NICE Health Technology Appraisal - Assessment Report On Colistimethate sodium and tobramycin for Cystic Fibrosis (pseudonimas lung infection) (ID342)	
TO: NICE	**FROM: Healthcare Improvement Scotland 02 May 2012**

It is immediately apparent that the critical problem for the reviewers has been the lack of appropriate evidence on which to formulate the policy. This vacuum is compounded by the difficulties in agreeing the exact definitions of critical surrogate markers of outcome in Cystic Fibrosis. Set against that context, it is hardly surprising that a paucity of evidence coupled to a paucity of agreement on what constitutes true clinical benefit was always likely to yield the outcome reported by the expert team.

Having taken this rather nihilistic stance, there are a number of points that need to be considered.

1. It is without doubt that antibiotics, and in particular their administration by the inhaled route, constitute an important part of management. The peculiarities of the antibiotic colomycin are rather interesting. This agent appears to target the Achilles heel of the pseudomonas protein which does not vary very much between different pseudomonas species. This has always been thought to explain the incredibly low resistance to this agent. Thus the agent itself is from a microbiological perspective at least a good candidate drug. Having said that, there seems to be such a mismatch between the efficacy and the patient and the micropharmicology of the drugs actions.

2. The therapeutic options per patient with Cystic Fibrosis are incredibly varied. In addition, the propensity to develop allergies to the various medications whether given by the inhaled route or whether delivered intravenously, can severely limit these options in the older patients. Plus any additional agent that might or might not be available to the clinician are most welcome.

3. The two points above are severely constrained by the time window the patients have to take therapies, to follow protocols and to, hopefully improve their health.

Hence the attraction of such dry powder devices is that there ease of carriage and opportunistic use is ? greater than the nebulised approach even allowing for the dramatic advances in nebuliser technology that have taken place in the last few years.

In summary the reviewers have set themselves a very difficult task. I will make my comments in the different sections of the report as I come across them.

<u>General Point</u>

In my reading of the literature I think we should clearly distinguish established infection from the child with a pristine lung, who is over the age of 6 and who has remained pseudomonas free since early childhood. In the former, we are playing the game of preventing decline. In the latter we are playing the game of preventing the acquisition of the potentially lung

destructive pathogen. From my perspective separating these two groups in relation to the therapy that is being proposed is of paramount importance.

Specific Points

Section 3.1.2

The first paragraph of this section is correct and incorrect at the same time. It must be remembered that the work of Stanke and colleagues in Germany clearly establishes the fact that you can have the same Cystic Fibrosis mutation and a very different outcome. Thus the outcome in Cystic Fibrosis is an amalgam of the contribution from the genetic defect and genes that are co-inherited at a different loci. The paragraph as its written implies causality which is incorrect and is technically incorrect in that the deletion of phenylalanine is not at codon 508. 508 refers to the amino acid. The second paragraph explains the dramatically different phenotypes that are found in this disease. With respect to the rest of section 3.1.2 the authors go on to describe the fact that over 90% of the Cystic Fibrosis population in 2010 had the common F508 del phe mutation and given that that relative homogeneity is present, it is a reflection of the complexity of the disease that so much variability exists between patient outcomes. The centre of the problem that the antibiotics discussed in this article relate to is described in the later aspects of this summary which show that they move from no infection to intermittent infection through to established infection is the critical window that is targeted by antibiotic and other therapies. Although not explicitly stated in this paragraph but eluded to in figures 1 to 4, there is going to be a c change in the management of this condition due to the introduction of newborn screening. This is best illustrated by the data from Northern Ireland which has had screening for many years where the proportion of the population that live in Northern Ireland and have Cystic Fibrosis exceeds the proportion that has the condition in other parts of the country where screening is not available. I merely point this out that the use of such antibiotics is likely to change in future years as now nearly all of the patients shown in figure 4 have been screened at birth. Indeed if taken to its logical conclusion, the expected steady state prevalence of patients with Cystic Fibrosis in future years is likely to be around 28 thousand patients should current trends in reduced mortality continue to occur. I think that figure 1 would be much more interesting if the age at diagnosis of the patients shown were also compared with the median age at death calculation that can be determined from that figure. This comment relates to the fact that the patients dying in older years between 40 and 50 might reflect a different population from those dying in their 20s and 30s.

Measurements of microbiological indicators of infection

At this point of the review we reach the central issue in relation to the use of antibiotics. It must be remembered that the sentence and I quote “the presence of a microbiological infection is ascertained using sputum colony density” illustrates the immediate problem in Cystic Fibrosis. This measures those bacteria that are actively able to grow on the dish. You only have to work in a Cystic Fibrosis clinic for a period of a few months to realise that there is a complete lack of correlation between what is grown in the laboratory, its supposed sensitivity to a range of antibiotics and the clinical response. This single factor bedevils the interpretation of data in this disease. The applicants comment on these difficulties in relation to the meaning of colony formation and I suppose that this is also illustrated by the fact that when you take a mucoid strain of pseudomonas from lung from a Cystic Fibrosis patient and culture it repeatedly in the test tube, the organism reverts away from its mucoid venotype and turns into a “normal” pseudomonas. Plus the local environment of the lung drives the pseudomonas to its mucoid status. The applicants comment on this on page 18.

Measuring acute exacerbations the authors comment on the Eurocare CF working group. The group’s recommendations and those of the EMA might differ somewhat but the critical point to remember is that the data, irrespective of the definition used, need to be gauged against the data from Kraynack et al in paediatric pulmonology (2011 46, p870-881.) these authors point out that given a case scenario approach where clinicians were sent a number of typical clinical cases, the individual Cystic Fibrosis doctors each interpreted the cases that were common to each in a different manner. Thus it is my contention that however much we define

an exacerbation, until we agree on how that data is interpreted by the individual doctor, then the data that are reported in registries are going to be flawed and this will cause considerable difficulty in the assessment of any medication in this disease.

The bottom line is if the patient, who is fully aware of their normal state of health, reports that they feel unwell, it is at this point that an intervention is commonly used. Commonly, if that feeling of being unwell is accompanied by weight loss then the clinician will take that very seriously and intervene with some form of antibiotic therapy.

Section 3.2.4

Variations in services and uncertainties about best practice

The authors make a very valid point in the first paragraph but given the variability between two patients with the same genetic form of Cystic Fibrosis, it is not surprising that there is an absence of clinical trial material. Indeed the European Cystic Fibrosis Society is trying to address this matter by setting out the criteria that will be in future years necessary for an individual Cystic Fibrosis centre to qualify as a clinical trial unit.

I notice in section 5 the relatively high withdrawal rate of patients from the trials that are reported in this review. I have always been very concerned about these high withdrawal rates and my own view is that if a medicine in Cystic Fibrosis is likely to be affective and is now killing large numbers of bacteria, it is to be expected, at least from my perspective, that these patients will have a worse dropout rate. This might explain the data on page 57 whereby the dropout rate was high compared to other control arm. Again from my perspective I think we are missing a trick here with some of these trials where a side effect is confused with a therapeutic effect.

Members of the Committee might wonder why I am departing along these lines of criticism. The comments made are not meant in any way to denigrate the efforts of the individuals who have written this report. However should the committee look at data that I have recently provided along with colleagues throughout Europe (Corvol et al, Journal of Cystic Fibrosis 2011) you will see that in a sample size of the CF population not to dissimilar from those reported in the current study, we find that 25% of the children within the cross sectional group that we studied carry a gene variant that is predicted to halter the response to infection. I merely point this out to the expert reviewers on your panel as one of the key frustrations of working in Cystic fibrosis, namely that loci (in this instance in the Corvol paper on chromosome 6 found in the MHC locus have the potential to profoundly influence the estimates within the population of the degree of confidence in which one might expect the results to lie.

So when we move on to section 5.3.3 where the detail of the exacerbation s is recorded, and we add on top of that the uncertainty of the comparability of the groups it makes the interpretation almost impossible.

Section 5.3.4

BMI

It would be wholly unexpected for BMI to show any changes.

I read the next session on cost effectiveness with great interest. I am not a health economist and do not profess to understand details of this section. My only comment relates to figures 9 and 10. I wonder what sort of distribution maps is the midpoint of the average of the three different methods. The reason I ask this is that I wonder whether figure 9 in particular maps to a ? distribution if it does then does this not suggest a random effects interaction of a multiple chance event leading to the end point of mortality. Figure 10 does not seem by eye to support such a model.

Section 6.6.2

My major quarrel with the conclusions relate to this section. They state that the results of this analysis suggest that colistimethate is expected to produce fewer gains than its nebulised tobramycin equivalent. The problem I have is that when you look at the N of one trial design, which was published a few years for the introduction of a non-antibiotic (DNAase) you see that only one third of patients with Cystic Fibrosis respond to that particular medication. Could it be that given the changes in the Cystic Fibrosis population that are about to occur due to the move from early preventative approaches based on screening versus older catch up approaches based on existing lung damage, will lead to a population of patients within five years that are vastly different from those that are currently being studied and treated with nebulised agents. I do worry about the credibility of the modelling proposed in this analysis.

Section 9

I would agree with the statements made that it is almost impossible to be certain as to the benefits from this medication. I would add the observation that since the European Cystic Fibrosis Society has invested considerable sums in creating a clinical trial network, it would be advisable to stop all small studies that do not fit with the rigorous criteria now established for clinical trials in Cystic Fibrosis. This would stop the waste of considerable resources in future years. Further, given the uncertainties in definition and uncertainties in the makeup of the patient whether it be due to the genetic factors outside the CF locus or due to totally imperfect definitions based on case scenario analysis for an individual clinician, due consideration should be given to the use of N of one trials in this rare disease. It would be an interesting addition to the literature if this expert committee would consider the minimum trial design size per group from an N of one perspective that could be useful in future studies in Cystic Fibrosis. My fear is unless we adopt a robust approach to future studies, we will never get to the bottom of the complexities of this disease.

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