

Seasonal onset of initial colonisation and chronic infection with *Pseudomonas aeruginosa* in patients with cystic fibrosis in Denmark

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Abstract

Background and methods To assess the relation between seasonal variation and the onset of initial and chronic *Pseudomonas aeruginosa* infection, 300 Danish patients with cystic fibrosis were investigated. A retrospective analysis based on case reports was performed to identify the date and year of initial and chronic *P aeruginosa* infection from 1965 to 1990. **Results** Sixty six per cent of the patients contracted their initial *P aeruginosa* colonisation and 68% contracted chronic infection during the winter months (October to March). Despite major changes in treatment, including improved and intensified antibiotic treatment, during the investigation period in our cystic fibrosis centre, the seasonal difference in *P aeruginosa* infection persisted.

Conclusions As respiratory virus infections have the same seasonal distribution in Denmark such infections may pave the way for *P aeruginosa* and thus explain the parallel seasonal occurrence of this pathogen in patients with cystic fibrosis.

The reason why chronic *Pseudomonas aeruginosa* infection is so prevalent in patients with cystic fibrosis is still unclear. During childhood most patients with cystic fibrosis have recurrent *Staphylococcus aureus* and *Haemophilus influenzae* lung infections.¹ With increasing age, however, *P aeruginosa* becomes more prevalent and most adult patients develop chronic *P aeruginosa* infection. Cross infection used to be responsible for most new chronic *P aeruginosa* infections in Danish children with cystic fibrosis; but with improved hygiene the yearly incidence was reduced to the "natural background" level of 1-2%, not associated with treatment at the centre.²

A few reports point, however, to a relation between respiratory virus infection, notably respiratory syncytial virus and onset or acute exacerbations of *P aeruginosa* infections.³⁻⁹ As respiratory virus infection usually occurs in the cold and wet winter months in Denmark (October to March) we speculated whether a similar seasonal variation of onset of *P*

aeruginosa colonisation and chronic infection could be detected in our patients with cystic fibrosis.

Methods

PATIENTS AND SURVEILLANCE

Since the Danish cystic fibrosis centre was established 26 years ago about 300 patients with cystic fibrosis have been followed. During the whole period patients have been seen once a month in the outpatient clinic. These visits include among other things a medical examination, measurement of lung function, and bacteriological examination of lower respiratory tract secretions, obtained by expectoration or nasolaryngeal suction. The bacteriological technique has been described.¹ Since 1976 patients with chronic *P aeruginosa* lung infection have been treated every third month with intravenous antipseudomonal chemotherapy for two weeks.¹⁰ The mean age of patients acquiring chronic *P aeruginosa* infection was 9.7 years during the study period.²

CLASSIFICATION OF *P AERUGINOSA* INFECTION

Since 1972 all patients have been examined at least once a year for serum precipitating antibodies to *P aeruginosa*.¹ The patients were said to be intermittently colonised when *P aeruginosa* was harboured in the respiratory tract for less than six months and there were less than two precipitins, and to have chronic *P aeruginosa* infection when bacteria were cultured continuously from sputum for six months or there was an antibody response of two precipitins or more.¹¹ These definitions have remained unchanged during the study period.

Case reports were scrutinised for all 300 patients followed in the Danish cystic fibrosis centre from 1 January 1965 to 31 December 1990 and the above definitions were applied to the data. Day, month, and year were recorded for (1) *initial colonisation*—that is, the date of the first sputum sample to be positive for *P aeruginosa* (these patients being designated as intermittently colonised until they fulfilled the criteria for chronic infection); and (2) day, month, and year of onset of *chronic P aeruginosa infection*—that is, of continuous culture of *P aeruginosa* from sputum for six months or an antibody response of two precipitins or more.

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ANALYSIS

Results are expressed as percentage values, with 99% confidence intervals (CI) and significance assessed by χ^2 test for categorical data.¹²

Results

During the study period 239 patients had intermittent *P aeruginosa* colonisation and 182 acquired chronic infection; all had been intermittently colonised previously.

INITIAL *P AERUGINOSA* COLONISATION

The seasonal distribution of initial colonisation during the successive periods of the study is shown in table 1. Sixty six per cent (99% CI 57–74%) of the initial colonisation took place during the winter months. No significant fluctuations were seen over the 26 years of the study ($p = 0.75$). The number of patients who acquired the initial colonisation each month over the entire study period is shown in figure 1. The lowest incidence was in July and the highest incidence in October.

CHRONIC *P AERUGINOSA* INFECTION

The seasonal distribution of the onset of chronic infection during the successive periods of the study is shown in table 2. Sixty eight per cent (99% CI 59–76%) of the chronic infections started during the winter. No significant fluctuations were seen over the 26 years ($p = 0.52$). Figure 2 shows the number of patients developing chronic infection each month from 1965 to 1990. The lowest incidence was in July and the highest in November.

INITIAL *P AERUGINOSA* COLONISATION DEVELOPING INTO CHRONIC INFECTION

In 33 of 182 patients with chronic infection (18% CI 11–26%) the initial episodes of colon-

isation developed into chronic infection; the other 149 patients (82%, 99% CI 73–89%) did not show any evidence of *P aeruginosa* for a time.¹³ The median interval before patients became chronically infected was 12 months (10th%–90th% percentile 0–68.8 months). Twenty seven of 160 patients (17%, 99% CI 10–26%) who became colonised initially before 1980 developed chronic infection, whereas only six of 79 patients (8%, 99% CI 2–19%) did so during the last 10 years ($p < 0.05$).

Discussion

The results show that both initial colonisation and chronic *P aeruginosa* infection begin in most patients during the winter season. The number of patients with an onset in July is probably an underestimate because of summer holidays but some of the July cases would be recorded during August, which may therefore have too high a number. Similarly, the number of patients with an onset in December and February may be too low owing to Christmas and the one week winter holiday respectively, with their cases recorded in January or March. Such imprecisions, however, would not influence the main finding that most patients contract *P aeruginosa* during the winter months.

Similar seasonal variations in the onset of *P aeruginosa* have not been published from other centres to our knowledge. A seasonal pattern has been reported for legionnaires' disease in Scotland with a late summer and autumn peak.¹⁴ The respiratory virus season is also during winter,^{15,16} and such virus infections have been reported to be closely associated with exacerbations of pulmonary symptoms in patients with cystic fibrosis.^{4,8,15} We have previously⁶ reported a possible synergism with non-bacterial agents, especially respiratory syncytial virus, and the development of chronic *P aeruginosa* infection. The same trend was reported by Wang *et al.*,⁵ who found a significant association between declining lung function and the annual incidence of viral infections in 49 patients with cystic fibrosis compared with 19 normal siblings, though this is in contrast to the findings of Ramsey *et al.*,¹⁷ who could not find any positive association between the frequency of viral infections and more rapid decline in lung function. Efthimiou *et al.*⁸ studied the importance of viruses and acute exacerbations in patients with stable and unstable cystic fibrosis. They found that the incidence of viral infections was not convincingly higher in patients with cystic fibrosis than in healthy controls but that the consequences of the infections were more serious, which is also in agreement with the findings of Deforest *et al.*¹⁸ Fewer stable patients showed serological evidence of non-bacterial infections than the unstable patients. Brocklebank *et al.*¹⁹ found that the interaction between respiratory virus infection and chronic respiratory diseases such as cystic fibrosis has become increasingly important for the health of these children as they are more likely to acquire severe lower

Table 1 Seasonal onset of initial *Pseudomonas aeruginosa* colonisation in 239 Danish patients with cystic fibrosis 1965–90

	1965–75*	1976–80	1981–5	1986–90	Total 1965–90
	No (%)	No (%)	No (%)	No (%)	No (%)
April–September	30 (34)	22 (31)	15 (42)	15 (42)	82 (34, CI 26–42)
October–March	59 (66)	49 (69)	21 (58)	28 (58)	157 (66, CI 58–74)

*Eleven rather than five years because of the small number of patients.
CI—99% confidence interval.

Figure 1 Month of onset (1–12 = January–December) of cases of initial *Pseudomonas aeruginosa* colonisation in 239 Danish patients with cystic fibrosis from 1965 to 1990. Proportion of infections with initial onset during the winter months (October–March) 66% and during the summer months (April–September) 34%.

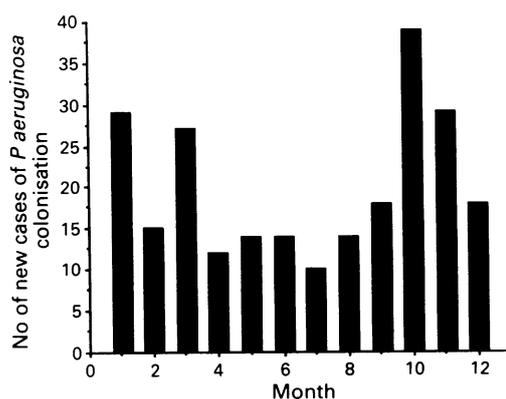
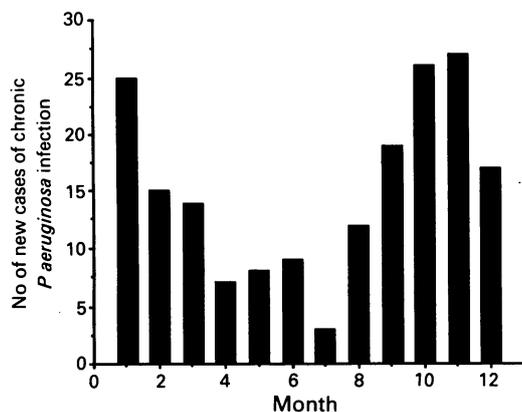


Table 2 Seasonal onset of chronic *Pseudomonas aeruginosa* infection in 182 Danish patients with cystic fibrosis 1965–90

	1965–75*	1976–80	1981–5	1986–90	Total 1965–90
	No (%)	No (%)	No (%)	No (%)	No (%)
April–September	14 (27)	26 (34)	11 (41)	7 (25)	58 (32, CI 24–41)
October–March	37 (73)	50 (66)	16 (59)	21 (75)	124 (68, CI 59–76)

*Eleven rather than five years because of the small number of patients.
CI—99% confidence interval.

Figure 2 Month of onset (1–12 = January–December) of cases of chronic *Pseudomonas aeruginosa* infection in 182 Danish patients with cystic fibrosis recorded during the period 1965–90. Proportion of cases of chronic infection starting during the winter months (October–March) 68% and during the summer months (April–September) 32%.



respiratory tract infection than other children. They therefore suggest the importance of rapid diagnosis and exclusion from the ward to reduce cross infection.¹⁹

As seasonal variations in infections might be influenced by other factors, we looked at the seasonal variation in the onset of the initial *P aeruginosa* colonisation and chronic infection against the background of the continuous improvement of our treatment regimens during the period of the study. These include the use of maintenance treatment for *P aeruginosa* infection every third month since 1976, additional colistin inhalation and oral antibiotics since 1986, and aggressive treatment of the initial infection since 1987.^{20 21} The resulting improved survival means that the mean age of the patients has increased and their family and social activities have changed as a consequence. Summer and winter camps have not, however, been used for patients with cystic fibrosis in Denmark.

The elimination of cross infection in the centre, by improvement of hygiene and the separation of infected and non-infected patients since 1980, may also be a factor. These changes, however, do not explain why the seasonal onset of *P aeruginosa* has not changed over the 26 years. The most likely explanation seems to be that respiratory virus infections pave the way for *P aeruginosa* colonisation and chronic infection in patients with cystic fibrosis.

Like other authors,^{3 4 22 23} we suggest that prophylactic procedures such as vaccination against respiratory viruses and intensive surveillance and treatment of patients with cystic fibrosis who have confirmed respiratory virus infections may be a way to decrease the high incidence of *P aeruginosa* colonisation and infection during the winter. Such measures may improve further the prognosis in cystic fibrosis.

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