Should we stop using intravenous gentamicin in patients with cystic fibrosis?

Christopher H Goss

Patients with cystic fibrosis (CF) have shown continual annual improvement in survival in many countries.[1–4] The improvements in outcome have been attributed to better treatments and a multidisciplinary approach to care focused in care centres with specific expertise in CF.[5–8] As survival improves, we may start increasingly to see adverse events related to intensive treatments used to battle the chronic airway infections and airway inflammation in CF.

Because of chronic lung infections, patients with CF receive repeated courses of oral, inhaled and intravenous antibiotics, some of which are known to be nephrotoxic drugs such as aminoglycosides. The primary defect in CF, the cystic fibrosis transmembrane regulator protein (CFTR), is expressed in the kidney but its function is unknown.[9] In this issue of *Thorax*, Smyth and colleagues[10] present data on the association of intravenous aminoglycosides—particularly gentamicin—and acute renal failure (ARF) in the UK (***see page 532***). The authors have published a previous report in *Thorax* in which they established an incidence of ARF in CF of 4.6–10.5 cases per 10 000 patients per year.[11] The associated use of aminoglycosides and renal failure in this population seemed clear, and most of the patients with ARF had received intravenous gentamicin treatment. In their current paper the authors have moved forward to assess these associations more formally by conducting a case-control study to determine which factors were associated with an increased risk of ARF in these patients. They found that intravenous aminoglycoside use (particularly gentamicin) was associated with ARF, with an odds ratio of 81.8 (95% CI 4.7 to 1427). When they evaluated aminoglycoside use during the previous year, gentamicin (and not tobramycin) was associated with ARF (gentamicin: 19/24 cases vs 1/42 controls, $p<0.001$; tobramycin: 9/24 cases vs 15/42 controls, $p = 0.9$). They also found that known risk factors for renal impairment were more common in cases than in controls (OR 24.0, 95% CI 3.1 to 186.6). Interestingly, they did not find a relationship between cumulative exposure to aminoglycosides in the preceding year and the development of ARF.

These findings are certainly a concern for patients with CF and their care providers. But is the strength of this evidence enough to markedly reduce intravenous aminoglycoside use and, more specifically, to abandon the use of gentamicin?

WHAT IS KNOWN ABOUT RENAL FAILURE IN CF?

Patients with CF clearly have risk factors for developing ARF, given their repeated doses of nephrotoxic agents (particularly aminoglycides), the moderate rates of CF-related diabetes and the predisposition for salt imbalances and dehydration. Previous case reports have noted cases of ARF or acute renal insufficiency associated with oral ciprofloxacin,[12 13] inhaled tobramycin[14] and intravenous aminoglycosides (both tobramycin and gentamicin).[11 15 16] More comprehensive studies of renal function in patients with CF are limited and include one study which carefully documented creatinine clearance in a population of patients with CF in Liverpool, UK.[17] Al-Aloul and colleagues found 42.5% of a consecutive cohort of patients with CF had a 24 h creatinine clearance rate below the normal range and there was an inverse association between the number of antibiotic courses and the creatinine clearance rate. This same group also found eight cases of ARF associated with an epidemic strain of *Pseudomonas* noted in their centre.[16] Smyth and colleagues have added substantially to this area of CF care by first conducting a careful prevalence study of ARF across CF centres as noted above,[11] and then by following this with a case-control study in this issue of *Thorax*.[10]

WHAT ARE THE LIMITATIONS OF CASE-CONTROL STUDIES?

To decide how to weigh the merits of any given study, one must fully understand the strengths and weaknesses inherent to the study design.[18 19] Case-control studies are ideal for evaluating rare outcomes (such as ARF in CF) and can provide an efficient and economical method to assess a potential association between a covariate and an outcome. Case-control studies yield odds ratios (OR) (a term often confused by readers as synonymous with risk ratios or relative risks) and, unfortunately, suffer from more opportunities for the introduction of bias and mistaken inference.[20 21] Case-control studies start with the outcome and work backwards to the predictor. This *retrospective* assessment of the predictor is one of the potential limitations of this study design. Other important limitations of the study design relate to the selection of controls and the assessment of the predictors of interest or exposures.[19 22] Ideally, the cases are all those with the outcome in a population (however, often it represents a sample of this population). The controls should be drawn from the same population and be at risk for the outcome; controls also need to be chosen independent of exposure.[18] Assessment of the exposure in both the cases and controls can be fraught with biases including recall bias and information bias. The primary means of addressing this limitation if a study involves chart review is standardised assessments of the chart review and blinding of chart reviewers to the status of the subject (case or control).

As in all observational studies, another problematic issue is confounding. Confounders are characteristics of study subjects that are associated with the exposure and the outcome that can have an impact on the association between the predictor and the outcome. To address confounding in case-control studies, investigators either restrict the population (if gender is a confounder, only evaluate one gender), matching on confounder (can no longer assess the impact of the confounder) or adjustment in the analysis using logistic regression or stratification with Mantel-Haenszel approaches.[19 23] One of the methodologies frequently used in case-control studies is matching; matching in this study design has been shown potentially to increase bias due to misclassification or overmatching.[21 24 25] Whenever matching is done in case-control studies, investigators must adjust for the matching variables to ensure no bias is

Correspondence to: Dr C H Goss, Division of Pulmonary and Critical Care Medicine, Department of Medicine, University of Washington Medical Center, Campus Box 356522, 1959 N E Pacific, Seattle, WA 98195, USA; goss@u.washington.edu

inadvertently introduced into the study.[21 26] If potential confounders were not collected during data acquisition or cannot be collected retrospectively, the results could be affected by residual confounding.

Smyth and colleagues[10] have conducted a careful case-control study with attention to these potential limitations. They first conducted a national survey to find cases,[11] defined as those with a raised plasma creatinine level for age with or without oliguria and a confirmed diagnosis of CF. Patients who had undergone organ transplantation were excluded. Controls were selected based on an age- and gender-matched sample drawn from the UK CF database at a ratio of four controls for each case. Exposure data were extracted from the cases and controls using a standard proforma. They effectively matched the date by collecting data on controls at the index date of ARF.

Several issues may affect one's interpretation of this study. First, the actual control population represents less than half of the randomly matched control population (42 of 96 subjects). The 42 controls in the study could have systematically differed from the 54 controls not in the study, particularly because prescribing patterns could have differed at centres not represented in the control population but present in the case population. Chart abstracters did use a standardised assessment, but they were not blinded to the disease state (case or control). The authors acknowledge these important limitations. In the analysis phase the authors used both conditional logistic regression and stratified Mantel-Haenszel analysis across strata of matched cases and controls. However, they did not adjust for calendar time. Because of the sample size, the authors could not adjust for potential confounders such as severity of illness (which might be highly associated with a prior history of receiving aminoglycosides and other potential nephrotoxic agents). There also may be effects driven by one or two specific centres (the eight cases of ARF noted at one centre).[16] Lastly, no data are available regarding drug levels, which may or may not explain the association found. The goal of case-control studies is to be able to infer causality between a predictor and an outcome variable. If bias is potential, would the bias affect the interpretation of the study? Bias favouring the null hypothesis in the current case would negate the concern over the presence of such biases. The limitations listed above could have significantly biased the results in favour of rejecting the null hypothesis (particularly in the case of the effect of intravenous gentamicin).

IS THERE ENOUGH EVIDENCE TO INITIATE A MORATORIUM ON THE USE OF INTRAVENOUS GENTAMICIN IN CF?

I believe that, while the present evidence is concerning, it does not support the call to ban the use of intravenous gentamicin in the CF population. Other countries should carefully evaluate their data regarding ARF and aminoglycoside use (particularly gentamicin) to see if similar associations are noted. Similar findings would raise concern that, indeed, something is unique about the ability of gentamicin to be more nephrotoxic than tobramycin.

Intravenous aminoglycosides remain an important treatment option for patients with CF. The anti-pseudomonal activity of this class of agents will continue to be important until more alternatives are available. What is clear from this work is that more careful assessment of renal function is warranted in patients with CF who receive intravenous aminoglycosides. Pre-existing risk factors for renal dysfunction should be mitigated before initiating aminoglycosides. All treatments have side effects, many of which only occur rarely. As the person-years of observation on those treatments increase, clinical researchers in CF must vigilantly reassess all of our interventions to ensure that we fully understand the risks that such treatments pose to our patients.

Competing interests: None.

Thorax 2008;**63**:479–480. doi:10.1136/thx.2007.094821

REFERENCES

1. **Cystic Fibrosis Foundation**. *Patient Registry 2006: annual data report*. Bethesda, MD: Cystic Fibrosis Foundation, 2007.
2. **Dodge JA,** Lewis PA, Stanton M, *et al*. Cystic fibrosis mortality and survival in the UK: 1947–2003. *Eur Respir J* 2007;**29**:522–6.
3. **Bellis G,** Cazes MH, Parant A, *et al*. Cystic fibrosis mortality trends in France. *J Cyst Fibros* 2007;**6**:179–86.
4. **Slieker MG,** Uiterwaal CS, Sinaasappel M, *et al*. Birth prevalence and survival in cystic fibrosis: a national cohort study in the Netherlands. *Chest* 2005;**128**:2309–15.
5. **Ramsey BW,** Pepe MS, Quan JM, *et al*. Intermittent administration of inhaled tobramycin in patients with cystic fibrosis. Cystic Fibrosis Inhaled Tobramycin Study Group. *N Engl J Med* 1999;**340**:23–30.
6. **Fuchs HJ,** Borowitz DS, Christiansen DH, *et al*. Effect of aerosolized recombinant human DNase on exacerbations of respiratory symptoms and on pulmonary function in patients with cystic fibrosis. The Pulmozyme Study Group. *N Engl J Med* 1994;**331**:637–42.
7. **Saiman L,** Marshall BC, Mayer-Hamblett N, *et al*. Azithromycin in patients with cystic fibrosis chronically infected with Pseudomonas aeruginosa: a randomized controlled trial. *JAMA* 2003;**290**:1749–56.
8. **Elkins MR,** Robinson M, Rose BR, *et al*. A controlled trial of long-term inhaled hypertonic saline in patients with cystic fibrosis. *N Engl J Med* 2006;**354**:229–40.
9. **Morales MM,** Carroll TP, Morita T, *et al*. Both the wild type and a functional isoform of CFTR are expressed in kidney. *Am J Physiol* 1996;**270**:F1038–48.
10. **Smyth A,** Lewis S, Bertenshaw C, *et al*. Case-control study of acute renal failure in patients with cystic fibrosis in the UK. *Thorax* 2008;**63**:532–5.
11. **Bertenshaw C,** Watson AR, Lewis S, *et al*. Survey of acute renal failure in patients with cystic fibrosis in the UK. *Thorax* 2007;**62**:541–5.
12. **Moffett BS,** Rosenstein BJ, Mogayzel PJ Jr. Ciprofloxacin-induced renal insufficiency in cystic fibrosis. *J Cyst Fibros* 2003;**2**:152–4.
13. **Bald M,** Ratjen F, Nikolaizik W, *et al*. Ciprofloxacin-induced acute renal failure in a patient with cystic fibrosis. *Pediatr Infect Dis J* 2001;**20**:320–1.
14. **Hoffmann IM,** Rubin BK, Iskandar SS, *et al*. Acute renal failure in cystic fibrosis: association with inhaled tobramycin therapy. *Pediatr Pulmonol* 2002;**34**:375–7.
15. **Drew J,** Watson AR, Smyth A. Acute renal failure and cystic fibrosis. *Arch Dis Child* 2003;**88**:646.
16. **Al-Aloul M,** Miller H, Stockton P, *et al*. Acute renal failure in CF patients chronically infected by the Liverpool epidemic Pseudomonas aeruginosa strain (LES). *J Cyst Fibros* 2005;**4**:197–201.
17. **Al-Aloul M,** Miller H, Alapati S, *et al*. Renal impairment in cystic fibrosis patients due to repeated intravenous aminoglycoside use. *Pediatr Pulmonol* 2005;**39**:15–20.
18. **Schulz KF,** Grimes DA. Case-control studies: research in reverse. *Lancet* 2002;**359**:431–4.
19. **Grimes DA,** Schulz KF. Compared to what? Finding controls for case-control studies. *Lancet* 2005;**365**:1429–33.
20. **Bjerre LM,** LeLorier J. Expressing the magnitude of adverse effects in case-control studies: "the number of patients needed to be treated for one additional patient to be harmed". *BMJ* 2000;**320**:503–6.
21. **Rothman KJ,** Greenland S. *Modern epidemiology*. 2nd ed. Philidelphia: Lippincott-Raven Publishers, 1998.
22. **Olson SH,** Voigt LF, Begg CB, *et al*. Reporting participation in case-control studies. *Epidemiology* 2002;**13**:123–6.
23. **Sorensen HT,** Gillman MW. Matching in case-control studies. *BMJ* 1995;**310**:329–30.
24. **Greenland S.** The effect of misclassification in matched-pair case-control studies. *Am J Epidemiol* 1982;**116**:402–6.
25. **Thomas DC,** Greenland S. The relative efficiencies of matched and independent sample designs for case-control studies. *J Chronic Dis* 1983;**36**:685–97.
26. **Garabrant DH.** Case-control study design: spurious associations between exposure and outcome. *J Occup Environ Med* 2007;**49**:941–2.