

# Invasive monitoring of airway inflammation

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FIBREOPTIC BRONCHOSCOPY, with or without biopsy or bronchoalveolar lavage, has increased our understanding of childhood asthma. For the purposes of this article, these techniques are regarded as invasive.

Techniques such as bronchoscopy with biopsy may provide invaluable information about the cellular events that initiate asthma, as well as those that sustain inflammation. They also offer the promise of monitoring cellular and molecular responses to therapy, predicting which young children with wheeze will develop the typical asthma phenotype, and determining individualised treatment regimens based on patterns of airway inflammation.

However, these potential benefits need to be balanced against the risks of the procedures, and there are widely divergent views about their invasiveness. In research involving adult volunteers, procedures such as endobronchial segmental allergen challenges with repeat bronchoscopy and segmental lavage and biopsy are routinely performed.<sup>1</sup> By contrast, biopsy studies in children appear to have been better accepted in Eastern European countries,<sup>1,2</sup> but elsewhere both safety and ethical concerns have limited the use of bronchoscopy and biopsy to assess childhood asthma. Furthermore, although bronchoalveolar lavage is well established in the diagnosis of pulmonary infections (especially in immunocompromised children), as recently as 2000 the European Respiratory Society Task Force on bronchoalveolar lavage in children noted the lack of clear recommendations on its methodology.<sup>3</sup> It nevertheless concluded that bronchoalveolar lavage "is likely to represent a useful tool in wheezing infants by documenting the patterns of inflammatory marker expressions at various stages of the disease."<sup>3</sup>

## Safety and ethics

Payne et al reported that bronchoscopy with bronchoalveolar lavage and endobronchial biopsy can be performed safely under general anaesthesia in children with difficult-to-control asthma.<sup>4</sup> This supplements a briefer report on a much larger population.<sup>1</sup> Of 278 endobronchial biopsies in an unspecified number of children, 71% were suitable for analysis.<sup>1</sup> In another report, suitable biopsy specimens were obtained from 23 of 31 children with asthma.<sup>5</sup> The predominant view is that these procedures are ethical only if they have the potential to contribute to the management of the child undergoing the procedure.<sup>4</sup> Extensive experience with bronchoalveolar lavage in children with conditions other

## ABSTRACT

### What we know

- Ethical concerns have limited research involving invasive bronchoscopy techniques in young children.
- No longitudinal studies have been conducted to compare the findings of bronchial biopsy or bronchoalveolar lavage in young children with transient episodic wheeze versus asthma.
- Children with atopic asthma have more airway eosinophils and mast cells than children with viral-associated wheeze.
- Both neutrophilic and eosinophilic patterns of inflammation are present in asthma.

### What we need to know

- Can we establish robust normal values for tissue and fluid samples obtained at bronchoscopy or bronchoalveolar lavage?
- Do biopsy specimens taken at the carina tell us about the pathological processes occurring in asthma?
- Can we use invasive procedures to predict which children with wheeze will continue to wheeze and develop a classical asthma phenotype?
- Can we use invasive procedures to guide asthma therapy?
- Can we expect airway inflammation to resolve with anti-inflammatory medication?
- Can we correlate invasive with non-invasive measures of inflammation?
- Can we use our understanding of pro- and anti-inflammatory pathways to develop new therapeutic interventions?
- Is there a presymptomatic phase of inflammation?

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than asthma has shown a low complication rate,<sup>3,6</sup> but, as Shields and Riedler point out, it is ethically difficult to justify the sedation or anaesthesia required for bronchoalveolar lavage in young children if the only purpose is research.<sup>6</sup>

## What have we discovered?

Different patterns of inflammation have been observed. Bronchoalveolar lavage in children with atopic asthma shows elevated levels of eosinophils and mast cells compared with those in children with viral-associated wheeze.<sup>7</sup> Neutrophil-mediated inflammation, and not just eosinophilic bronchitis, is well recognised in children with asthma.<sup>8</sup> Bronchoalveolar lavage in children aged 0–18 months with recurrent wheeze who do not respond to bronchodilators produces a variety of findings, many of which suggest viral

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or bacterial infection or aspiration rather than asthma.<sup>9</sup> As might be expected, there are some similarities in the airway inflammation observed in children and adults.<sup>10,11</sup> In children with poorly controlled asthma (despite taking oral prednisolone), simultaneous measurement of exhaled nitric oxide and mucosal eosinophilic inflammation showed a modest correlation between non-invasive and invasive markers of inflammation.<sup>5</sup> Finally, young adults with asthma (mean age, 21 years) who were in clinical remission and had not taken asthma medications for at least 12 months (median duration of remission, five years) were found to have ongoing markers of airway inflammation.<sup>12</sup>

These studies support the view that we cannot extrapolate from adult studies and hope to gain a complete picture of asthma in young children. We have learned much from adult studies, but we need to know about the events that initiate inflammation, rather than what sustains it or what is its end-result. This highlights the importance of studies in children. Furthermore, young children with wheeze appear to belong to several phenotypes, and no adult model is applicable.

Some researchers espouse the view that children with asthma who respond poorly to corticosteroids, particularly those in whom unconventional therapies are being considered, should undergo bronchoscopy and endobronchial biopsy and their treatment should be tailored according to the information obtained. Thus, biopsy evidence of steroid-resistant eosinophilic inflammation in a symptomatic child would support use of an agent such as methotrexate or cyclosporin. On the other hand, a patient whose biopsy shows neutrophilic inflammation might be given a long-acting  $\beta$ -agonist or continuous subcutaneous terbutaline.<sup>4,13-15</sup> This approach may be correct, but the lack of longitudinal data means that its appropriateness in children remains to be established.

## Conclusion

We are in an exciting phase in research using invasive methods to investigate childhood asthma. A number of researchers have decided that the potential benefits outweigh any ethical and safety concerns. Within the next decade we should be in a much better position to evaluate whether bronchoscopy with biopsy and/or bronchoalveolar lavage should only be used for research, or whether, in addition, they will have an important impact on the care of individual children.

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