CYSTIC FIBROSIS

Survey of acute renal failure in patients with cystic fibrosis in the UK

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Background: There has been a recent increase in the number of reported cases of acute renal failure (ARF) in cystic fibrosis (CF). A study was undertaken to determine the incidence risk of ARF in patients with CF in the UK and to identify possible aetiological factors.
Methods: All doctors working at UK CF centres were asked if they had been involved with the management of a patient with CF who had developed ARF. Those responding positively were asked to request informed consent for entry into the study and the patient's case notes were then reviewed. The analysis was restricted to patients developing ARF between 1997 and 2004. A second questionnaire sought information on aminoglycoside prescribing practice.
Results: Responses were received from 55 of 56 centres with 64 reports, 9 of which were duplicates, leaving 55 cases. Consent was obtained for data extraction in 26 cases, of which 24 fitted the criteria for ARF (verified data). Median age at presentation with ARF was 9.7 years (range 0.4–31.8) and 12 cases were male. The incidence risk of ARF was 4.6 (verified data) to 10.5 cases (all data)/10 000 CF patients/year. In 21 cases (88%) an aminoglycoside was prescribed at onset of ARF or in the preceding week; 16 (76%) of those receiving an aminoglycoside had gentamicin. A renal biopsy was performed in 7 cases and histological examination revealed acute tubular necrosis in 6, all of whom had received gentamicin. Renal dialysis was required in 13 cases (54%). Complete recovery was seen in 22/24 patients (92%).
Conclusions: ARF is increasingly being recognised in patients with CF. There is significant morbidity with most patients requiring dialysis. This study implicates intravenous aminoglycosides, particularly gentamicin, in the aetiology of ARF in CF.

Until recently there have been no case reports of acute renal failure (ARF) in cystic fibrosis (CF). This is surprising as these patients are prescribed frequent and repeated courses of antibiotics which are associated with drug-induced nephrotoxicity. In addition, non-steroidal anti-inflammatory drugs (NSAIDs), which can also be nephrotoxic, may be prescribed in an attempt to slow the decline in pulmonary function and as symptomatic treatment of arthropathy.

The registry of the Nottingham supraregional paediatric renal unit (catchment area population of 6 million) shows no cases of ARF in patients with CF between 1985 and 1998. However, since 1999 six cases have been referred and, in each case, there was a history of treatment with gentamicin and a cephalosporin.[1 2] There have been other reports of renal failure in patients with CF treated with gentamicin and ceftazidime,[3 4] with ciprofloxacin,[5 6] following concomitant use of an aminoglycoside and ibuprofen[7 8] and with nebulised tobramycin.[9] ARF has also been reported in adults with CF, associated with dehydration during hot weather.[10] More recently, Al-Aloul *et al* reported eight cases of ARF in adult patients with CF, all of whom were prescribed an aminoglycoside, six in combination with intravenous colistin. A number of their patients had also received NSAIDs.[11]

In the light of the recent increase in the number of reported cases of ARF in CF, we conducted a national questionnaire survey and case note review to estimate its incidence risk in the UK and to identify potential aetiological factors.

METHODS

A questionnaire was sent to all consultant paediatricians and physicians in each UK specialist CF centre listed by the UK CF Trust asking: (1) Have you ever been involved with the management of a patient with CF who has developed ARF? (2) In what year did the patient present? (3) Did the patient receive dialysis? (4) Have you any other comments you wish to make? Those doctors who reported a case were contacted again and asked to seek consent from each patient and/or their guardian for the case notes to be examined by a researcher and, if appropriate thereafter, for inclusion in the study. For pragmatic reasons, we elected to confine data extraction to cases occurring in the 8 year period from 1997 to 2004 inclusive.

After written informed consent was obtained, the hospital records of each patient were scrutinised by a visiting researcher (CB) and the reported case of ARF evaluated for inclusion in the study. The inclusion criteria were: (1) the presence of ARF, defined as raised plasma creatinine for age with or without oliguria; and (2) a prior diagnosis of CF made by sweat test or genotyping in a patient with clinical features of CF. Patients who had undergone solid organ transplantation were excluded. There were no other exclusion criteria.

A detailed demographic and clinical dataset was extracted on each case enrolled and recorded on a case record form before entry on an electronic database. Data were collected on past drug history, recognised risk factors for ARF, drug history at the time of ARF, management of the episode of ARF and outcome. Data missing from the case notes were requested by letter from the reporting clinician and from other doctors involved with the case. In addition, each clinician originally surveyed was sent a second questionnaire. This requested information on the number of patients attending the centre; number of courses of intravenous antibiotics; which aminoglycosides were used;

Abbreviations: ARF, acute renal failure; CF, cystic fibrosis; NSAID, non-steroidal anti-inflammatory drug

Table 1 Age, sex and risk factors for acute renal failure (ARF)

No	Age (y)	Sex	Aminoglycoside	Prior/concurrent*	Ceftazidime	Nebulised antibiotic†	Other nephrotoxic drug	Other risk factor
1	0.4	M	Gentamicin	Prior	Yes	Colistin (e)		Diarrhoea and vomiting
2	21.1	F	Gentamicin	Concurrent	Yes	Colistin (e)	Diclofenac (c)	
3	6.9	M	Gentamicin then tobramycin	Prior/concurrent	Yes	None		
4	5.0	M	Gentamicin	Concurrent	Yes	None		Fever
5	5.7	M	Gentamicin	Concurrent	No	Gentamicin (c)		Neonatal renal cortical necrosis
6	11.9	F	Tobramycin	Concurrent	No	Colistin (c)	Ibuprofen (c)	Fever
7	4.4	M	Gentamicin	Prior	Yes	Colistin (e)		
8	18.6	F	None			Colistin (c)		'Flu-like illness following oral rifampicin and ciprofloxacin. CFRD
9	12.3	F	Gentamicin	Prior	Yes	Tobramycin (c)	Ciclosporin (e)	
10	17.0	F	Tobramycin	Concurrent	No	Colistin (c)		Toxic shock. *Clostridium difficile* toxin in stool
11	31.8	F	Gentamicin	Prior	Yes	Gentamicin (e)		CFRD and diabetic nephropathy
12	9.6	M	Gentamicin	Concurrent	Yes	Colistin (c)	Ciclosporin (c)	CFRD
13	3.6	M	Gentamicin	Concurrent	Yes	Colistin (c)		Diarrhoea and vomiting
14	7.4	M	Gentamicin	Prior	Yes	Colistin (c)		Previous pseudo Barter's syndrome
15	9.8	M	Tobramycin	Concurrent	No	Gentamicin (e)	Indomethacin (c)	
16	15.0	M	Tobramycin	Concurrent	No	Tobramycin (c)		CFRD, ventilated, MRSA septicaemia
17	15.9	F	Tobramycin	Concurrent	No	Colistin (c)	Colistin (IV)	CFRD
18	9.8	M	Gentamicin	Concurrent	No	None	Naproxen (e) and diclofenac (e)	Constipation, osmotic laxatives
19	3.6	M	Gentamicin	Concurrent	Yes	Colistin (c)		Gastro-oesophageal reflux, vomiting
20	12.1	F	None			None	Naproxen (c)	RhF +ve arthritis
21	17.3	F	None			Colistin (e)		CFRD
22	8.0	F	Gentamicin	Prior	Yes	Colistin (c)		
23	8.0	F	Gentamicin	Concurrent	Yes	Colistin (c)		
24	9.0	F	Gentamicin	Prior	Yes	Colistin (c)		

c, concurrent; e, ever; IV, intravenous; CFRD, cystic fibrosis-related diabetes; MRSA, methicillin-resistant *Staphylococcus aureus*;
*Timing of aminoglycoside in relation to ARF: concurrent, at the time ARF diagnosed; prior, within the week prior to ARF.
†Patients receiving nebulised tobramycin had intravenous solution in nebulised form.

which dosing regimen and whether any changes had taken place in the last 10 years.

The study protocol was approved by the North-West Multi Centre Research Ethics Committee (MREC) and by the relevant local research ethics committees and hospital Research and Development (R&D) departments.

Statistical methods

Continuous variables were expressed as medians with ranges. Categorical variables were expressed as prevalence and percentages.

RESULTS

Incidence risk of ARF in patients with CF

The initial questionnaire was sent to 99 doctors in 56 UK CF centres (30 paediatric and 26 adult). Responses were received from 94/99 doctors and 55/56 centres. Of the 56 centres surveyed, 38 reported experience of ARF in patients with CF. There were 64 reports between 1997 and 2004. Nine were duplicates, leaving 55 cases. Informed consent for study screening and enrolment was obtained in 26 of the 55 cases. All 26 sets of case notes were reviewed and in 24 of these the enrolment criteria were satisfied and data were extracted for further analysis. The excluded cases were an adult with nephrotic syndrome without evidence of ARF, and a child with a transient rise in creatinine which did not exceed the upper limit of normal.

In 2001, 6558 patients in the UK were registered with the UK CF database, with figures for 2002 and 2003 indicating a stable population.[12] Over the 8 year period of our study the 24 verified cases and 55 reported cases give a mean annual number of cases of 3 and 6.9 per annum, respectively. Based on a UK CF population of 6558, this gives an incidence risk of between 4.6 and 10.5 cases of ARF/10 000 CF patients/year, depending on whether the verified cases or all the reported cases are used as the numerator. The 24 cases came from 20 centres; 17 recruited one case, two recruited two cases and one recruited three cases.

Risk factors for ARF

Table 1 shows the age, sex and risk factors for ARF in the 24 patients studied. In 21 cases there was a history of aminoglycoside administration at the time of onset of ARF or in the preceding week. Of those who had an aminoglycoside, 15 (71%) had gentamicin and 5 (24%) had tobramycin (one patient had both). The most common antibiotic combination was gentamicin and ceftazidime (14 patients). As well as receiving an aminoglycoside, patient 9 had received ciclosporin 2 years previously (for comorbid asthma) and patient 12 was currently having ciclosporin (for allergic bronchopulmonary aspergillosis). Of the three cases who did not receive an aminoglycoside, patient 8 had a suspected hypersensitivity reaction while on oral rifampicin, ciprofloxacin and azithromycin; patient 20 was receiving regular naproxen (for rheumatoid factor positive arthritis); and patient 21 had CF-related diabetes but no other risk factors for ARF.

Table 2 shows the dosing regimen, recorded levels and previous exposure to aminoglycosides. The maximum recommended dose of gentamicin or tobramycin in UK guidelines is 12 mg/kg/day,[13] and this was exceeded in eight cases. Two patients received once daily aminoglycosides. Eight patients received treatment with an intravenous aminoglycoside for

Table 2 Dosing regimen, recorded levels & previous exposure to aminoglycosides

No.	Aminoglycoside	Dose/kg	Times/day	Duration of IV aminoglycoside*	Maximum trough aminoglycoside level	Previous aminoglycosides	No. previous courses of IV antibiotics†	Interval since last IV aminoglycoside (months)
1	Gentamicin	2.91	3	15	1.6	No	0	
2	Gentamicin	5.06	3	27	11.0	Yes	35	3
3	Gentamicin + tobramycin	3.92	3	10	9.8	Yes	1	8
4	Gentamicin	4.29	3	11	1.0	Yes	1	30
5	Gentamicin	2.52	3	9	5.9	No	0	
6	Tobramycin	4.08	2	3	0.2	Yes	13	2
7	Gentamicin	4.19	3	17	0.7	Yes	8	1
8	None					Yes	25	6
9	Gentamicin	NR	NR		13	Yes	22	11
10	Tobramycin	3.25	3	15	0.9	Yes	25	2
11	Gentamicin	2.58	1	13	<1	Yes	72	4
12	Gentamicin	3.33	3	11	1.8	Yes	15	4
13	Gentamicin	5.16	3	14	1.3	No	0	
14	Gentamicin	4.16	3	15	2.1	No	0	
15	Tobramycin	4.49	3	49	2.9	Yes	25	3
16	Tobramycin	10.00	1	34	0.2	Yes	14	7
17	Tobramycin	4.12	3	6	5.6	Yes	15	2
18	Gentamicin	3.29	3	7	<1	Yes	35	12
19	Gentamicin	3.98	3	11	<1	Yes	6	7
20	None					Yes	5	4
21	None					Yes	15	2
22	Gentamicin	3.70	3	10	6.7	Yes	2	8
23	Gentamicin	3.33	3	9	4.5	Yes	2	8
24	Gentamicin	3.28	3	19	2.1	Yes	2	59

IV, intravenous; NR, not recorded.
*Not always possible to determine from the case notes whether a course of treatment included an aminoglycoside.

more than 2 weeks (median duration 13 days, range 3–49). In nine patients a trough aminoglycoside level above the recommended value of 2 mg/l was recorded,[14] but in some cases this was after the onset of renal failure. Twenty patients had received one or more courses of intravenous antibiotics previously (median 11 courses, range 0–72). The median interval between the patient developing ARF and their previous course of antibiotics (including an aminoglycoside) was 5 months (range 1–59).

Management and outcome of ARF

Fourteen patients had a renal ultrasound scan at the time of ARF but the findings were not diagnostic (table 3). No renal stones were reported. Acute tubular necrosis was seen in six of seven renal biopsies (with co-existing interstitial nephritis in one) and all these patients had been treated with gentamicin. The remaining biopsy (patient 20) showed post-infectious glomerulonephritis. In all cases the maximum serum creatinine level was raised above the upper limit of normal for age

Table 3 Management and outcome of ARF

No	Renal ultrasound scan	Biopsy*	Urine output	Max creatinine (μmol/l)	Dialysis†	Duration (days)
1	Enlarged; consistent with ATN	No	Not recorded	494	PD	4
2	Enlarged; consistent with ATN or PIGN	No	Not recorded	727	No	
3	Not done	ATN	Anuric	678	PD	13
4	Enlarged and echogenic	No	Anuric	768	HD	5
5	Small and bright cortex	No	Not recorded	161	No	
6	Not done	No	Normal	183	No	
7	Not done	ATN	Oliguric	874	PD	6
8	Normal	No	Normal	768	No	
9	Not done	ATN	Oliguric	1492	PD	20
10	Enlarged and echogenic	No	Anuric	886	CVVH	11
11	Normal	No	Not recorded	864	HD	5
12	Echogenic	No	Not recorded	288	No	
13	Enlarged and echogenic	No	Anuric	669	HD	NR
14	Not done	ATN	Oliguric	782	HD	4
15	Not done	No	Normal	143	No	
16	Not done	No	Polyuric	241	HF and HD	23
17	Not done	No	Not recorded	168	No	
18	Not done	ATN	Oliguric	850	No	
19	Echogenic	No	Anuric	436	HD	3
20	Normal	PIGN	Not recorded	124	No	
21	Not done	No	Normal	229	No	
22	Enlarged and echogenic	No	Anuric	891	PD	9
23	Normal	No	Normal	542	No	
24	Echogenic	ATN and IN	Oliguric	1972	HD and PD	13

NR, not recorded.
*Biopsy appearances: ATN, acute tubular necrosis; PIGN, post infectious glomerular nephritis. IN, interstitial nephritis.
†Dialysis: PD, peritoneal dialysis; HD, haemodialysis; CVVH, continuous venovenous haemofiltration; HF, haemofiltration.

(median 674 μmol/l, range 124–1972). Serum magnesium levels were recorded in 14 cases and 2 cases had hypomagnesaemia (<0.7 mmol/l). Thirteen patients (54%) had dialysis, all of whom had been given an intravenous aminoglycoside shortly before the onset of ARF. Complete data on duration of dialysis were available in 12 cases (median 7.5 days, range 3–23). Several months after the episode of ARF 22 of the 24 patients had made a full recovery. Patient 11 required long term dialysis but had biopsy evidence of diabetic nephropathy prior to the episode of ARF. Patient 20 required long-term antihypertensive treatment. Patients 4 and 13 had minor high frequency sensorineural hearing loss at follow-up (both had received gentamicin). Follow-up audiograms were not widely performed.

Aminoglycoside prescribing patterns

Replies were received from 44/56 centres to the second questionnaire requesting information regarding aminoglycoside prescribing practice. Gentamicin was used in 13 centres (30%) and tobramycin in 37 (84%) (6 centres used both). In the centres using gentamicin, 8 used a three times daily dosing regimen. In the centres preferring tobramycin, 26 prescribed a once daily regimen.

DISCUSSION

This study has enabled us to estimate the incidence risk of ARF in CF at between 4.6 and 10.1 cases/10 000 CF patients/year. The overall incidence of ARF in children is estimated as 7.5/million/year[15] and in adults 125/million/year.[16] The risk of renal failure in patients with CF is therefore considerably greater than the background rate (approximately 100 times greater in children). Although the cystic fibrosis transmembrane conductance regulator (CFTR) is expressed throughout the nephron, it is not known to cause impairment in renal function.[17] It is therefore likely that ARF occurs as a complication of comorbid disease or treatment. In over half of the cases a previous or current comorbid condition may have increased susceptibility to renal failure. We found that 88% of cases had received an aminoglycoside intravenously at the time of onset of ARF or in the preceding week, often in combination with a cephalosporin. It is noteworthy that, while 71% of the cases who developed ARF after receiving an aminoglycoside had gentamicin, only 13/44 (30%) of UK CF centres reported using gentamicin during this time period. Of the cases who went on to require dialysis, all had received an aminoglycoside. All but two patients had normal renal function on follow-up, but the glomerular filtration rate was measured in only one patient (in whom it was reduced) and mild or moderate renal impairment in other patients cannot be ruled out.

A total of 34 patients with CF who have developed ARF are reported in the world literature (16 children and 18 adults).[1–11] Individual case series do not allow estimates of disease incidence; this requires a systematic survey. Our study is the first report of a national survey, it is the largest single case series, and it gives the first estimate of the incidence of ARF in patients with CF. The earliest report of ARF in patients with CF was published in 1998, which suggests that either this is a new complication in CF or that awareness of the problem has increased in recent years, prompting clinicians to report the association. The fact that our own paediatric renal unit (covering a population of 6 million) had managed no cases of ARF in patients with CF before 1998 supports the suggestion that this is a new phenomenon. Most patients with CF who develop ARF need dialysis and all patients in our catchment area requiring dialysis are referred to our unit, so it is unlikely that cases were missed before 1998. As well as frank renal failure, there is evidence that patients with CF are susceptible to subclinical renal impairment. Al-Aloul *et al* reported that 31–42% of adults with CF in their unit had reduced creatinine clearance, and this correlated strongly with the number of previous courses of aminoglycosides.[18]

We experienced difficulty in obtaining informed consent from patients or their parents/guardians for inclusion in the study. Some patients had moved on and could not be traced. In some cases the patient could not be approached for consent because they were acutely ill or the local CF team did not have time to explain the study and request consent. Hence the number of cases initially reported (n = 55) was considerably less than the number of case notes reviewed (n = 26). It was a requirement of ethics approval that the local CF team requested consent, so we could not do this directly. These difficulties are inherent in any national survey, but the fact that not all of the case notes were examined weakens the generalisability of our findings and means that we can only describe the range wherein the incidence risk of ARF in patients with CF may lie.

Only 5/24 patients (21%) were over 16 years of age at the time of their ARF, whereas there are approximately equal numbers of children and adults with CF in the UK.[12] One would expect that there should be more adults developing ARF because of factors such as cumulative aminoglycoside exposure and CF-related diabetes which increase with age. A large adult centre has since independently reported eight cases of ARF.[11] If these cases were added to our case series, then 13/32 patients (41%) would be over 16 years of age at the time of ARF, which is close to an equal distribution of cases in children and adults.

Aminoglycosides are widely prescribed to patients with CF and are likely to retain an important role in the management of CF lung disease for the foreseeable future. Tobramycin in particular remains highly active against *Pseudomonas aeruginosa*,[19] has been shown to penetrate effectively into the sputum of patients with CF[20] and acts synergistically with β-lactam antibiotics.[21] A once daily dosing regimen is becoming more widely used in UK CF centres. The TOPIC study found that once daily dosing with tobramycin was as effective as thrice daily dosing and may be less nephrotoxic in children.[22] These findings are supported by a Cochrane systematic review.[23] These agents should be prescribed and treatment monitored with care in order to ensure optimal efficacy while minimising the risk of nephrotoxicity. There is no general consensus regarding screening for aminoglycoside-induced toxicity. When prescribing once daily tobramycin, the UK CF Trust recommends that renal function should be checked before the first dose and again before the eighth dose, and trough tobramycin levels taken before the second and eighth doses.[24] If no dosage adjustment is required, all tests should be repeated weekly while the aminoglycoside is continued. In addition, patients should be advised not to take a NSAID while receiving an intravenous aminoglycoside. In view of the significant number of patients with subclinical impairment of renal function reported by Al-Aloul *et al*,[18] it may be sensible to consider measuring the glomerular filtration rate at the annual assessment in patients who have received multiple courses of aminoglycosides.

Patients with CF are commonly prescribed large numbers of drugs, many of which may be nephrotoxic either alone or in combination. In addition, they may have comorbid conditions which further increase their risk of renal impairment. The data on aminoglycoside prescribing practices in CF centres must be interpreted with caution as this is based on questionnaire report alone. However, this study does suggest that the use of intravenous aminoglycosides, particularly gentamicin, has an important role in the aetiology of ARF in CF. We plan to test this hypothesis in a forthcoming case-control study which we hope will enable firmer inferences to be drawn regarding the

causation of ARF in CF and allow avoidable precipitating factors to be identified.

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