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By email: rebecca.pye@nice.org.uk

Dear Ms Pye,

Colistimethate sodium powder for lung infection with Pseudomonas aeruginosa in CF

I am writing to comment upon the recent NICE assessment. Having prepared this letter, and its accompanying article, I then found that I was unable to paste it into the space provided on your website, and so I am emailing it to you and also sending you a hard copy.

I am a general medical paediatrician, the lead for paediatric CF in the North West where we provide sole care or shared care for approximately 350 patients with CF aged under 18 years.

As I understand it, NICE's Appraisal Committee's preliminary recommendations are as follows:

1.1 Tobramycin dry powder for inhalation is recommended as an option for treating chronic pulmonary infection caused by Pseudomonas aeruginosa in people with cystic fibrosis if:

- nebulised tobramycin is considered an appropriate treatment, that is, when nebulised colistimethate is contraindicated, not tolerated or has not produced an adequate clinical response and

- the manufacturer provides tobramycin dry powder for inhalation with the discount agreed as part of the patient access scheme to primary, secondary and tertiary care in the NHS.

1.2 Colistimethate sodium dry powder for inhalation is not recommended, within its marketing authorisation, for treating chronic pulmonary infection caused by P.aeruginosa in people with cystic fibrosis.

I have a few brief comments to make, which go to the heart of the underlying assumptions.

1. **A basic fact is that in the UK, the management of CF differs widely from centre to centre in the UK, and also differs widely between children and adults with CF.** Whilst there are approaches common to many CF centres, there are a number of very notable differences. For example at centre A, there is considerable use of long term oral corticosteroids, whereas at centre B there is enthusiasm for the use of enteral feeding by gastrostomy. There are notable differences in the enthusiasm for the use of regular 3 monthly intravenous anti-Pseudomonas antibiotics, our own policy being at the enthusiastic end of the spectrum.

Maybe the most stark illustration is that the model of care for paediatric patients is treatment by the CF centre for children with live near to a centre, and so-called "shared care" or "networked care" for those who live closest to a district general hospital (DGH). The shared care model provides all basic CF care by the local DGH CF team, with regular input from the regional CF centre team. For example, I visit and conduct a joint CF clinic with the local CF team in Blackpool and Lancaster twice a year, with the result that all patients with CF in those cities are seen by a specialist from the regional CF centre at least twice a year. Between clinic visits there is regular communication between the DGH and regional centre CF teams, and for specialised diagnostic or therapeutic procedures (e.g. bronchoscopy) the patient travels to the regional centre. In contrast, adult regional CF centres have turned their back on any form of shared care, and insist on all patients travelling to the regional centre, even when this involves considerable distances.

Thus the fundamental management of the CF changes in the UK at the age of 18, this change having no evidence in support from RCT's.

2**. The study in question, between tobramycin dry powder and colismethate sodium dry powder, has little relevance or applicability to our own management of CF.** Comparison of these two treatments implies that they are likely to be used in a similar way, in similar clinical situations. I reality our own use of these two inhaled antibiotics is completely different. Starting with the nebulised drugs, we have used colistimethate by nebuliser for many years, in patients whose lungs are colonised with Pseudomonas aeruginosa. This has been (i) either as part of a so-called "eradication" regimen in children in whom PA has been isolated for the first time, when treatment is given with a combination of oral ciprofloxacin (for 6 weeks) and twice daily nebulised colistimethate, usually for 6-12 months or more, depending upon whether there is a re-growth of PA, or (ii) on a long term basis for patients chronically colonised with PA in whom there are significant symptoms in between the regular 3 monthly courses of intravenous anti-PA antibiotics we give to all patients chronically colonised with PA.

Inhaled tobramycin plays no part in either of these regimens, for a number of reasons. One is that despite prolonged use over many years, the development of resistance of PA to colistimethate is extra-ordinarily unusual, so the antibiotic can be given indefinitely without the development of resistance. I can recall only a single case in which this occurred. Another

reason is that we regard intravenous tobramycin as being of particular value, and we greatly rely on its use. An important drawback to the use of nebulised tobramycin is the development of resistance, which is the reason why the drug cannot be administered for more than 1 month at a time. Another drawback to one particular brand of tobramycin, namely TOBI, is that the formulation is irritant and poorly tolerated. As a consequence, we have not used nebulised TOBI for some years, and on the infrequent occasions when we have used nebulised tobramycin we have used the BRAMITOB formulation, which is far less irritant.

Nebulised colistimethate has one major drawback, which is that it requires to be given via a nebuliser, which is time consuming. This is seen by children and families as a huge drawback. A good illustration of this was given by a parent who gave a paper on her experiences as a parent of two children with CF to one of the annual conferences on CF which I have organised for many years at the Royal Society of Medicine. I have attached a copy of the paper. It describes the very time consuming nature of administering nebulised medication to children with CF. This message was rather strikingly emphasised by the speaker explaining how when nebulised DNAse had been commenced in one of her children, the mother admitted that she had actually hoped it would not work because of her concern about the burden of an additional nebulised medication.

It is self evident that a dry powder formulation of colistimethate has the potential to make a great deal of difference to our patients and their families, and I would be concerned were this treatment to be unavailable. We are aware, of course, of the availability of a dry powder formulation of TOBI, but this requires the administration of 4 capsules which has been estimated to take a similar amount of time to the administration of a nebulised dose, but far more importantly the powder cannot be used continuously for more than 4 weeks and is therefore unsuitable for our patients who are receiving long term nebulised colistimethate. A final point is that we reserve nebulised tobramycin for the most severely affected patients, who tend to have poor lung function, making it difficult for them to use the Podhaler device, which as a result I have yet to prescribe or recommend.

In conclusion, the concern is that the limited expert advice that has been offered has failed to reflect what happens in clinical practice, and that the provisional decision will severely limit patient choice.

Yours sincerely,

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Hunter, V. The daily grind and how to stay sane as a mother of two children with cystic fibrosis. Journal of the Royal Society of Medicine 2003; 96 (suppl.43):51-56.