Eradication of Pseudomonas from tracheotomised children: mission impossible?

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Case report

The patient is a 23-month-old boy who was born at 34 weeks with low birth weight 1550 gm. He has suffered from severe congenital laryngomalacia with tracheostomy performed at one month old. He also had tetraplegic cerebral palsy, global developmental delay and gastroesophageal reflux with fundoplication and gastrostomy performed. There were frequent recurrent febrile illnesses with persistent *Pseudomonas aeruginosa* (PsA) isolated from tracheal aspirate or bronchoalveolar lavage since the age of 8 months. Initially antimicrobial treatment was not specifically targeted for PsA as the transtracheal aspirate yield no white cell but at least four other organisms. The frequency of febrile illnesses was reduced after the repair of a large hiatus hernia. However, he had frequent febrile illnesses again since 12 months old. Clinically he usually had change in the sputum character but no other focus of infection. Milk scan and esophageal pH monitoring ruled out significant gastroesophageal reflux and immunological workup ruled out immunodeficiency. The diagnosis of recurrent PsA respiratory tract infection was more definite as there were a large amount of white cells and pure growth of PsA from the transtracheal aspirate. Intravenous ceftazidime or piperacillin and/or an aminoglycoside such as gentamicin or amikacin were administered for these episodes when he had fever, leucocytosis and change in sputum character. Pneumonia was diagnosed if there was new infiltrate on chest X-ray. Otherwise the diagnosis of tracheitis was made provided that there was no other focus of infection. Over a period of 3 months from January to April 2004, there were four episodes of these acute febrile illnesses. Intravenous antibiotics were given for a total of 64 days (i.e., 70% of the days). Furthermore, he had very difficult intravenous access and long line insertion was attempted for three times with one of them was inserted under general anaesthesia. Inhaled gentamicin was commenced in late April 2004. Thereafter, there was one more episode of similar acute febrile illness, which required systemic antibiotics. He was otherwise free from febrile illness up till October 2004. Gentamicin inhalation was continued for 2 months. PsA has been absent from the tracheal culture but recurred a few months later. All of the isolates were still sensitive to antibiotics being tested including gentamicin, ceftazidime and piperacillin.

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Literature review

Epidemiology

PsA is a common pathogen for nosocomial infection. In the National Nosocomial Infections Surveillance (NNIS) System Report (1990-1999), it accounted for 4.9%, 22.4% and 14.3% of bloodstream infection, pneumonia and urinary tract infection respectively in participating paediatric intensive care units (PICU) in US.[1] Surveillance in a single PICU in Europe showed that it accounted for 23.6% of all nosocomial infections.[2] PsA also accounted for 11.7% of nosocomial pneumonia in high-risk nurseries participating in the NNIS system in US from 1986 to 1993.[3]

PsA is also a common organism of colonisation and infection of respiratory tract in children with cystic fibrosis (CF). A prospective cohort study of 42 children with CF presented at age 15 months or younger in US demonstrated that 18%, 34% and 33% of them had PsA isolated by bronchoalveolar lavage (BAL) at 1, 2 and 3 years of age respectively.[4] Another prospective study in Australia showed that 45% of the children (86% presented in the neonatal period) had PsA isolated by BAL at a mean age of 45 months.[5] A large prospective study of 3625 children with CF diagnosed within 36 months of age showed that

colonisation of PsA (by sputum or BAL) had been acquired in 40-45% by 5 years of age and 70-80% by 10 years of age. Acute exacerbation of respiratory illness was also correlated with the colonisation of PsA.[6] The annual prevalence of chronic infection with PsA in children with CF in UK was found to be 24.5% before introduction of a PsA eradication program in 1990.[7]

Tracheostomy is a possible risk factor for respiratory tract infection. More tracheostomies were performed since 1980s[8] and it may be due to the improved survival of critically ill infants and children who would then have conditions like acquired subglottic stenosis.[9] Thirty-four percent of these patients with tracheostomies suffered from late complications that were mainly lower respiratory tract infection.[8] PsA was one of the most common organisms of colonisation of trachea from adult patients with long-term tracheostomy.[10-12] A study of paediatric patients with long-term tracheostomy also showed that they all have bacterial tracheal colonisation. They also had 2.8 episodes of pneumonia per patient per year. PsA was one of the organisms more frequently isolated in cases with pneumonia.[13]

PsA is an opportunistic pathogen but once infection is established, it is highly virulent and once there is colonisation particularly in respiratory tract, it is difficult to be eradicated and chronic infection may persist.[14] It was shown that the colonisation of PsA in paediatric patients with long-term tracheostomy could not be eradicated by treatment with gentamicin.[13]

Intravenous antibiotics

It was recommended by many experts that empirical therapy with a β-lactam and an aminoglycoside is acceptable for neonates with PsA infection.[15] More clinical trials comparing single with combination therapy were conducted in patients with CF. However, the results of a systematic review for pulmonary exacerbations in CF were not conclusive.[16]

In the Cochrane review by Elphick (2003), 9 relevant studies (1977-1999) were analysed. The range of patients' age was 2 to 44 years. Almost all of them had pulmonary infection with PsA. Monotherapy included a β-lactam such as ticarcillin, piperacillin or ceftazidime or an aminoglycoside such as gentamicin or tobramycin. Combination therapy involved a β-lactam plus an aminoglycoside. Most of the therapy were given for 10-14 days.[16]

When monotherapy group was compared with combination therapy group, there was no statistically significant difference in the improvement of clinical condition,[17-21] inflammatory markers,[17-19,21] chest X-ray [17-19,22] or lung function.[18,20-23] There was no difference in the adverse events.[17-21,23] However, in the most recent randomised study by Smith (1999) involving 76 subjects aged 6 to 44 years, there was a longer clinical remission in patients receiving combination therapy (azlocillin 450 mg/kg/day and tobramycin 240 mg/m^2/day) than those receiving azlocillin alone. There were fewer patients readmitted on day 80 (30% in combination therapy vs 62% in monotherapy, $p<0.01$).[21]

Concerning eradication of PsA, one study showed that there was no difference in the decrease of PsA density between two groups[22] whereas the other three studies demonstrated that eradication was greater in the combination therapy group. Padoan (1987) showed that decrease of PsA density was 60% in ceftazidime-sisomycin group versus 30% in ceftazidime-alone group ($p=0.082$).[19] McCarty (1988) showed that decrease of PsA density was 63% in piperacillin-tobramycin group versus 26% in piperacillin-alone group ($p<0.03$).[20] Lastly Smith (1999) showed a greater decrease in PsA density in azlocillin-tobramycin group than in azlocillin-alone group at 2 weeks ($p=0.034$) but there was no difference in 4 to 8 weeks.[21]

There were contradictory results concerning the acquired resistant strains after treatment. The resistant strain to azlocillin, tobramycin or both at 1-2 weeks after start of treatment was greater in azlocillin-tobramycin group than in azlocillin-alone group (28% vs 7%, $p<0.001$)[21] whereas another study showed that acquired azlocillin-resistance was greater in azlocillin-alone group than in azlocillin-tobramycin group (53% vs 21%, $p=0.13$).[22] At follow-up, the pattern of acquired azlocillin-resistance persisted in the latter study whereas another one showed that ceftazidime-resistance was greater in ceftazidime-sisomycin group than in ceftazidime-alone group (30% vs 7%).[19] In each of other 2 studies, there was only one persistent resistant-strain at follow-up.[17,21]

There was an European consensus that intravenous administration of 2 different classes of antibiotics were recommended for CF patients with moderate to severe acute pulmonary infection with PsA.[24]

Inhaled antibiotics

In patients with CF, mucoid strain of PsA is uniformly present in chronic pulmonary infection. The resulting biofilm would protect the organism from phagocytosis and action of antibiotics.[24] The concentration of antibiotics in bronchial secretions should be as high as 10 times the minimum inhibitory concentration to allow penetration of antibiotics into biofilms, suppress inhibitory factors and promote bactericidal effectiveness.[25] Administration of antibiotics by inhalation has the advantages of achieving high antibiotic concentration at the site of infection of respiratory tract with minimising systemic concentration and thus their resultant toxicity.[26]

A systematic review was performed to evaluate the administration of inhaled antibiotics in CF patients. It analysed 11 clinical trials (1981-2002) with a total of 874 patients of aged 5 to 42 years. Nearly all of them had chronic pulmonary infection with PsA. They commonly compared inhalation of an aminoglycoside such as gentamicin or tobramycin or other anti-pseudomonas antibiotics with normal, hypertonic or hypotonic saline as placebo. Duration of therapy usually ranged from 1 to 6 months. It was concluded that the treatment could reduce exacerbations of respiratory infection and improve lung function without significant adverse effects up to 6 months. However there was report of increased tobramycin-resistance of PsA. Any longer term risk and benefit was uncertain. [27]

There were other studies of inhaled antibiotics for CF patients that were not included in the systematic review. Burns (1999) studied the administration of inhaled tobramycin 300 mg twice daily versus placebo for 4-week-on followed by 4-week-off for 3 cycles in CF patients older than 6 years with 98% of them having PsA colonisation or chronic infection. It was shown that there was more tobramycin-resistance of PsA at 20 weeks (26% vs 17%, p=0.03) and at 24 weeks (23% vs 8%, p<0.001).; and more Candida albicans (22% vs 16%, p=0.06) and Aspergillus species (18% vs 8%, p=0.001) isolated in the treatment group.[28] Gibson (2003) studied the use of tobramycin in patients younger than in other studies (aged 6 months to 6 years). At the end of treatment for 4 weeks, there was 100% in PsA eradication in the treatment group versus 7.4% in the placebo group (p<0.0001). However, there was no difference in the clinical benefits, adverse event and inflammatory markers between 2 groups.[29]

There were studies of inhaled antibiotics in non-CF adult patients with bronchiectasis having chronic pulmonary PsA infection. A small study (n=17) showed that after 12-month therapy with inhaled ceftazidime and tobramycin, there were fewer episodes of admission (0.6 vs 2.5, p<0.05) and shorter duration of hospitalisation days (13.1 vs 57.9, p<0.05), when compared with control group. There was no difference in the use of oral antibiotics and pattern of resistant organisms.[30] A larger study (n=74) showed that after the inhalation of tobramycin 300mg twice daily for 4 weeks, the patients had smaller density of PsA in their airway (p<0.01) when compared with the placebo-controlled group. In addition, more patients in the treatment group had clinical improvement (62% vs 38%; odds ratio 2.7, 95% confidence interval 1.1 to 6.9).[31]

There was an European consensus that inhaled antibiotic was clinically effective and suggested for chronic pulmonary PsA infection in CF patients. However, there was no evidence to support the therapy in acute infection.[24]

There has been no consensus about the use of inhaled antibiotics for bronchiectasis patient without CF. There has been no relevant study or recommendation for children with long-term tracheostomy. A survey of paediatric pulmonologist showed that in a minority of the US centres, inhaled gentamicin or tobramycin would be an empirical treatment of pulmonary infection for children with tracheostomy.[32]

Oral antibiotics

Quinolone has the advantages of extended antimicrobial spectrum, satisfactory gastrointestinal absorption and excellent tissue penetration. It may be one of the ideal choices of therapy with PsA infection. However, the use of this class of antibiotics has been limited in children because of their potential to induce arthropathy in juvenile animals.[33] On the other hand, the issue of paediatric application has

recently been re-visited. It was reviewed that quinolone arthropathy was described in juvenile animals but similar extrapolation to children and adolescents was not justified.[34]

The efficacy and safety of quinolone was studied in a multicenter clinical trial. One hundres and eight CF patients of aged 5 to 17 years who had acute bronchopulmonary exacerbations with PsA were randomised into 2 treatment groups: oral ciprofloxacin 15 mg/kg (maximal 750 mg) twice daily and intravenous ceftazidime and tobramycin. At the end of therapy for 2 weeks, clinical improvement was observed in 93% and 96% of the ciprofloxacin group and ceftazidime/tobramycin group respectively although the PsA suppression was lower in the ciprofloxacin group (24% vs 63%). There was no evidence of cartilage toxicity as shown by ultrasound examination and magnetic resonance imaging.[35] Oral ciprofloxacin was employed as a longer-term therapy in another study. In 34 CF patients of aged 8 to 25 years with acute broncho-pulmonary exacerbations with PsA who had completed and responded to a 2-week intravenous therapy of ceftazidime and amikacin, oral ciprofloxacin 30 mg/kg/day was given with or without inhaled amikacin as maintenance therapy for 3 months. Thirty-eight percent of them were found to have sustained PsA eradication but 23% of sputum isolates were found to have ciprofloxacin-resistance at the end of treatment. The treatment was well tolerated. There were no severe or serious adverse events, no signs of quinolone-related arthropathy and no growth impairment.[36] Another observational cohort study has also described the administration of oral ciprofloxacin and/or inhaled tobramycin for 3 months following a 2-week therapy of intravenous antibiotics in 24 CF children at a mean age of 45 months with PsA infection.[5]

A survey of paediatric pulmonologist showed that in a minority of the US centres, oral ciprofloxacin would be an empirical treatment of pulmonary infection for children with tracheostomy.[32] There was an European consensus that quinolone could be critically and cautiously used in children with specific infections in special conditions such as PsA infection in CF when alternative safe therapy was not available.[33] Schaad (1999) recommended that quinolone should never be used in children for routine treatment when alternative safe and effective antibiotic therapy was known. However, selected children should not be deprived of the therapeutic advantages of this class of antibiotics.[37]

Discussion

Intravenous administration of a β-lactam and an aminoglycoside is generally accepted as the empirical therapy for PsA infections. In clinical situations such as chronic bronchopulmonary infection in cystic fibrosis, long-term of inhaled antibiotics such as tobramycin has also been recommended. However, in acute pulmonary exacerbations of CF, the role of inhaled antibiotics is uncertain. In addition, there has been no well-designed study of inhaled antibiotics in other non-CF children such as those with tracheostomy or other aetiologies of bronchiectasis. Oral quinolone has been studied in children with CF and it may be an alternative when there is no other safe or reliable choice. Further clinical trials were required to determine whether these modalities of therapy were beneficial in these situations.

CF is a rare condition in our population but the principle of inhaled antimicrobial therapy may be applied to some individual children like our patient with recurrent or chronic respiratory tract infection with PsA.

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