Immunizations

Vaccination program in cystic fibrosis

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Background

CF patients are advised to comply with the recommended vaccination schedule (diphtheria, tetanus, poliomyelitis, acellular pertussis, *Haemophilus influenzae* type B, *Streptococcus pneumoniae*, hepatitis B, rotavirus, measles-mumps-rubella, meningococcus), as well as with hepatitis A and influenza vaccination. Recently SARS-COV-2 pandemic disease confirms prioritization of vaccination programmes in people with CF.

Strategies to prevent CF pathogens such as bacteria of the *Burkholderia cepacia* complex, *Pseudomonas aeruginosa* , or *Mycobacterium*

Influenza

As previous observational studies have suggested an adverse outcome in terms of lung function and disease progression in people with CF following infection with Influenza A virus and other viral respiratory tract infections, including enterovirus and Coxsackievirus Bs (Stone VM et al, 2022), annual influenza vaccination is commonly recommended in people with CF. A CVB vaccine, currently undergoing clinical development, prevents infection and CVB-instigated lung damage in a murine model of CF.

Antiviral agents, including the neuraminidase inhibitors zanamivir and oseltamivir, may also have a place in the prevention and treatment of influenza.

Covid-19

Pandemic SARS-COV-2 confirms prioritization of vaccination programmes in people with CF, as there is also evidence of increased risk for post-transplant patients and in those with advanced lung disease (Mathew HR et al, 2021).

A recent systematic review (Shahrebabak AZ et al, 2025) evaluates the efficacy and safety of COVID-19 vaccines in pwCF. A systematic search of major databases conducted between December 2019 and January 2024 identified eight cohort studies comprising 1,361 CF patients. Studies without subgroup analyses specific to CF patients were excluded. COVID-19 vaccines generally induced robust serological responses following the second and third doses, although reduced antibody levels were observed in lung transplant recipients. Factors influencing humoral response included prior SARS-CoV-2 infection, age, inhaled corticosteroid use, and immunosuppressive therapy. Vaccination-related adverse events were predominantly mild. Severe COVID-19 outcomes were infrequent among vaccinated CF patients. The evidence supports the immunogenicity and safety of COVID-19 vaccines in the CF patients. However, individualized vaccination strategies may be necessary for CF lung transplant recipients and those on immunosuppressive therapies.

Pseudomonas Aeruginosa

Once colonization of the lungs with Pseudomonas aeruginosa (PA) occurs in CF, it is almost impossible to eradicate, resulting in progressive lung damage. Vaccines versus PA, aimed at reducing infection with PA, have been developed in the past, including LPS exstracts from different serotypes, conjugated or not, antigens derived from flagellum and alginate and outer membrane proteins (Killough M et al, 2022). Currently no licenced vaccines exist to prevent PA infections. Recently it has been proposed a novel subunit vaccine that targets the *P. aeruginosa* type III secretion system (T3SS), including a fusion of the novel antigen PaF (Pa Fusion), a fusion of the T3SS needle tip protein, PcrV, and the first of two translocator proteins, PopB. This fusion can activate dendritic cells *in vitro* and promotes IgG and IgA titers in mice model when administered intranasally (Das S et al, 2021).

Streptococcus Pneumoniae

Streptococcus Pneumoniae (SP) has been found to be the fourth most common bacterial organism isolated from the sputum of people generally associated with mild respiratory involvement with no cases of invasive pneumococcal disease. Pneumococcal vaccination is recommended. No relevant data are available on epidemiology of S. pneumoniae that is expected could be modified by the early intervention of modulators.

Staphylococcus Aureus and Haemophilus Influenzae

Pulmonary exacerbations in CF are more frequently associated with Staphylococcus aureus (SA), PA and Haemophilus influenzae (HI). No specific vaccines are available for Sa and HI.

RSV

The strength of current evidence is insufficient to allow conclusions on the use of the active vaccination to prevent RSV in children with CF (see also *the topic "Palivizumab for the prevention of RSV infection in children with cystic fibrosis"*).

Other microrganisms

A few data are available concerning Achromobacter xylosoxidans or mycobacteria.

Issues

1. To assess the effectiveness of influenza vaccination particularly on morbidity in the 12 months after vaccination; changes in the rate of progression of lung function, nutritional status, numbers of intravenous antibiotic use, *P. aeruginosa colonization* or infection and death, adverse effects, clinical variability when comparing different types of vaccines.
2. To assess the efficacy of neuraminidase inhibitors for controlling influenza.
3. To assess the effectiveness of vaccination against *P. aeruginosa* in CF and to compare the effects of different vaccines.
4. To assess the efficacy of pneumococcal vaccines in reducing morbidity and mortality in people with CF.
5. to assess the efficacy of vaccines on other microrganisms.

What is known

Issue 1

1 CDSR (Dharmaraj P et al, 2014) was performed with the aim to compare any influenza vaccine with a placebo. Two out of four studies enrolling 179 subjects with CF (80% were children aged 1 to 16 years) compared an intranasal applied live vaccine to an intramuscular inactivated vaccine and the other two studies compared a split virus to a subunit vaccine and a virosome to a subunit vaccine (all intramuscular). There were no studies comparing a vaccine to a placebo or a whole virus vaccine to a subunit or split virus vaccine. The total adverse events rate ranged from 24% for the intranasal live vaccine to 43% for the split virus vaccine. None of the events was severe. All studies showed a satisfactory serological antibody response generated from influenza vaccinations. However, this response may not result in protection against influenza infection or lung damage. None of the included studies reported clinical outcome measures, such as its impact on PA infection, lung function, length of hospital stay or nutritional status.

According to current practice CF centers recommmed vaccination for influenza in people with CF on an annual basis.

1 non-RCT (Boikos C et al, 2017) involved 198 patients with CF aged 2-19 with CF. Adverse events following live-attenuated intranasal influenza vaccination were most common 0-6 days after LAIV administration, but they were generally benign and self-limiting. Pulmonary exacerbations did not increase in frequency.

Issue 2

1 CDSR (updated 2015) is available. No randomised or quasi-randomised controlled trials on the efficacy of neuraminidase inhibitors for the treatment of influenza infection in people with CF were included in the analysis.

Issue 3

1 CDSR (Johansen HK et al, 2015) was comphensive of trials comparing PA vaccines (oral, parenteral or intranasal) with control vaccines or no intervention in CF. Six trials were identified. Two trials were excluded since they were not randomised and one small trial because it was not possible to assess whether it was randomised. Three trials were evaluated including 483, 476 and 37 patients, respectively. No data have been published from one of the large trials, but the company stated in a press release that the trial failed to confirm the results from an earlier study and that further clinical development was suspended. In the other large trial, relative risk for chronic infection was 0.91 (95% CI 0.55; 1.49), and in the small trial, the risk was also close to one. In the large trial, one patient was reported to have died in the observation period. In that trial, 227 adverse events were registered in the vaccine group and 91 in the control group. There was a marked rise in flagella antibody titres in the vaccine group and no change in the placebo group ($p<0.0001$). In particular, one study (Doring G et al, 2007) showed that active immunization of patients with CF with a marked rise in flagella antibody titres lowered the risk for initial infection with PA. Although many of these patients may acquire PA infections later in life, delaying the onset of chronic infection with PA should result in longer survival of these patients. However, several adverse events were registered in the vaccine group compared to placebo group. So vaccines against PA cannot be recommended.

A phase III Study RCT (NCT01455675) has been completed in June 2017 in order to evaluate clinical efficacy and safety of avian polyclonal anti-pseudomonas antibodies (IgY) in prevention of recurrence of PA infection in CF patients. Results are not available.

A post-marketing study (NCT00633191) completed in 2012 evaluated th effect of "Anti-pseudomonas IgY" i prepared from eggs of hens that have been vaccinated with PA. Patients with CF who are intermittently infected with PA started to gargle with a solution of "anti-pseudomonas IgY" every night to prevent a new infection. Preliminary results showed that it takes a significantly longer time to get a new infection and that the patients get fewer infections than control patients. Any new opportunistic bacteria or fungi (B. Cepacia, S. Maltophilia, A. Xylosoxidans, atypical Mycobacteria, Aspergillus Fumigatus) was found; the use of antibiotics was greatly diminished; t the lung functions and nutritional conditions were maintained in preventing recurrence of PA infections in the two next years.

Issue 4

Several countries as UK and USA include immunization against pneumococcus as part of the routine immunization schedule for children. Children with chronic diseases have a 1.4- fold increased risk of invasive pneumococcal disease compared to healthy children. 1 CDSR is available (Burgess L et al, 2016). In an Italian study the authors (Giannattasio A et al, 2010) speculated that the low uptake rates of pneumococcal vaccination found in less than 20% of children with CF might be due to a lack of awareness of the severity of pneumococcal disease.

Another study (Esposito S et al, 2016) was performed to evaluate *Streptococcus pneumoniae colonization* rates of school-age children and adolescents with CF showing that it is more prevalent than previously thought. Pneumococcal conjugate vaccination administered in the first year of life does not reduce the risk of re-colonization in later childhood and adolescence.

A recent prospective, observational study at an Adult Italy CF Center (Milan) from March 2017 to September 2019, including data from 129 patients, has been assessed with the aim to evaluate the prevalence of SP DNA and serotype in adults with CF naive to pneumococcal vaccination. SP was found in 24 subjects (19%) and the most common serotypes were 19F (16%), 4 (6%), and 9VA (3%). Higher FEV1 and non-pseudomonas infection significantly were associated with SP on sputum (Gramegna a et al, 2021).

Issue 5

Recently a study aimed to determine how Bacille Calmette-Guérin (BCG) vaccination may impact NTM infection, using a murine model of *Mycobacterium abscessus* infection and observational data derived from a non-BCG vaccinated CF cohort in Sydney, Australia and a BCG-vaccinated CF cohort in Cape Town, South Africa. In mice, BCG vaccination induced multifunctional antigen-specific $CD4^+$ T cells circulating in the blood and was protective against dissemination of bacteria to the spleen. In the clinical CF cohorts, the overall rates of NTM sampling during a three-year period were equivalent; however, rates of NTM colonisation were significantly lower in the BCG-vaccinated (Cape Town) cohort, which was most apparent for *M. abscessus*. This study provides evidence that routine BCG vaccination may reduce *M. abscessus* colonisation in individuals with CF, which correlates with the ability of BCG to induce multifunctional $CD4^+$ T cells recognising *M. abscessus* in a murine model (Warner S et al, 2023).

An epitope-based vaccine candidate for Achromobacter xylosoxidans using16S rRNA amplification and immunoinformatic techniques was constructed. Achromobacter xylosoxidans is an aerobic, catalase-positive, non-pigment-forming, Gram-negative, and motile bacterium. It potentially causes a wide range of human infections in CF and non-CF patients. The vaccine construct demonstrated structural stability, thermostability, solubility, and hydrophilicity. These results highlight the value of employing immunoinformatic tools in vaccine development, paving the way for more precise approaches to prevent microbial threats (Naveed M et al, 2024).

In order to improve the immunization of people with CF reverse vaccinology has been suggested as a promising tool used to develop a broad spectrum vaccine using proteins that are well conserved across different species starting from a pathogen genome ,including Burkholderia cepacia complex, Haemophilus influenzae, Mycobacterium abscessus complex, Pseudomonas aeruginosa and Staphylococcus aureus (Cocorullo M et al, 2023).

Unresolved questions

Relatively to issue 1:

There is a need to assess the effectiveness of influenza vaccination on important clinical outcome measures and to define efficacy and safety of different types of influenza vaccines.

Issue 2:

Adequately powered, randomised controlled clinical trials have to be performed in order to increase evidence for the effectiveness of these interventions in people with CF.

Issue 3:

Caution should be considered for further trials in humans when new vaccines will be developed.

Issue 4:

Further epidemiological studies are needed to establish whether pneumococcal vaccines reduce the morbidity and mortality in people with CF. As many countries now include pneumococcal immunisation in their routine childhood vaccination schedule it is unlikely that future randomised controlled trials will be initiated. Longitudinal epidemiological studies may offer the opportunity to evaluate the efficacy of pneumococcal vaccination in reducing morbidity and mortality in people with CF.

In the next years the impact of HEMT on clinical course of lung disease could modify microbiological sputum of people with CF and consequently the prevention program of infections.

Keywords

Influenza A virus; Virus; Immunization;