

Pulmonary exacerbations in children with cystic fibrosis

Citation for published version (APA):

van Horck, M. W. P. (2017). *Pulmonary exacerbations in children with cystic fibrosis: risk factors, early detection, and health-related quality of life*. [Doctoral Thesis, Maastricht University]. Maastricht University. <https://doi.org/10.26481/dis.20170922mvh>

Document status and date:

Published: 01/01/2017

DOI:

[10.26481/dis.20170922mvh](https://doi.org/10.26481/dis.20170922mvh)

Document Version:

Publisher's PDF, also known as Version of record

Please check the document version of this publication:

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Valorisation

Valorisation

The knowledge derived from this thesis can be of societal and economical value in different ways. The valorisation of the acquired knowledge about risk factors for pulmonary exacerbations (PEX), strategies to early detect PEX, and factors influencing health-related quality of life (HRQoL) in children with cystic fibrosis (CF) is presented in this chapter.

CF is the most common life-shortening genetic disease in the Caucasian population,¹ with an incidence in the European Union of 1 in 2000-3000 newborns, and approximately 1500 people with CF living in the Netherlands.² Newborn screening has led to earlier diagnosis and therapy and consequently to improved survival.³ Recently, gene-modifying drugs that target the underlying genetic defect have been developed and resulted in clinical improvement.⁴ Life expectancy improved to 40-50 years for a child born with CF today.⁵ However, despite these advances, CF is one of the most challenging diseases to manage and is still life-shortening. The treatment regimen is intensive and takes on average 2-4 hours per day.⁶ Moreover, research has shown that a large proportion of individuals with CF and their parents have symptoms of depression and anxiety.⁷ In these ways, CF highly impacts the lives of children and their families.

Prediction of PEX in combination with early treatment may lead to less (severe) PEX, more stable disease, and eventually to an improved overall health status and a better prognosis. More stable CF in children with less (severe) PEX will have a favourable influence on quality of life and work absenteeism of their parents. Ultimately, prevention of PEX may induce fewer hospital admissions, fewer prescriptions of (chronic) medication, and perhaps even fewer lung transplants and a better survival. In this way also health costs will be lower, which is economically relevant in order to have an affordable and sustainable health care system for our society.

Electronic home monitoring of symptoms and lung function may be a step forward in prediction of PEX, especially if combined with exhaled volatile organic compounds (VOCs) measurements in the future.

The non-invasive assessment of exhaled VOCs is innovative and very promising, not only in children with CF but also in asthma and other pulmonary diseases.^{8,9} In addition, VOCs can also give information about inflammation processes in other organs.¹⁰ One of the next steps is to further determine which VOCs are most discriminatory for PEX in CF in a

large cohort. Thereafter, an RCT should be performed to assess the impact of early treatment based on prediction of PEx by VOCs on lung disease progression and HRQoL.

Several patients and parents experienced direct benefit from electronic home monitoring of lung function and symptoms: they felt supported by the availability of a home monitor, and were better able to objectify their feelings about their (child's) health status. Some children even used it on a daily basis. A home monitor gives direct objective information and therefore may enforce the self-supportiveness of these families. In this way electronic home monitoring may also positively influence HRQoL.

By means of the home monitor, the CF team was able to identify changes in respiratory symptoms or lung function on a weekly basis instead of only at check-ups every 3 months. In daily practice, home monitor data can be used by the physician in several ways, for example to discuss symptom recognition and necessary changes in management strategies.

It is possible that an eHealth approach with use of the home monitor is able to partly reduce the frequency of visits to the hospital, which in turn may have a beneficial influence on HRQoL. Next steps are to investigate electronic home monitoring in a larger (international) cohort. Further research is necessary to increase the reliability of and the adherence to the home monitor, and to assess in a larger randomised controlled trial (RCT) whether intervention based on home monitor data is indeed able to reduce PEx. If this further research supports our findings, home monitoring might be included in (inter)national CF guidelines.

The combination of electronic home monitoring with measurement of exhaled VOCs to further complete information on the patients' clinical status would be even more innovative. For this purpose industrial companies will be involved because a new, comprehensive, handheld device should be developed. Besides, the transfer of home monitor information to the CF team can be improved, an application for mobile devices is one of the future steps to make, involving information technology companies. Another step could be to incorporate even more functions in this new device, such as a serious game for children to improve mucus clearance or a tool for medication checks.

Shared decision making is an important topic in medicine. For this purpose decision aids are being developed. In advanced CF, when patients are considering lung transplant, a decision tool increased knowledge and realistic expectations while decreasing decisional conflict.¹¹ This thesis showed that an older age (above 12 years) and PEx are important

factors that negatively influence HRQoL. With this knowledge it is important to especially engage adolescents with CF to discuss possible 'obstacles' in daily life with their CF team. In this way compliance may be improved and changes in treatment may have less effect on HRQoL. Future steps could be to develop and test decision tools directed specifically at adolescents. For the implementation of such decision tools, national and international CF foundations should be involved.

Finally, this thesis showed that the use of PPI may be a risk factor for future PEx. It is not clear whether GERD or PPI use itself is the actual risk factor. One of the hypotheses why the use of PPI may lead to PEx is that the bacterial colonisation of the airways may alter as a consequence of a less acid environment of the stomach and oesophagus. The safety and possible adverse effects of PPI use in CF should be investigated in an RCT. Assessment of GERD and the airway microbiome should be part of such a trial.

References

1. O'Sullivan BP, Freedman SD. Cystic fibrosis. *Lancet*. 2009;373(9678):1891-904.
2. Foundation DCF. Dutch Cystic Fibrosis Registry, Report 2014. 2014.
3. Dijk FN, McKay K, Barzi F, Gaskin KJ, Fitzgerald DA. Improved survival in cystic fibrosis patients diagnosed by newborn screening compared to a historical cohort from the same centre. *Arch Dis Child*. 2011;96(12):1118-23.
4. Wainwright CE, Elborn JS, Ramsey BW. Lumacaftor-Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del CFTR. *N Engl J Med*. 2015;373(18):1783-4.
5. Dodge JA, Lewis PA, Stanton M, Wilsher J. Cystic fibrosis mortality and survival in the UK: 1947-2003. *Eur Respir J*. 2007;29(3):522-6.
6. Sawicki GS, Ren CL, Konstan MW, Millar SJ, Pasta DJ, Quittner AL, et al. Treatment complexity in cystic fibrosis: trends over time and associations with site-specific outcomes. *J Cyst Fibros*. 2013;12(5):461-7.
7. Smith BA, Georgiopoulos AM, Quittner AL. Maintaining mental health and function for the long run in cystic fibrosis. *Pediatr Pulmonol*. 2016;51(S44):S71-S8.
8. van de Kant KD, van der Sande LJ, Jöbsis Q, van Schayck OC, Dompeling E. Clinical use of exhaled volatile organic compounds in pulmonary diseases: a systematic review. *Respir Res*. 2012;13:117.
9. Fens N, van der Schee MP, Brinkman P, Sterk PJ. Exhaled breath analysis by electronic nose in airways disease. Established issues and key questions. *Clin Exp Allergy*. 2013;43(7):705-15.
10. Miekisch W, Schubert JK, Noeldge-Schomburg GF. Diagnostic potential of breath analysis--focus on volatile organic compounds. *Clin Chim Acta*. 2004;347(1-2):25-39.
11. Vandemheen KL, O'Connor A, Bell SC, Freitag A, Bye P, Jeanneret A, et al. Randomized trial of a decision aid for patients with cystic fibrosis considering lung transplantation. *Am J Respir Crit Care Med*. 2009;180(8):761-8.