by a large number of muscles (including mouth, pharynx, larynx, oesophagus, and diaphragm). It is not surprising that this choreography is profoundly disturbed by muscle weakness in neuromuscular conditions and by dystonia and poor coordination in cerebral palsy.<sup>3</sup> Although the overall incidence is not known, videofluoroscopy in selected samples (referred for investigation of feeding difficulties) of children<sup>4</sup> and adults<sup>5</sup> with severe learning problems and/or cerebral palsy has shown aspiration in 26% and 27% respectively. Failure of proper bolus formation, oesophageal peristalsis, glottic closure, and "turn taking" between swallowing and breathing leads to recurrent aspiration of solids and liquids during feeding. Thin liquids are particularly prone to be aspirated.<sup>6</sup> Even between feeds, there is likely to be recurrent aspiration of non-sterile oral and upper respiratory secretions into the (normally sterile) lower airways because of inadequate protective reflexes.

*Gastro-oesophageal reflux (GOR).* For reasons poorly understood and little researched, GOR appears to be more common, persistent, and severe in children with cerebral palsy. This may be partly caused by spasticity of abdominal muscles causing increased intra-abdominal pressure, but it is likely that incoordinate oesophageal and sphincter muscle activity also plays a part. Any material which refluxes may not be actively cleared as a result of disturbed peristalsis, and is more likely to be aspirated as discussed above. As well as predisposing to chest infections, reflux episodes may provoke profound apnoea and/or laryngeal spasm. Estimates of the incidence of GOR in cerebral palsy vary from 32%<sup>7</sup> to 75%,<sup>8</sup> depending on the population studied and definition of GOR.

Recurrent aspiration, by either or both of these mechanisms, results in acute lower respiratory infections (clinically obvious) and in chronic lower airway inflammation and damage. The latter may go unnoticed for some time, but ultimately may cause both bronchiectasis and lung parenchymal damage. Once bronchiectasis has occurred, this further impairs clearance of airway secretions and predisposes to lower airway

See end of article for authors' affiliations

Dr P C Seddon, Royal Alexandra Children's Hospital, Dyke Road, Brighton BN1 3JN, UK; paul.seddon@brighton-healthcare.nhs.uk

Accepted 16 July 2002

**Abbreviations:** BHR, bronchial hyper-reactivity; CP, cerebral palsy; DMD, Duchenne muscular dystrophy; GOR, gastro-oesophageal reflux; NMD, neuromuscular disease; OSA, obstructive sleep apnoea; SMA, spinal muscular atrophy

infection. Aspiration in the child with disability often occurs “silently”—that is, without obvious cough or choking.<sup>4</sup> However, the relation between aspiration and lung damage is not a straightforward “linear” one, suggesting that other factors (including those discussed below) are involved: some children seem to tolerate aspiration without developing severe lung disease.

Although the two mechanisms can coexist, it is important to distinguish their contributions as far as possible, as their management is distinct. For aspiration “from above”, options range from modified feeding strategies and feed thickening, via complete nasogastric or gastrostomy feeding, to epiglottoplasty<sup>9</sup> or more extreme surgical measures (rarely used in the UK) such as laryngotracheal separation.<sup>10</sup> For aspiration “from below”, the options progress from medical (thickeners, H<sub>2</sub> antagonists/proton pump inhibitors, prokinetics) to surgical (fundoplication).

### Poor cough and airway clearance

Again, coughing is a complex activity which requires both forceful contraction of expiratory abdominal and intercostal muscles, and precise coordination and timing of expiratory and glottic muscles. The cough mechanism is often unsatisfactory in children with CP and NMD. The consequences are:

- Poor protection of the lower airway when aspiration (see above) occurs
- Inadequate clearance of lower airway secretions, particularly during respiratory infections.

Children with CP and severe learning difficulties often appear to have diminished sensitivity to cough, perhaps as a result of desensitisation of airway irritant receptors from chronic aspiration. They may not cough even during quite severe respiratory infections: this may delay recognition and treatment, though their carers often learn to recognise subtle signs.

In healthy children, exercise induces deep breathing which aids clearance of secretions and opens up underventilated lung regions; the child with disability, unable to take part in vigorous exercise, is prone to atelectasis, infection, and hypoxaemia. Chest physiotherapy techniques, adapted to the level of physical impairment and cooperation, may be required either daily or at the onset of respiratory infections.

### Respiratory muscle weakness

This occurs as a direct consequence of the underlying pathology in NMD and spinal cord lesions. In the different neuromuscular syndromes, although the rate of progression varies, the *sequence* is similar. Intercostals are affected relatively early,<sup>11</sup> causing paradoxical breathing (chest wall sucked in as abdomen goes out) and a bell shaped chest. Diaphragm weakness occurs later and heralds the onset of respiratory failure.<sup>12</sup> Hypoventilation tends to occur during sleep first, as weak intercostals become even more hypotonic during REM sleep; respiratory drive is decreased and upper airway obstruction may also occur<sup>13</sup> (see below).

In spinal lesions, respiratory problems are dependent on the level and completeness of the lesion. Upper thoracic lesions do not cause respiratory muscle paralysis per se, but may cause poor cough and retention of secretions as a result of abdominal muscle paralysis. Mid-cervical lesions will cause intercostal weakness, and high cervical lesions will paralyse all respiratory muscles except the accessory muscles.<sup>14</sup> Lesions at all these levels, as well as NMD, can cause kyphoscoliosis.

Ideally, respiratory muscle weakness should be identified and monitored directly by measuring vital capacity and maximal inspiratory and expiratory pressures. In practice, this may be difficult because of cooperation and difficulties sealing round a mouthpiece. Overnight oximetry is a useful if crude screening measurement. Management options (see below) are various forms of respiratory support: positive pressure by

mask or tracheostomy, negative pressure by tank or cuirass, or (for spinal lesions) phrenic nerve pacing.

### Kyphoscoliosis

Spinal curvature frequently occurs in all types of neurological handicap because of unequal muscle tone and gravity. Chest wall deformity secondary to severe kyphoscoliosis restricts lung function by decreasing chest wall compliance and decreasing the mechanical advantage of the respiratory muscles. In addition scoliosis can result in unequal lung expansion (basal atelectasis on the concave side and overexpansion of the convex side), leading to ventilation/perfusion mismatch. These factors together increase the work of breathing and predispose to respiratory failure. If scoliosis develops early in childhood, lung growth itself may be impaired.

Unlike idiopathic scoliosis, in CP and NMD curvature may continue to progress even when growth has ceased. Thoracolumbar spinal supports are often ineffective, and can further restrict lung function<sup>15</sup>; surgery should be considered early if scoliosis is progressing, while lung function allows.<sup>16</sup>

### Sleep apnoea

The pharyngeal muscles play a complex and vital role in maintaining upper airway patency during the swings in pressure which take place during the normal respiratory cycle. Normally, the respiratory centre stimulates pharyngeal muscle contraction to stiffen the pharynx just before diaphragmatic contraction, otherwise the negative pressure in the pharynx would cause it to collapse.<sup>17</sup> In children with CP and pseudobulbar palsy, this process is disturbed. Upper airway obstruction is often apparent by noisy breathing even during wakefulness, but becomes exaggerated during sleep. Obstructive sleep apnoea (OSA) is common in children with CP<sup>18</sup> (though the exact prevalence is unknown), with potential sequelae including disturbed sleep, failure to thrive, and pulmonary hypertension. Bulbar palsy in NMD can have a similar effect, though usually, rather than frank OSA, the hypotonic airway contributes (with muscle weakness and scoliosis) to cause hypoventilation and hypoxaemia during sleep.<sup>19</sup> There is also evidence of reduced central respiratory drive in myotonic dystrophy,<sup>20</sup> though not in Duchenne muscular dystrophy (DMD).<sup>21</sup> In Down's syndrome and some other dysmorphic conditions, hypotonic upper airway muscles combine with anatomical factors to cause severe OSA. In some children (for example, those with Down's syndrome, Prader-Willi syndrome, DMD) obesity is a further factor.

The Chiari malformation associated with spina bifida and hydrocephalus can cause both maldevelopment of the brain stem respiratory control centres, causing *central* sleep apnoea,<sup>22</sup> and bulbar palsy causing *obstructive* apnoea. Central apnoea can also occur with isolated acute hydrocephalus, because of pressure on the brain stem, and in Leigh's encephalomyelopathy because of degeneration of the brain stem respiratory nuclei.<sup>22</sup>

### Asthma and bronchial hyperreactivity (BHR)

There is no evidence that asthma is more common in CP, but both are common conditions, and coexisting asthma is often difficult to recognise in the child with CP. In addition, GOR, recurrent aspiration, and bronchiectasis are all associated with BHR, which may need treatment. Diagnosis is based on a suggestive history (especially if there is personal or family atopy) and a response to a trial of therapy. A history of “wheeze” should be clearly distinguished from other respiratory noises (for example, stridor, snoring, gurgling of unswallowed saliva). Treatment delivery needs to be individualised (see below).

### Nutrition

Maintaining adequate nutritional status is always a problem in CP: feeding problems, GOR, and additional energy

expenditure<sup>23</sup> contribute. Malnutrition subjects the respiratory muscles to catabolism, leading to atrophy, weakness, and reduced lung function,<sup>24</sup> as well as increasing bacterial colonisation of the airways and reducing resistance to infection.<sup>25</sup> Joint input from dietician and speech therapist is essential: appropriate feeding modification and supplements will be sufficient in some children, while others will require nasogastric feeding; if this is likely to be long term we would usually advocate gastrostomy.

By contrast, DMD and Down's syndrome, for example, are often associated with obesity, which increases work of breathing by reducing chest wall compliance, and predisposes to OSA.

### Miscellaneous factors

Some neurologically impaired children will have other predisposing factors specific to the condition which resulted in their disability, or secondary to their treatment. Examples are:

- Bronchopulmonary dysplasia in a preterm survivor
- Immune problems in Down's syndrome
- Lipid aspiration owing to mineral oil treatment for constipation
- Reduced lung growth in skeletal dysplasias.

### HOW DO RESPIRATORY PROBLEMS PRESENT? IS OUR CLINICAL RESPONSE DIFFERENT?

Respiratory problems may present in a variety of ways, but most often as variations on the following themes (with examples of possible underlying conditions):

- Recurrent "chest infections" (pneumonia, aspiration, asthma)
- Noisy breathing (asthma, upper airway obstruction, aspiration with stridor)
- Persistent cough (asthma, aspiration)
- Life threatening apnoeic episodes (obstructive sleep apnoea, GOR)
- Respiratory failure during fairly minor respiratory infection (respiratory muscle weakness, severe scoliosis).

Difficulties in communication with the disabled child can lead to both a delay in the recognition of respiratory problems and difficulty in establishing the precise diagnosis. The clinician remains dependent on an indirect history from the parent or carer, even in older children. Delays particularly occur when the carer (for example, in respite care) is unfamiliar with the child. On the other hand, an experienced parent or carer may become acutely tuned to detect problems in their child and may also be more sophisticated than the average parent in both their medical knowledge and their use of the health care system. The wise clinician will listen to and value the experienced parent's opinion, but will also be careful to distinguish what is direct observation, and what is interpretation.

Another problem is that severely disabled children, like neonates, tend to have a limited repertoire of responses to a variety of problems. For example, the child may respond by simply becoming quiet and withdrawn, whether the problem is a urinary tract infection, constipation, pneumonia, or sexual abuse.

Respiratory investigations, such as peak flow measurements or spirometry, are difficult to perform for children with cerebral palsy or neuromuscular weakness, making diagnosis and monitoring difficult. Newer techniques, making measurements during tidal breathing, and using an adapted face mask rather than mouthpiece,<sup>26</sup> may prove useful. Imaging is also problematic: a computed tomography scan is likely to require general anaesthesia, with additional risks.

The same problems (cooperation, coordination, and sealing round a mouthpiece) affect options for inhaled therapy. Our

preference in the severely handicapped is to use a metered dose inhaler/spacer/mask system as first choice, with nebuliser as second choice, as for able bodied preschool children. Unfortunately, most spacers come with masks to fit infant faces; the adult Aerochamber with mask is a useful exception, or an appropriately sized anaesthetic mask can be fitted.

Finally, our clinical response must take account of the child's prognosis, level of understanding, quality of life, and wishes (as far as the last two can be accurately assessed).

### RECOMMENDATIONS

Our personal practice has been based on the following principles:

- Every child, no matter what the degree of disability, deserves individualised assessment of her/his respiratory problems. Even if ultimately nothing constructive can be done (and this is rarely the case), the child merits the effort.
- Assessment is based on the pattern of symptoms and contributing factors given the underlying disability. Multidisciplinary assessments are often required to tease out the multifactorial aetiology.
- Intervention is aimed at optimising *quality of life* for the child foremost. The views and welfare of the parents must be taken into account.
- Some interventions are ethically problematic and need to be carefully considered.

### Stages of assessment and management

- (1) Careful history, from as many of the child's regular carers as feasible, and examination.
- (2) Based on this, statement of the likely *nature* of the respiratory problem (for example, wheezy episodes, recurrent lower respiratory infections, sleep apnoea).
- (3) Listing of the possible *contributing factors* (for example, wheezing episodes: probable asthma, possible aspiration with/without reflux, scoliosis).
- (4) Plan of investigation to clarify contributing factors, concentrating on those which are both *most likely* and *amenable to treatment*. This is formulated after discussion with parents/carers of the invasiveness and risk of each investigation versus the possible benefit.
- (5) Restatement, after investigations, of the probable contributing factors with a list of therapeutic options (if any) for each. Continuing the above example:
  - asthma: bronchodilator only, bronchodilator plus inhaled steroid
  - GOR: H<sub>2</sub> antagonist/proton pump inhibitor only or with prokinetic agent, fundoplication
  - aspiration during feeds: speech therapy input, thickening, stopping oral feeds
  - scoliosis: brace, surgery.
- (6) Plan of treatment based on the above, again after discussion with parents/carers. Wherever possible, specific therapy based on known contributing factors should be tried first. However, if this is not possible or these remain unclear, we would consider:
  - a trial of asthma or antireflux therapy for a limited period (2–3 months)
  - for troublesome recurrent chest infections, a trial of prophylactic antibiotics (azithromycin three days per fortnight or trimethoprim twice daily) over a winter.
- (7) Honest discussion about likely prognosis, and about how far treatment should be taken in the event of deterioration. It is better to have at least discussed these issues in principle before a crisis occurs. This discussion (and some

of the steps above) will need to be revisited if a child's condition and quality of life deteriorate.

We would like to conclude by briefly flagging up some of the difficult ethical issues in treatment.

### Respiratory support

At the least invasive end, we have no doubt that children with Down's syndrome and obstructive sleep apnoea should be offered a trial of nasal mask CPAP; we would also attempt a trial in a child with cerebral palsy and OSA not improvable by adenotonsillectomy, but clear targets based on quality of life (not just oxygen saturation parameters) must be set. We believe that early institution of nasal mask bi-level positive pressure support in children with type II spinal muscular atrophy (SMA) is justifiable and improves quality (for example, improved sleep and weight) as well as duration of life, and there is growing evidence for this in DMD.<sup>27</sup> However, few in the UK would support this in type I (Werdnig-Hoffman) SMA. In the teenager with DMD, it is important to monitor lung function and sleep oximetry to identify when he is approaching the threshold of respiratory failure (usually when vital capacity is below 30% predicted and/or there is hypoxaemia during sleep). At this point we would discuss with the boy and parents the options for respiratory support, rather than waiting until decompensation with a respiratory infection occurs; the young person who is already seriously ill on a ventilator cannot make an informed choice about their future.

### Aspiration

Fundoplication is an invasive procedure requiring general anaesthesia, but we believe it is justified in a child with demonstrable reflux, unresponsive to maximal medical management and troublesome symptoms. In many centres the procedure can now be performed endoscopically. Stopping oral feeding should not be an automatic response in the face of an abnormal videofluoroscopy report but a measured decision in a child with repeated aspiration episodes, when altering textures and feeding technique have been ineffective. Severely disabled children vary widely in the pleasure (or discomfort) they derive from oral feeding, and their closest carers are in the best position to judge; this factor must also enter into the decision. We would be reluctant to stop all oral intake in the child who aspirates but who nevertheless derives pleasure from oral feeding; we would try small, low volume "tasters" but with most nutrition by gastrostomy.

### Consent to intervention

In children with learning and communication difficulties it is extremely problematic to assess the degree of understanding and acquire informed consent. Often professionals respond to the parent's wishes, as it may be virtually impossible to elicit those of the child. This is further complicated if there are secondary and tertiary level paediatricians involved, each bringing their own concept of "quality of life".

### ACKNOWLEDGEMENTS

The authors are grateful for the support of the Chailey Heritage Foundation and the Rockinghorse Appeal, and for the help of Abigail Jones in preparing the manuscript.

.....

### Authors' affiliations

**P C Seddon**, Royal Alexandra Children's Hospital, Dyke Road, Brighton, UK

**Y Khan**, Chailey Heritage Clinical Services, Beggars Wood Road, North Chailey, Lewes, UK

### REFERENCES

- 1 **Pliophlys AV**, Kasnicka I, Lewis S, *et al*. Survival rates among children with severe neurological disabilities. *South Med J* 1998;**91**:161-72.
- 2 **Hollins S**, Attard MT, von Fraunhofer N, *et al*. Mortality in people with learning disability: risks, causes and death certification findings in London. *Dev Med Child Neurol* 1998;**40**:50-6.
- 3 **Casas MJ**, Kenny DJ, McPherson KA. Swallowing/ventilation interactions during oral swallow in normal children and children with cerebral palsy. *Dysphagia* 1994;**9**:40-6.
- 4 **Arvedson J**, Rogers B, Buck G, *et al*. Silent aspiration prominent in children with dysphagia. *Int J Pediatr Otorhinolaryngol* 1994;**28**:173-81.
- 5 **Rogers B**, Stratton P, Msall M, *et al*. Long-term morbidity and management strategies of tracheal aspiration in adults with severe developmental disabilities. *Am J Ment Retard* 1994;**98**:490-8.
- 6 **Mirrett PL**, Riski JE, Glascott J. Videofluoroscopic assessment of dysphagia in children with severe spastic cerebral palsy. *Dysphagia* 1994;**9**:174-9.
- 7 **Gustafsson PM**, Tibbling L. Gastro-oesophageal reflux and oesophageal dysfunction in children and adolescents with brain damage. *Acta Paediatr* 1994;**83**:1081-5.
- 8 **Abrahams P**, Burkitt BF. Hiatus hernia and gastrooesophageal reflux in children and adolescents with cerebral palsy. *Aust Paediatr J* 1970;**6**:41-6.
- 9 **Remacle M**, Marza L, Lawson G. A new epiglottoplasty procedure for the treatment of intractable aspiration. *Eur Arch Otorhinolaryngol* 1998;**255**:64-7.
- 10 **Lawless ST**, Cook S, Luft J, *et al*. The use of a laryngotracheal separation procedure in pediatric patients. *Laryngoscope* 1995;**105**:198-202.
- 11 **Burke SS**, Grave NM, Houser CR, *et al*. Respiratory aspects of pseudohypertrophic muscular dystrophy. *Am J Dis Child* 1971;**121**:230.
- 12 **Killburn KH**, Eagan JT, Sieker HO, *et al*. Cardiopulmonary insufficiency in myotonic and progressive muscular dystrophy. *N Engl J Med* 1959;**261**:1089-96.
- 13 **Khan Y**, Heckmatt JZ. Obstructive apnoeas in Duchenne muscular dystrophy. *Thorax* 1994;**49**:157-61.
- 14 **Bohn D**, Armstrong D, Becker L, *et al*. Cervical spine injuries in children. *J Trauma* 1990;**30**:463-5.
- 15 **Noble-Jamieson CM**, Heckmatt JZ, Dubowitz V, *et al*. Effect of posture and spinal bracing on respiratory function in neuromuscular disease. *Arch Dis Child* 1986;**61**:178.
- 16 **Jenkins JG**, Bohn D, Edmonds JF, *et al*. Evaluation of pulmonary function in muscular dystrophy patients requiring spinal surgery. *Crit Care Med* 1982;**10**:645.
- 17 **Brouillette RT**, Thach BT. A neuromuscular mechanism maintaining extra-thoracic airway patency. *J Appl Physiol* 1979;**46**:772-9.
- 18 **Kortagal S**, Gibbons VP, Stith JA. Sleep abnormalities in patients with severe cerebral palsy. *Dev Med Child Neurol* 1994;**36**:304-11.
- 19 **Smith PEM**, Calverley PMA, Edwards RHT. Hypoxemia during sleep in Duchenne muscular dystrophy. *Am Rev Respir Dis* 1988;**137**:884.
- 20 **Begin R**, Bureau MA, Lupien L, *et al*. Control and modulation of respiration in Steiner's myotonic dystrophy. *Am Rev Respir Dis* 1980;**121**:281-9.
- 21 **Begin R**, Bureau MA, Lupien L, *et al*. Control of breathing in Duchenne's muscular dystrophy. *Am Rev Respir Dis* 1980;**69**:227-34.
- 22 **Beckerman RC**, Hunt CE. Neuromuscular diseases. In: Beckerman RC, Brouillette RT, Hunt CE, eds. *Respiratory control disorders in infants and children*. Baltimore: Williams & Wilkins, 1992:251-70.
- 23 **Lundberg A**. Oxygen consumption in relation to workload in students with cerebral palsy. *J Appl Physiol* 1976;**40**:873-5.
- 24 **Sullivan PB**, Rosenbloom L. Feeding the disabled child. In: *Clinics in developmental medicine*. MacKeith Press, 1999:140.
- 25 **Martin TR**. The relationship between malnutrition and lung infections. *Clin Chest Med* 1987;**8**:359.
- 26 **Bisgaard H**, Klug B. Lung function measurements in awake young children. *Eur Respir J* 1995;**8**:2067-75.
- 27 **Simonds AK**, Muntoni F, Heather S, *et al*. Impact of nasal ventilation on survival in hypercapnic Duchenne muscular dystrophy. *Thorax* 1999;**53**:949-52.



## Respiratory problems in children with neurological impairment

P C Seddon and Y Khan

*Arch Dis Child* 2003 88: 75-78

doi: 10.1136/adc.88.1.75

---

Updated information and services can be found at:

<http://adc.bmj.com/content/88/1/75.full.html>

---

### References

*These include:*

This article cites 24 articles, 6 of which can be accessed free at:

<http://adc.bmj.com/content/88/1/75.full.html#ref-list-1>

Article cited in:

<http://adc.bmj.com/content/88/1/75.full.html#related-urls>

### Email alerting service

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

---

### Topic Collections

Articles on similar topics can be found in the following collections

[Epidemiologic studies](#) (925 articles)

[Child health](#) (2025 articles)

[Asthma](#) (266 articles)

[Immunology \(including allergy\)](#) (1167 articles)

---

### Notes

---

To request permissions go to:

<http://group.bmj.com/group/rights-licensing/permissions>

To order reprints go to:

<http://journals.bmj.com/cgi/reprintform>

To subscribe to BMJ go to:

<http://group.bmj.com/subscribe/>