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Renal impairment following aminoglycoside therapy in cystic fibrosis

Cystic fibrosis (CF) is a chronic respiratory, life limiting illness in the Caucasian population. Chronic infection with *Pseudomonas aeruginosa* occurs in more than 80% of adults and this contributes to deterioration in lung function over time.[1] A reported long term complication includes renal impairment from presumed cumulative aminoglycoside antibiotics. Aminoglycosides are highly effective against *Pseudomonas aeruginosa* and effectively penetrate the sputum of patients with CF, achieving more effective bacterial killing.[2] The nephrotoxicity of aminoglycosides is reported to be caused by proximal tubular alteration of cell function and cell necrosis.[3]

The study by Smyth *et al*[4] demonstrates increased renal toxicity measured by plasma creatinine following a case controlled analysis of patients undergoing gentamicin therapy for the treatment of cystic fibrosis exacerbation. The authors did not specify the timing of plasma creatinine measurements in relation to gentamicin dosing (ie, was it collected before the gentamicin dose was given or at an interval following the dose). This would have been important to clarify whether renal impairment was present prior to dosing or occurred subsequently. Of further interest is the measurement of creatinine levels following cessation of gentamicin to elucidate whether renal impairment was persistent or document evidence of renal function recovery. Plasma creatinine reflects glomerular function rather than tubular function, which was not measured in this study. Plasma creatinine levels are subject to factors such as dehydration, nutrition and body size, and may not be a sensitive test in detecting renal impairment until well established disease has occurred.[5]

The challenge in quantifying renal impairment in cystic fibrosis is to describe the site of damage (ie, renal tubules versus renal glomeruli) and manifestations of early injury. Early and more accurate measurements of glomerular filtration rate may be attained by measuring the protein, cystatin C,[6] or by utilising nuclear medical scans which provide validated measures by renal clearance of exogenous filtration markers, most commonly diethylenetriaminepentaacetate (DTPA).[7] With regard to tubular injury, excretion of urinary proteins have been proposed as early markers of aminoglycoside induced tubular toxicity. Steinkamp *et al*[8] demonstrated that acute tubular injury measured by excretion of urinary enzymes achieve almost complete recovery after 4 weeks from cessation of aminoglycosides. Ideally, prospective studies should measure renal function (both glomerular and tubular) in aminoglycoside naïve cystic fibrosis subjects and document early renal changes following aminoglycoside administration in a dose dependent manner.

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Authors' response

We welcome Dr Tai's comments on our paper. We described a case control study of acute renal failure in cystic fibrosis (CF)[1] and not a study designed to measure the prevalence, severity or risk factors for renal impairment. Patients with acute renal failure (ARF) were reported to us from 20 UK CF centres and clinical data were extracted retrospectively from the case notes. We therefore adopted a pragmatic definition of ARF (raised plasma creatinine for age with or without oliguria). We agree that substantial renal impairment may occur before a rise in creatinine is seen. However, our intention was to investigate those patients with renal failure requiring dialysis (needed in 13/24 cases) or close monitoring of renal function.[2]

In an earlier paper, we have published the maximum plasma creatinine values seen in patients with ARF, recorded after gentamicin, where this was administered (median creatinine 674 mmol/l (range 124–1972)).[2] At follow-up, 22 of 24 patients had made a full recovery, with a normal plasma creatinine. One patient required long term dialysis (biopsy evidence of diabetic nephropathy prior to ARF) and another long term antihypertensive treatment.

The design of this study did not allow us to assess whether renal impairment was present prior to ARF. The prevalence of renal impairment in adults with CF is reported as 31–42% but the prevalence in children is unknown.[3] We agree that a well designed study of the prevalence and risk factors for renal impairment in children with CF would be useful. We would suggested measuring GFR, using the chromium 51 ethylene diamine tetra acetate (EDTA) test.[4]

Six patients with ARF in our series had biopsy evidence of acute tubular necrosis and two had hypomagnesaemia, which suggests tubular damage.[2] We have previously shown that there is a smaller elevation in proximal tubular enzymes with once daily tobramycin administration than with traditional three times daily treatment.[5] Measures of proximal tubular impairment could be included in a future study of renal impairment in children with CF.

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Bronchial asthma on Mount Kilimanjaro is not a disadvantage

Every year, an increasing number of people travel to high altitude and travellers with asthma are becoming more common in remote environments.[1] It is well recognised that certain situations at high altitude, such as exercising in cold air, may provoke symptoms.[2] However, the mountain

Table 1 Data for 2700 m and 4700 m

	Patients with asthma	Patients without asthma	p Value
2700 m			
RR	16.21 (2.16)	17.91 (7.29)	0.39
HR	90.38 (15.1)	85.41 (13.7)	0.99
Sao_2	95.50 (2.40)	94.0 (6.10)	0.36
LLS (median (range))	0 (0–7)	0 (0–1)	0.97
Peak flow	563.64 (167.27)	623.29 (188.02)	0.62
4700 m			
RR	16.93 (2.92)	17.95 (3.54)	0.29
HR	98.27 (9.87)	97.94 (15.3)	0.98
Sao_2	81.93 (6.37)	81.50 (7.36)	0.82
LLS (median (range))	2 (0–7)	3 (0–11)	0.48
Peak flow	623.29 (118.02)	562.06 (171.11)	0.36
Summit day			
LLS (median (range))	6 (0–15)	6 (0–21)	0.98

HR, heart rate; LLS, Lake Louise Score; RR, respiratory rate; Sao_2, arterial oxygen saturation.

environment offers a reduced pollutant and allergen load, potentially causing fewer exacerbations.[3] Additionally, increased sympathetic tone and adrenocortical output caused by hypoxia counteract bronchospasm. Acetazolamide, used widely by trekkers for the prophylaxis of acute mountain sickness (AMS), has an additional benefit in patients with asthma of reducing airway hyperreactivity.[4] To our knowledge, this is the first prospective study comparing lung function, physiology and success in mountain summiting among subjects with asthma and their non-asthmatic counterparts.

We studied altitude physiology and the incidence of AMS in tourist trekkers attempting the summit (Uhuru Peak) of Mount Kilimanjaro (5895 m) in August 2005. All subjects gave written informed consent and ethics approval was obtained from the Tanzanian Commission for Science and Technology (2005-261-NA-2005-62). Lake Louise Score for AMS and basic physiological measurements were taken on ascent. All subjects ascended the mountain over 4 or 5 days.

We compared 18 subjects with asthma (nine males, nine females, mean age 30 years (SD 6.2), mean body mass index 22.9 (1.9)) with 291 subjects without asthma (175 males, 116 females, mean age 34.5 (12.3) years, mean body mass index 22.9 (3.2)). Four were taking acetazolamide. Five subjects were controlled with occasional β agonists, six with regular β agonists, two with inhaled steroids and five were unsure of their medication. None declared any comorbidities and two were smokers.

No significant differences were found in any of the physiological parameters between subjects with and without asthma on ascent. There was an increase in peak expiratory flow rate (Micro Plus device; Micro Medical, Chatham, Kent, UK) in patients with asthma at higher altitude, but its significance ($p = 0.123$) was limited by underpowering and the fluctuation of readings that meters are subject to at different altitudes.

The incidence of AMS was not different between subjects with and without asthma at any altitude (2700 m: 0/18 vs 3/291, $p = 0.665$; 4700 m: 9/16 vs 141/224, $p = 0.602$) and there was no difference in summit success (50% of subjects with asthma vs 61% of subjects without asthma, $p = 0.523$). No subjects reported any asthma exacerbations.

This study shows that well controlled mild to moderate asthma should not preclude trekkers from attempting to reach high altitude, does not increase the risk of high altitude illness and does not decrease their chance of reaching the summit. This is similar to trekkers with other chronic diseases.[5] However, we recognise that these individuals have self-selected; only those with well controlled disease participate in such physical exertion and we are relying on unverified diagnoses. We recommend optimal asthma control before travel, an awareness of the logistics and availability of health care at the destination (including adequate travel insurance), a stock of sufficient medication (including rescue therapy) and, as with all high altitude trips, adequate time for acclimatisation.

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