Title: Investigating the variation in the incidence of new *Pseudomonas aeruginosa* infection between paediatric cystic fibrosis centres.

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A new isolate of *Pseudomonas aeruginosa* (PA) in an individual with cystic fibrosis (CF) is a significant event with potential clinical and psychological consequences.[1,2] Although the prevalence of chronic PA infection is well reported, the SPACE (Sensitivity and specificity of PA detection using the hydrogen Cyanide concentration of Exhaled breath) study was the first to report the incidence of new PA infection in children with CF.[3] We now present the PA incidence data for the eight CF centres included in the study and review the infection control policies at each centre.

The SPACE Study investigated exhaled breath hydrogen cyanide (HCN) as an early marker of PA infection. A large cohort of children with CF who had not isolated PA for at least 12 months from were recruited from eight centres and followed for 2 years. As part of this study, prospective data were collected on the acquisition of PA infection. The breath analysis results and the overall incidence of PA infection have previously been reported.[3] We now report the incidence of new PA infection for each of the eight centres as well as a survey of the infection control policies that were in place during the study to prevent the transmission of PA between patients.

The PA incidence rates were calculated by: numerator / denominator. The numerator was the number of children with a new isolate of PA during the study period and the denominator was the ‘person-time at risk’. The person-time at risk was the sum of the time from recruitment to new PA isolate for those who isolated PA and the total follow-up time for those who did not isolate PA.

At the time of recruitment 212 children had not isolated PA for ≥12 months and were not receiving anti-PA nebulisers. Sixty of these children had a new isolate of PA during the study period. The overall incidence (95% CI) of new PA isolates was 0.17 (0.14, 0.22) cases per patient year. The incidence (95% CI) of new PA infection varied between 0.08 (0.04, 0.18) and 0.28 (0.14, 0.49) cases per patient year at the different centres. See Table 1. This resulted in the proportion of children remaining free from PA infection at the end of the study varying between 56% (Centre 3) and 83% (Centre 7). The incidence of new PA infection was lower in the tertiary centres when compared to the shared care centres (0.16 vs 0.25 cases per patient year) but this did not reach statistical significance: incidence rate difference (95% CI) = 0.09 (-0.02, 0.19), p=0.11.

The details of the infection control policies at each of the recruiting centres are shown in Table 1. All centres ensured that patients stayed in a single room for their out-patient appointment and cleaned the rooms between patients. All centres educated patients and families about cross-infection. Half of the centres segregated out-patient clinics according to PA status. The incidence of new PA infection was lower in centres that segregated clinics (0.15 vs 0.22 cases per patient year) but this did not reach statistical significance: incidence rate difference (95% CI) = 0.07 (-0.016, 0.025), p=0.14. Six centres could always guarantee patients would be accommodated in a side room with en-suite facilities but only two had access to negative pressure cubicles for in-patients. One centre used different wards for PA and non-PA patients.

Table 1: Infection control policies in place at the recruiting centres

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Centre** | **Type of Centre** | **Incidence of new PA infection** | **In-patient** | | | **Out-patient** | | | |
| Different wards for PA and non-PA patients | All patients in side room with en-suite | Negative pressure side rooms available | Segregation of clinics according to PA status | Avoidance of communal areas | Patient remains in same room throughout clinic | Cleaning of rooms between patients |
| 1 | T | 0.22  (0.10-0.40) | Yes | Yes | No | Yes | Yes | Yes | Yes |
| 2 | T | 0.18  (0.10-0.29) | No | No | No | No | Yes | Yes | Yes |
| 3 | SC | 0.27  (0.15-0.43) | No | Yes | No | No | Yes | Yes | Yes |
| 4 | T | 0.19  (0.12-0.29) | No | Yes | Yes | Yes | Yes | Yes | Yes |
| 5 | T | 0.13  (0.07-0.25) | No | Yes | Yes | Yes | Yes | Yes | Yes |
| 6 | SC | 0.26  (0.14-0.49) | No | No | No | No | Yes | Yes | Yes |
| 7 | T | 0.08  (0.04-0.18) | No | Yes | No | Yes | Yes | Yes | Yes |
| 8 | SC | 0.22  (0.10-0.40) | No | Yes | No | No | Yes | Yes | Yes |

T: Tertiary, SC: Shared Care, PA: *Pseudomonas aeruginosa*.

Incidence of new PA infection presented as cases per patient year (95% CI)

These data demonstrate wide variation in the incidence of new PA infection at different paediatric CF centres. To our knowledge this is the first time that such data have been published. Variation in infection control practices between centres was identified but no single policy could explain the difference in incidence of new PA infection. There were non-significant trends for lower rates of new PA infection in the Tertiary Centres and in Centres that segregated their clinics according to PA status, however this study was not powered to detect such differences.

PA cross-infection can occur by contact transmission (direct or in-direct), droplet transmission (large infectious droplets spread over short distances) or through airborne transmission (small infectious droplets potentially spread over significant time and distance).[4] Infection control measures, particular the segregation of patients in clinic have reduced PA transmission between patients.[5] Other factors that may influenced PA acquisition include contact between CF patients outside of the hospital, the size of the CF centre, the age of the patients, the severity of their lung disease and exposure to environmental sources of PA.

In summary, we have demonstrated variation in the incidence of new PA infection between different paediatric CF centres. Although we identified differences in the infection control policies, we were unable to identify a single factor to explain the changes. Monitoring the incidence of new PA infection is an important quality measure for CF centres and may be something that the National CF Registries should consider collecting.

DECLARATIONS

Ethics approval and consent to participate

Ethical approval for the SPACE Study was granted by the Coventry and Warwickshire Research and Ethics Committee (Ref: 10/H1211/48).

Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

FG was the Lead Investigator for the SPACE Study, he analysed the data and wrote the first draft of the manuscript. WL was the Chief Investigator who devised the study. AS and KS were Principal Investigators for the SPACE Study at their centres and reviewed / edited the manuscript. AJ and AW were involved in the protocol development and reviewed / edited the manuscript. All authors have approved the final version.

References

1 Nixon GM, Armstrong DS, Carzino R, *et al.* Clinical outcome after early Pseudomonas aeruginosa infection in cystic fibrosis. *J Pediatr* 2001;**138**:699–704. doi:10.1067/mpd.2001.112897

2 Palser SC, Rayner OC, Leighton PA, *et al.* Perception of first respiratory infection with Pseudomonas aeruginosa by people with cystic fibrosis and those close to them: an online qualitative study. *BMJ Open* 2016;**6**:e012303. doi:10.1136/bmjopen-2016-012303

3 Gilchrist FJ, Belcher J, Jones AM, *et al.* Exhaled breath hydrogen cyanide as a marker of early Pseudomonas aeruginosa infection in children with cystic fibrosis. *ERJ Open Res* 2015;**1**:00044-2015. doi:10.1183/23120541.00044-2015

4 Knibbs LD, Johnson GR, Kidd TJ, *et al.* Viability of Pseudomonas aeruginosa in cough aerosols generated by persons with cystic fibrosis. *Thorax* 2014;**69**:740–5. doi:10.1136/thoraxjnl-2014-205213

5 Jones AM, Dodd ME, Govan JRW, *et al.* Prospective surveillance for Pseudomonas aeruginosa cross-infection at a cystic fibrosis center. *Am J Respir Crit Care Med* 2005;**171**:257–60. doi:10.1164/rccm.200404-513OC