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A survey of acute renal failure in cystic fibrosis patients in the United Kingdom

Corresponding Author: Alan Smyth

Institution: Division of Child Health, University of Nottingham, UK
Address: Clinical Sciences Building
Nottingham City Hospital
Hucknall Road
Nottingham
NG5 1PB
United Kingdom
Email: alan.smyth@nottingham.ac.uk
Tel: +44 115 823 1703
Fax: +44 115 823 1946

First Author:
Carol Bertenshaw: Department of Paediatrics, Nottingham City Hospital, UK.

Co-authors:
Alan R Watson: Department of Paediatrics, Nottingham City Hospital, Nottingham, UK.
Sarah Lewis: Academic Division of Respiratory Medicine, University of Nottingham, Nottingham, UK.
Alan Smyth: Division of Child Health, University of Nottingham, Nottingham, UK.

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Authors: Carol Bertenshaw, Alan Watson, Sarah Lewis, Alan Smyth

ABSTRACT

Background: There has been a recent increase in the number of reported cases of acute renal failure (ARF) in cystic fibrosis (CF). We sought to determine the incidence risk of ARF in patients with CF in the UK and to identify possible aetiological factors.

Methods: We asked all doctors working at UK CF Centres 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. The patient's case notes were then reviewed by a researcher. We restricted the analysis to patients developing ARF between 1997 & 2004. A second questionnaire sought information on aminoglycoside prescribing practice.

Results: Responses were received from 55/56 centres, with 64 reports in 1997-2004, and 9 duplicates, leaving 55 cases. Consent was obtained for data extraction in 26 cases, of which 24 fitted our 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 between 4.6 (verified data) and 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. Sixteen (76%) of those receiving an aminoglycoside had gentamicin. A renal biopsy was performed in 7 cases and in 6 histological examination revealed acute tubular necrosis. Each of these latter cases had received gentamicin. Renal dialysis was required in 13 cases (54%). A compete recovery was seen in 22/24 (92%) patients (normotensive and not requiring dialysis at follow up).

Conclusions: There is increasing recognition of ARF in patients with CF and there is a significant morbidity with the majority of patients requiring dialysis. This study implicates intravenous aminoglycosides, particularly gentamicin, in the aetiology of ARF in CF. We plan to test this hypothesis in a forthcoming case control study.

INTRODUCTION

Until recently there have been no case reports of acute renal failure (ARF) in cystic fibrosis (CF). This is surprising as this patient group 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 supra-regional paediatric renal unit (catchment area population of 6 million) shows no cases of ARF in CF patients 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 8 cases of ARF in adult patients with CF, all of whom were prescribed an aminoglycoside; 6 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 United Kingdom (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 elevated plasma creatinine for age with or without oliguria and
2. A prior diagnosis of CF having been made by sweat test or by 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; 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 (LREC) 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 CF patients:

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 CF patients. 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 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 centres recruited 1 case; 2 centres recruited 2 cases and 1 centre recruited 3 cases.

Risk factors for ARF:

Table 1 shows the age, sex and risk factors for ARF in the 24 patients studied. In 21/24 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 two years previously (for co-morbid 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 whilst 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 8 cases. Two patients received once daily aminoglycosides. Eight patients received more than 2 weeks of intravenous aminoglycoside treatment (median duration 13 days, range 3-49 days). In 9 patients a trough aminoglycoside level above the recommended value of 2 mg/L[14] was recorded 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 months).

Management & 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 6 of 7 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 (median 674 micromol/L, range 124-1972 micromol/L). Serum magnesium was recorded in 14 cases and 2 cases had hypomagnesaemia (< 0.7mmol/l). Thirteen patients (54%) had dialysis and each of these had been given an intravenous aminoglycoside shortly before the onset of ARF. There was complete data on duration of dialysis in 12 cases (median 7.5 days, range 3-23 days). Several months after the episode of ARF, 22/24 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:

We received replies 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.

No.	Age (y)	Sex	Aminoglycoside	Prior/Concurrent[1]	Ceftazidime	Nebulised antibiotic[2]	Other nephrotoxic drug[3]	Other risk factor[4]
1	0.4	M	Gentamicin	Prior	Yes	Colistin (e)		Diarrhoea & 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 & 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 & diabetic nephropathy
12	9.6	M	Gentamicin	Concurrent	Yes	Colistin (c)	Ciclosporin (c)	CFRD
13	3.6	M	Gentamicin	Concurrent	Yes	Colistin (c)		Diarrhoea & 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) & Diclofenac (e)	Constipation, osmotic laxitives
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)		

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

1. Timing of aminoglycoside in relation to ARF: Concurrent = at the time ARF diagnosed. Prior = within the week prior to ARF.
2. Patients receiving nebulised tobramycin had intravenous solution in nebulised form. c = concurrent. e = ever.
3. IV = intravenous
4. CFRD = Cystic fibrosis related diabetes. MRSA = Methicillin resistant *Staphylococcus aureus.*

No.	Aminoglycoside	Dose / kg	Times / d	Duration of IV[1] aminoglycoside	Maximum trough aminoglycoside level	Previous aminoglycosides	No. previous courses of IV antibiotics[2]	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	Dose & regimen not recorded			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

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

1. Not always possible to determine from the case notes whether a course of treatment included an aminoglycoside.
IV = intravenous

No.	Renal Ultrasound Scan	Biopsy[1]	Urine output	Max creatinine (micromol/L)	Dialysis[2]	Duration (days)
1	Enlarged. Consistent with ATN	No	Not recorded	494	PD	4
2	Enlarged. Consistent with ATN or GN	No	Not recorded	727	No	
3	Not done	ATN	Anuric	678	PD	13
4	Enlarged & echogenic	No	Anuric	768	HD	5
5	Small & 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 & echogenic	No	Anuric	886	CVVH	11
11	Normal	No	Not recorded	864	HD	5
12	Echogenic	No	Not recorded	288	No	
13	Enlarged & echogenic	No	Anuric	669	HD	Not recorded
14	Not done	ATN	Oliguric	782	HD	4
15	Not done	No	Normal	143	No	
16	Not done	No	Polyuric	241	HF & 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 & echogenic	No	Anuric	891	PD	9
23	Normal	No	Normal	542	No	
24	Echogenic	ATN & IN	Oliguric	1972	HD & PD	13

Table 3. Management & Outcome of ARF

1. Biopsy appearances: ATN = acute tubular necrosis. PIGN = post infectious glomerular nephritis. IN = interstitial nephritis
2. Dialysis: PD = peritoneal dialysis. HD = haemodialysis. CVVH = continuous venovenous haemofiltration. HF = haemofiltration.

DISCUSSION

This study has allowed 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 one hundred 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] Therefore it is likely that ARF occurs as a complication of co-morbid disease or treatment. In over half of the cases a previous or current co-morbid 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 GFR was measured in only one patient (in whom it was reduced) and mild or moderate renal impairment in other patients cannot be ruled out.

There are a total of 34 CF patients who have developed ARF 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 CF patients. The earliest report of ARF in CF patients 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 CF patients before 1998 supports the suggestion that this is a new phenomenon. The majority of patients with CF, developing ARF, need dialysis and all patients our catchment area requiring dialysis are referred to our unit, so it is unlikely that cases were missed prior to 1998. As well as frank renal failure, there is evidence that patients with CF are susceptible to subclinical renal impairment. Al Aloul *et al* have reported that between 31% and 42% of adult CF patients in their unit had a reduced creatinine clearance. Reduced creatinine clearance 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 (55) was considerably less than the number of case notes reviewed (26). It was a requirement of ethics approval that the local CF team requested consent and 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 CF patients may lie.

Only 5/24 (21%) patients were over 16 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 8 cases of ARF.[11] If these cases were added to our case series, then 13/32 patients (41%) would be over 16 years 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 therapy 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 there is a recommendation from the UK CF Trust *Antibiotic treatment for Cystic Fibrosis* document that renal function should be checked before the first dose and again before the 8th dose, and trough tobramycin levels taken before the 2nd and 8th 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 whilst receiving an IV 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 GFR at 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 co-morbid 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 allow firmer inferences to be drawn regarding the causation of ARF in cystic fibrosis and allow avoidable precipitating factors to be identified.

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