**Unwarranted use of intravenous aminoglycosides at UK paediatric cystic fibrosis centres**

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Due to their efficacy against *Pseudomonas aeruginosa,* intravenous aminoglycosides are frequently used to treat infective exacerbations in individuals with cystic fibrosis (CF). This clinical utility has to be balanced against their side effects which include acute kidney injury (AKI), chronic kidney disease (CKD), hearing impairment and vestibular toxicity.[1] The incidence of AKI in adults and children with CF is 4.6-10.5/10,000 CF patients/year.[2] The risk increases >80 fold if an aminoglycoside was administered in the previous week.[3] The risk of aminoglycoside induced CKD in CF is associated with cumulative exposure leading to the hypothesis that CKD results from subclinical kidney damage caused by repeated courses of aminoglycosides. Aminoglycosides are also known to be ototoxic with the prevalence of hearing impairment in patients with CF who have received multiple courses being as high as 17%.[1] Specific mitochondrial ribosomal mutations increase the risk of severe aminoglycoside induced hearing loss. Aminoglycoside induced vestibulotoxicity can occur independently of ototoxicity causing dizziness and vertigo.[1] A number of strategies have been tried to reduce the toxic effects of aminoglycosides with varying degrees of success. The most effective way to prevent these unwanted effects is to only use them if there is no equally effect but less toxic alternative.

Our objective was to clarify under what circumstances IV aminoglycosides are prescribed for children with CF in the UK. We developed a questionnaire using clinical vignettes to clarify the first choice intravenous antibiotic regimen for infective respiratory exacerbations in children with CF who have never had PA, who are free of PA for >12 months and who have chronic PA infection.[4] See Appendix 1. The link to this questionnaire was emailed to the clinical lead at the 27 tertiary paediatric CF centres in the UK who was asked to complete it to reflect practice at their centre.

We obtained responses from all 27 UK centres. The first choice antibiotic regimens are shown in Figure 1. 10/27 (37%) centres used ceftazidime and tobramycin as first line antibiotic regimen for the treatment of infective respiratory exacerbations in children who had never isolated PA. 15/27 (56%) used the same combination in those free of PA for >12 months. Three of these stated they would change from ceftazidime and tobramycin to co-amoxiclav or cefuroxime if the child remained free of PA for >2 years. All centres used ceftazidime and tobramycin as the first line IV antibiotic regimen to treat infective exacerbations in children with chronic PA infection.

This survey has established more than one third of UK tertiary paediatric CF centres use tobramycin as part of their first line IV regimen to treat infective pulmonary exacerbations in children who have never isolated PA and more than one half in those free of PA for at least 12 months. The use of IV tobramycin in children free of PA, whilst not strictly necessary is perhaps justifiable as there is a reasonable probability of PA being present. However, a more conservative approach in which IV aminoglycosides are withheld until PA has been demonstrated would subject the child to lower risks of complications and protect them from harm; upholding one of the central tenets of medical ethics, *primum non nocere.* It is even more difficult to justify the use of aminoglycosides as first line therapy in all children with CF given their well-established toxicity. Presumably tobramycin and ceftazidime are being used in this situation ‘just in case’ there is a hitherto unidentified PA infection. If this were the case, the logic is somewhat flawed as there is a high risk of eradiation being unsuccessful without addition of a nebulised anti-PA antibiotic. We acknowledge the limitations of this survey. In particular, it will not have identified variation in clinical practice between clinicians at individual centres or identified those children in whom the antibiotic regimen is changed mid-course due to microbiology results.

Overreliance on IV aminoglycoside antibiotics increases the risks to children with CF with no additional benefit in the absence of PA infection. This raises the possibility that UK clinicians lack confidence in the current diagnostic options to identify pulmonary PA infection in children. Given the proven sensitivity and feasibility of induced sputum and flexible bronchoscopy[5] we advocate considering one of these investigations in children with an infective exacerbation unwell enough to warrant IV antibiotics but with no identified organism.

**Conflict of Interest Statement**

The authors do not have any conflicts of interest to declare.

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Figure 1A: Number of UK CF centres using different IV antibiotic regimens as first line treatment for infective pulmonary exacerbations in children with CF who have an A) never grown *Pseudomonas aeruginosa* (PA) and B) are free of PA for >12 months.

