The Impact of MRSA Infection in the Airways of Children with Cystic Fibrosis; a Case-Control Study

Abstract:

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The prevalence of Methicillin Resistant Staphylococcus Aureus (MRSA) in patients with Cystic Fibrosis (CF) has risen dramatically over the past 10 years. The clinical significance of MRSA in CF patients remains undetermined. We conducted a review of patients with CF infected with MRSA over a 10 year period at Our Lady's Children's Hospital, Crumlin between 1999 and 2009. We collected data from 24 patients infected with MRSA and 24 control patients without MRSA. There was a significant difference between the two groups in the rate of decline in percentage FEV1 two years after MRSA infection (Difference: -17.4, 95% CI: -30.48, -4.31, p=0.01). A similar trend was seen for FVC% and FEF25-75% predicted. This study suggests that persistent MRSA infection in the airways of children with CF is associated with diminished lung function two years post acquisition, when compared to a matched control cohort without MRSA.

Introduction

Cystic fibrosis (CF) is the most common life threatening autosomal recessive condition affecting the Caucasian population. With one in 1460 live births affected, Ireland has the highest incidence of CF in the world. CF is characterized by recurrent respiratory tract infections resulting in irreversible airway damage. Respiratory failure remains the main cause of premature death. The prevalence of methicillin resistant Staphylococcus aureus (MRSA) in patients with CF has risen dramatically over the past 10 years. The clinical significance of MRSA in patients with CF remains undetermined. Recent reports suggest persistent infection is associated with a more rapid decline in lung function. In contrast Sawicki et al concluded that incident MRSA detection is not associated with a change in the rate of FEV1 decline. The aim of this study is to assess the impact of persistent MRSA detection in the airway samples on the clinical progress of children with CF. Our secondary aim is to identify risk factors for MRSA acquisition.

Methods

This was a single centre case control study. The microbiology results from airway samples of all patients attending the paediatric CF clinic at Our Lady's Children's Hospital, Crumlin, Dublin, were reviewed for a ten-year period from July 1999 to June 2009. Patients in whom microbiological analysis of their airway samples (defined as throat swabs, sputum samples and bronchoalveolar lavage samples) demonstrated persistent MRSA infection (defined as three or more positive isolates over the course of a year) were identified. A control cohort of patients with CF, in whom MRSA was never detected in airway samples during the study period, was matched with the case cohort according to gender, age, and presence of co-infection with Pseudomonas aeruginosa. The following baseline characteristics were recorded: date of birth, gender, genotype, the presence of a sibling with MRSA, the presence of a totally implantable central venous access port, and/or a gastrostomy feeding tube.

To allow a direct comparison of the impact of MRSA on clinical progress between subjects, the first time MRSA was detected in an airway sample was set as time 0, the study was then divided into four equal time periods: two years before (-2), one year before (-1), one year after (+1), and two years after (+2) first acquisition of MRSA. Data relating to the controls were recorded from the same calendar periods as their matched case. For each of these time periods the following information was retrieved: number of admissions for intravenous antibiotics, number of days in hospital, number of courses of home intravenous antibiotics, number of clinics attended, number of unscheduled clinical reviews, number of courses of oral antibiotics, the use of long-term nebulised antibiotics, forced expiratory volume in one second (FEV1), forced vital capacity (FVC), and forced expiratory flow (FEF25-75). The spirometry measurements were expressed as percent predicted values using Zapletal's prediction equations.

An attempt was made to eradicate MRSA in all patients. There was no single agreed MRSA eradication protocol at the hospital during the study period. Consequently patients received a range of treatment regimens. Statistical analysis was performed using SPSS version 16.0. Normally distributed continuous data were compared using Mann Whitney U test and Wilcoxon rank-sum test, K-S test and the Shapiro-Wilk test were both used to determine whether the data was normal or non-normal. Categorical data were compared using c2 tests. Approval for this clinical audit was obtained from the ethics committee of the participating hospital.
From a paediatric CF clinic population of 160 patients, 24 (15%) patients were identified with persistent MRSA infection of airway samples between 1999 and 2009. The mean age of first acquisition of MRSA was 12.2 years (range 3 to 18 years). When compared with matched controls, patients with persistent MRSA, had a significantly higher prevalence of siblings infected with MRSA, and a trend towards higher prevalence of gastrostomy tubes in-situ (Table 1). There were no significant differences between the two groups in the number of admissions, days in hospital, courses of home intravenous antibiotics, or clinics attended in the two years pre and post acquisition of persistent MRSA (Table 2). In the year following MRSA acquisition, infected children attended twice as many unscheduled reviews as their matched controls (Table 2).

Where it was recorded in the notes, 65% of children received both topical and oral treatments which typically included mupirocin and one of either trimethoprim, rifampicin or linezolid. The remaining (35%) received intravenous antibiotic treatment, the commonest being vancomycin. In the two years preceding the acquisition of MRSA there were no differences in lung function between the two cohorts (Table 3). However, one year after acquisition, the children with MRSA were trending towards a lower lung function than their matched controls. At two years post acquisition this trend reached statistical significance with a mean reduction in the FEV1% predicted of 17.4% (Table 3 and Figure 1). A similar trend was seen for FVC% (14.55, 95%CI: -24.79; -4.31, p=0.007) and FEF25-75% predicted (21.10, 95%CI: -37.99; -4.21, p=0.01).

Figure 1: Change in FEV1% predicted over the time period studied
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Discussion

This study suggests that the detection of persistent MRSA infection in the airways of children with CF is associated with significantly diminished lung function two years post acquisition, when compared to a matched control cohort without MRSA. The presence of a sibling with MRSA appears to be a risk factor for acquiring persistent MRSA. These findings are consistent with others who have 1,2,3 demonstrated the negative impact of MRSA on the lung function of patients with CF. The presence of a sibling with MRSA appears to be a risk factor for acquiring persistent MRSA. These findings are consistent with others who have demonstrated the negative impact of MRSA on the lung function of patients with CF. Ren et al, using a large database of adult and paediatric patients, demonstrated that of 1,834 patients with Staphylococcus aureus in their respiratory cultures, those less than 18 years old with MRSA only, had a mean FEV1 of 80.7% predicted versus 89.4% predicted in those with methicillin sensitive S. aureus only 4. However, the study did not match patients according to age or gender, and patients with co-existing infections such as P. aeruginosa were excluded, all of which are significant confounders which could have influenced the outcome. Furthermore, patients could be included in the MRSA group with just one positive culture. However, it has been demonstrated that up to 69% of patients are only transiently colonized with MRSA at the time of culture and may not have any subsequent MRSA infection. The large number of subjects is a strength of this study. However, this may also be a shortcoming, as the groups differed significantly in other known physiologic and clinic characteristics that influence lung function, which required a post-hoc adjustment, and thus may have underestimated the impact of MRSA infection.

Our study revealed that the presence of a sibling with MRSA was a significant risk factor for persistent MRSA, in keeping with previous studies that reported that exposure to individuals with MRSA increased the likelihood of acquiring it 5,6. Studies in patients with and without CF have demonstrated several other risk factors for MRSA acquisition including previous antibiotic use, in particular co-trimoxazol, previous hospitalization 7,11, previous admissions to ICU 12, however these factors were not found to be significant in our cohort. Although the presence of intravenous access devices is a known risk factor 12, this was not found in our cohort, while the presence of a gastrostomy feeding tube was. The limitations of this study are its retrospective design and limited number of subjects. However, we attempted to compensate for this by carefully matching our cases with a contemporaneous control cohort in our centre. It is difficult to be certain from previous studies if MRSA is simply a marker of more advanced CF disease, and in particular of P. aeruginosa infection 8. Our study found that 54.2% of patients with persistent MRSA infection were co-infected with P. aeruginosa, which is similar to that found by Dassenbrook et al. at 69.3%. We were careful to match controls based on their P. aeruginosa status (along with age and gender) in an effort to see the additional effect of the presence of persistent MRSA infection.

A further limitation to our study is that the group with persistent MRSA infection appears to have a slightly lower lung function from the outset of the study (Figure 1). However, this difference did not reach statistical significance until 2 years after MRSA infection. So while there was difference in lung function, the clinical courses of both groups were identical prior to MRSA infection. There were no differences between the two groups in the use of either prophylactic or treatment courses of antibiotics or in the number of admissions to hospital in the two years leading up to MRSA acquisition. If there was a difference in the number of antibiotics given between the two groups, we may have contributed to the slower lung function more likely to be treated with antibiotics and therefore select for more resistant pathogens, such as MRSA. But this was not the findings of this study. The persistent presence of MRSA in the airways of children with CF does appear to be a risk factor for a more rapid clinical deterioration, as an recent study which demonstrates an association between MRSA and a worse survival rate in CF. 13 The implications of our findings suggest that MRSA infection may be associated with a reduction in lung function, and this effect may be greater than previously thought, and hence strengthens the argument for the development of aggressive evidence based MRSA eradication regimes.

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References


