Dental Utilization for Medicaid-Enrolled Children with Cystic Fibrosis

April 23 – 24, 2015 Elise Sarvas, DDS







Testing a Multifactorial Caries Model for Patients with Cystic Fibrosis at Seattle Children's Hospital



http://www.catalinashope.org/wp-content/uploads/2011/03/giraffe1.jpg







Rare Diseases



http://www.dailymail.co.uk/health/article-2299282/Parents-heartache-THREE-children-diagnosed-life-threatening-condition-cystic-fibrosis.html







Outline

- Cystic fibrosis overview
- Cystic fibrosis and oral health
- Study aims
- Methods
- Results
- Discussion
- Conclusion
- Acknowledgements
- Selected references







CYSTIC FIBROSIS







Overview of CF

- Most common life-limiting genetic disease in Whites
- Worldwide: 70,000 individuals
- United States: 30,000 individuals
- Prevalence overall:
 - European Union (27 countries): 0.737/10,000
 - United States: 0.797/10,000
- Prevalence by race:

| Whites | Hispanics | Blacks | Asians |
|---------|-----------|----------|----------|
| 1:3,200 | 1:7,000 | 1:15,000 | 1:31,000 |



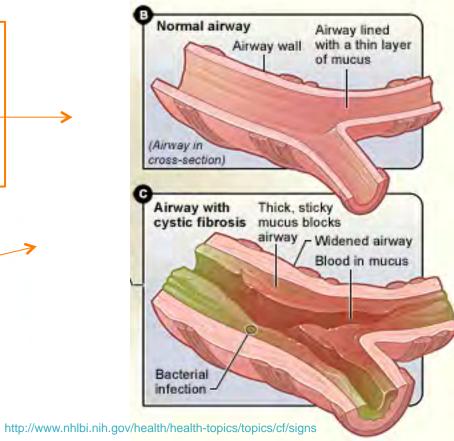




Clinical effects on organ systems: Lungs

Haemophilus influenza
Pseudomonas aeruginosa
Burkholderia cepacia
Staphylococcus aureus

Candida Aspergillus



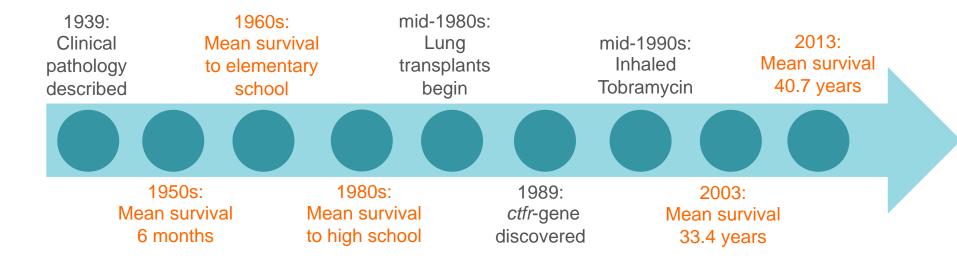
- Lung tissue damage
- Irreversible bronchiectasis and progressive respiratory failure

Seattle Children's





Life expectancy









CYSTIC FIBROSIS & ORAL HEALTH







Caries prevalence







Caries prevalence

- Lower than non-CF, healthy matched controls
 - Primosch 1980
 - Kinirons 1983, 1989, 1992
 - Aps & Martens 2004
 - Ferrazzano et al 2009
- Lower than non-CF, healthy siblings
 - Jagels & Sweeney 1976
 - Aps & Martens 2004
- Lower than individuals with chronic respiratory conditions
 - Narang et al 2003
- Lower than cohort of children with handicaps (undefined)
 - Swallow et al 1967







Risk factors for dental caries







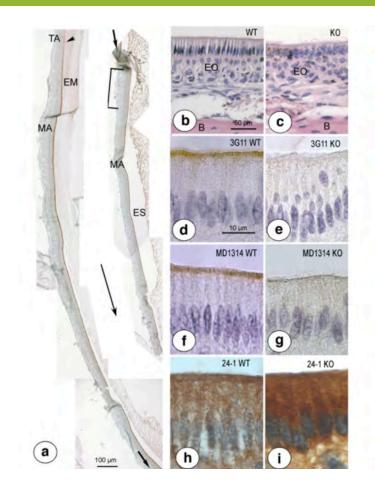
Enamel defects



Fig. 4. Diffuse hypoplasia affecting the permanent first molar.



Fig. 5. Pitted hypoplasia of the maxillary lateral incisor.



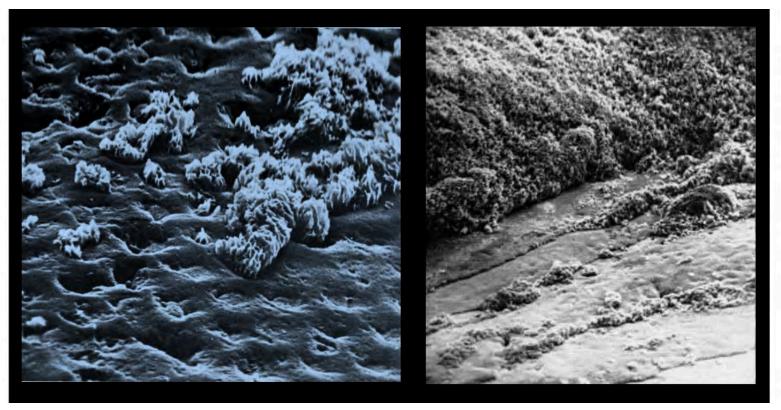






Enamel defects

- Weaken outer tooth structure
- Provide haven for microbes



http://www.ada.org/~/media/ADA/Education%20and%20Careers/Files/05_enamel_hypoplasia-caufield_bromage_b.ashx

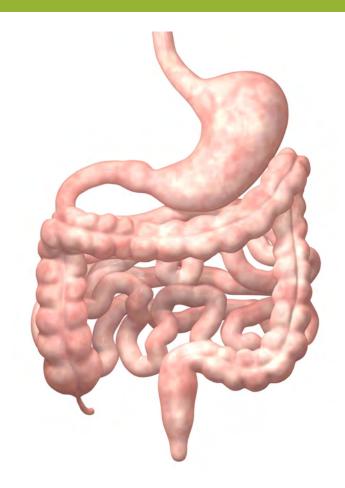






GERD

- GERD affects 55 76% of infants, children and adults with CF
- Individuals with GERD have higher caries experience than healthy siblings
 - Linnett et al 2002



http://www.interactive-biology.com/tag/intestines/







Medications

- Inhaled β-adrenergic receptor agonists
- Antibiotics
- Certain medications may increase caries risk



Fig. 2. Example of dentition demonstrating enamel hypoplasia in direct association with tetracycline discoloration.

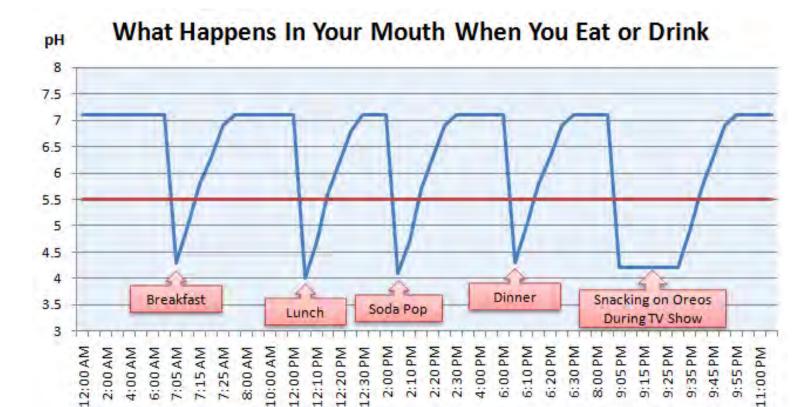
Primosch 1980







Diet



--- Critical pH at Which Teeth Start Dissolving





ORAL ANSWERS



pH in Mouth

Risk factors

- Increased risk factors:
 - Enamel defects
 - GERD
 - Antibiotics
 - Xerostomic medications

- Possible increased risk factors:
 - Oral bacteria counts
 - Periodicity of eating

Reported low caries prevalence?







Health care use

Cystic Fibrosis Foundation accredits 110 CF centers across the US

- Blank Children's CF Center: Des Moines, IA
- Mary Greenley Hospital: Ames, IA
- University of Iowa: Iowa City, IA



- Children with CF meet with their medical management team every 3 months routinely
 - Pulmonologist, nutritionist, physical therapist, respiratory therapist, nurse, social worker and others







STUDY AIMS







Study aim 1

- To compare dental use for Medicaid-enrolled children with and without CF
- Given their chronic medical condition that requires the increased use of medical care beyond what is considered normal, this may encourage families of children with CF to use dental care
- We will test the hypothesis that children with CF use dental care at a higher rate than children without CF







Study aim 2

- To compare if the types of dental care individuals with CF use are different from individuals without CF
- We will test the hypothesis that children with CF use more diagnostic and preventive care and less restorative care than children without CF







METHODS







Data

- Administrative enrollment and medical and dental claims obtained from Iowa Department of Human Services
- Ages 3 17
- Enrolled in Medicaid at least 11 months







Study population: Medicaid enrollment

607,992

Children 3 – 17 years in Iowa 2012 July estimate

234,556

- Children ages 3 17 years enrolled in Medicaid
 - Iowa requirement: 0 − 133% of the FPL

156,268

Children 3 – 17 years with at least 11 months enrollment in Medicaid







Cystic fibrosis in Iowa

380

Number of individuals with CF in Iowa according to CFF in 2012

190

• Estimated number of children with CF in Iowa as half of individuals with CF are under 18 years old

101

• Estimate as 53% of children with CF have state or Medicaid insurance. This is not mutually exclusive of other types of insurance

99

• Individuals with CF identified in our study between 3 – 17 years

85

 Individuals with CF in our study with at least 11 months enrollment in Medicaid







Study variables: Independent & Dependent

- Independent variable: CF status
 - Case: ICD-9 CF codes (277.00, 277.01, 277.02, 277.03 or 277.09)
 - Control: No ICD-9 CF codes

- Dependent variable: Use of dental care
 - Use defined as any CDT code claimed
 - Further categorized as Diagnostic, Preventive, Routine Restorative or Complex Restorative







Study variables: Other

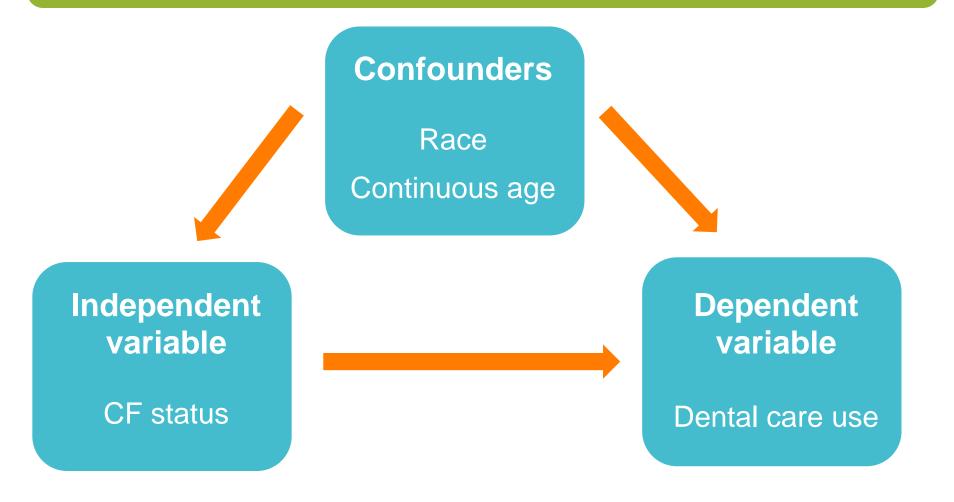
- Continuous age calculated from January 1, 2015
- Categorical age corresponding to diphyodont stages
 - 3 5 years: Primary dentition
 - 6 − 12 years: Mixed dentition
 - 13 17 years: Permanent dentition
- Gender
- Race
 - White
 - Black
 - Hispanic Includes Hispanic and Multi-Hispanic
 - Other Includes American Indian, Asia, Pacific Islander, Multi Other
 - Unknown







Confounders









RESULTS







Bivariate statistics: Dental care use







Dental care use

| Any dental care | | | | |
|--------------------|------------|-----------------|--|--|
| | With CF | Without CF | | |
| Number of children | 43 (50.6%) | 104,409 (69.7%) | | |

p < 0.001







Dental care use

| Types of dental care (number of children) | | | | | |
|---|------------|-----------------|---------|--|--|
| | With CF | Without CF | p-value | | |
| Diagnostic | 42 (49.4%) | 104,409 (66.9%) | 0.177 | | |
| Preventive | 41 (48.2%) | 102,718 (65.8%) | 0.201 | | |
| Routine restorative | 5 (5.9%) | 30,602 (19.6%) | 0.100 | | |
| Complex restorative | 6 (7.1%) | 18,714 (12.0%) | 0.935 | | |







Multiple variable regression models: Dental care use







Dental care use

| Any dental care (adjusted for race and age) | | | |
|---|-------------|---------|--|
| IRR | 95% CI | p-value | |
| 0.819 | 0.80 - 0.84 | < 0.001 | |







Dental care use

| Types of dental care (adjusted for race and age) | | | | |
|--|------|-------------|---------|--|
| | IRR | 95% CI | p-value | |
| Diagnostic | 1.21 | 0.89 - 1.64 | 0.225 | |
| Preventive | 1.19 | 0.88 - 1.63 | 0.264 | |
| Routine restorative | 0.50 | 0.19 - 1.34 | 0.165 | |
| Complex restorative | 0.82 | 0.31 - 2.16 | 0.684 | |







DISCUSSION







Study aim 1

- Study conducted to compare dental use for Medicaidenrolled children with and without CF
 - Children with CF are more integrated into the health care system
 - Hypothesis tested that children with CF use dental care at a higher rate than children without CF.
- Only about half of Medicaid-enrolled children with CF used dental care in 2012
 - Significantly less use than children without CF
 - Relationship holds true even when adjusted for race and age
- Other health care obligations
- Resource constraints
- Few dental referrals from CF team







Study aim 2

- Study conducted to compare if the types of dental care individuals with CF use are different from individuals without CF.
 - Hypothesis that children with CF use more diagnostic and preventive care and less restorative care than children without CF
- Children with CF use more diagnostic and preventive services than children without CF, but this difference is not significant
 - Relationship holds true when adjusted for race and age
- Some other etiology behind their low caries risk (i.e. a biological explanation)
- Sub-optimal services for everyone







Study aim 2

- Children with CF use less restorative care than children without CF, but this different is not significant.
 - Relationship holds true when adjusted for race and age
 - Holds true for both routine and complex restorative care
- May lend support to the literature that children with CF have lower caries prevalence than children without CF
- May be a result of children with CF using less dental care than children with CF

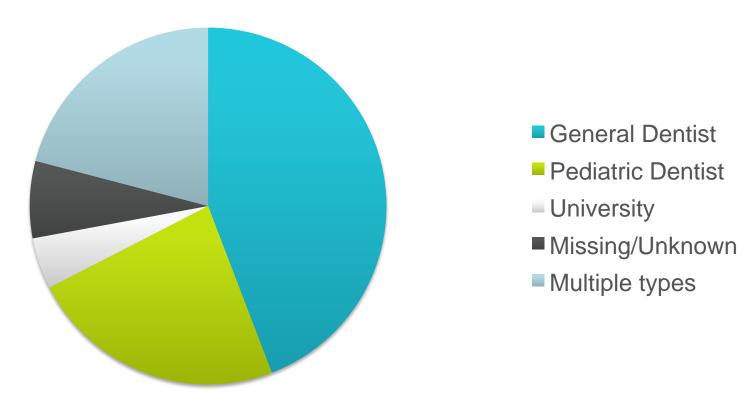






Dental provider type

Provider Types









Study strengths

- Adds previously missing analysis of dental care use to the small but growing body of knowledge about the oral health of individuals with CF
 - Previous studies focus on oral health characteristics, caries prevalence
- Our study compares similar groups of children who may be missed from traditional studies of dental care
 - Previous studies have inherent bias because they rely on families and children who present to academic medical centers.







Study limitations

- Study only encompasses one year and only one state
 - Future studies should look at multiple years and/or states
- Dental provider type assessed only for children with CF
 - Unable to currently do a statistical analysis
- Dental utilization rates do not give an accurate picture of existing dental needs
 - Just because children with CF did not use dental care does not mean they do not have dental needs.







Clinical recommendations

CF team

- be more cognizant about oral health
- increase dental referrals

General dentists

- increase
 pre-doctoral
 education for
 treating patients
 with SHCNs
- recognize caries risk

Individuals with CF

- recognize increased caries risk factors
- understand oral health implications on overall health







Future directions



- Further research into what types of dental providers individuals with CF use
 - Direct future dental education
- Look at dental use trends over multiple years and in multiple states
- Survey families on barriers to dental care
- Conduct clinical trials to look at risk factors for dental caries in individuals with CF.







CONCLUSION







Conclusion

- Children with CF face increased risk factors for developing dental caries, but the literature reports they paradoxically have an overall lower caries prevalence
- Increased dental care use is not a probable etiology for this lower caries prevalence as children with CF use less than children without CF
- Future population and clinical studies are needed to determine why children with CF have lower caries prevalence







Rare Diseases



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REFERENCES







Selected references

- AAP. (1975). American Academy of Pediatrics. Committee on drugs. Requiem for tetracyclines. Pediatrics, 55(1), 142–3.
- AAPD. (2013). Guideline on periodicity of examination, preventive dental services, anticipatory guidance/counseling, and oral treatment for infants, children, and. *Pediatric Dentistry*, *35*(5), E148–56.
- AAPD. (2014). AAPD Residency Programs. Retrieved from http://www.aapd.org/residency-program/.
- Alfaro, E. V., Aps, J. K. M., & Martens, L. C. (2008). Oral implications in children with gastroesophageal reflux disease. *Current Opinion in Pediatrics*, 20(5), 576–83. doi:10.1097/MOP.0b013e32830dd7df
- Aps, J. K. M., & Martens, L. C. (2004). [Oral health risks in patients with cystic fibrosis]. Revue Belge de Médecine Dentaire, 59(2), 114–20.
- Aps, J. K., Van Maele, G. O., Claeys, G., Martens, L. C. (2001). Mutans streptococci, lactobacilli and caries experience in cystic fibrosis homozygotes, heterozygotes and healthy controls. *Caries Research*, 35(6), 407–11.
- Arquitt, C. K., Boyd, C., & Wright, J. T. (2002). Cystic Fibrosis Transmembrane Regulator Gene (CFTR) is Associated with Abnormal Enamel Formation. *Journal of Dental Research*, 81(7), 492–496. doi:10.1177/154405910208100712
- Azevedo, T., Feijo, G., & Bezerra, A. (2006). Presence of developmental defects of enamel in cystic fibrosis patients. *Journal of Dentistry for Children (Chicago, III.)*, 73(1), 159–163.
- Berlinski, A., Chambers, M. J., Willis, L., Homa, K., & Com, G. (2014). Redesigning care to meet national recommendation of four or more yearly clinic visits in patients with cystic fibrosis. *BMJ Quality & Safety*, 23 Suppl 1, i42–9. doi:10.1136/bmjgs-2013-002345
- Blacharsh, C. (1977). Dental aspects of patients with cystic fibrosis: a preliminary clinical study. *Journal of the American Dental Association* (1939), 95(1), 106–10.
- Blondeau, K., Pauwels, a, Dupont, L., Mertens, V., Proesmans, M., Orel, R., Sifrim, D. (2010). Characteristics of gastroesophageal reflux and potential risk of gastric content aspiration in children with cystic fibrosis. *Journal of Pediatric Gastroenterology and Nutrition*, 50(2), 161–6. doi:10.1097/MPG.0b013e3181acae98
- Bronckers, A., Kalogeraki, L., Jorna, H. J. N., Wilke, M., Bervoets, T. J., Lyaruu, D. M., ... de Jonge, H. (2010). The cystic fibrosis transmembrane conductance regulator (CFTR) is expressed in maturation stage ameloblasts, odontoblasts and bone cells. *Bone*, *46*(4), 1188–96. doi:10.1016/j.bone.2009.12.002
- Catalán, M. a, Scott-Anne, K., Klein, M. I., Koo, H., Bowen, W. H., & Melvin, J. E. (2011). Elevated incidence of dental caries in a mouse model of cystic fibrosis. *PloS One*, 6(1), e16549. doi:10.1371/journal.pone.0016549
- Chi, D. L. (2013). Dental caries prevalence in children and adolescents with cystic fibrosis: a qualitative systematic review and recommendations for future research. *International Journal of Paediatric Dentistry / the British Paedodontic Society [and] the International Association of Dentistry for Children*, 23(5), 376–86. doi:10.1111/jpd.12042







Selected references

- Chi, D. L., Momany, E. T., Kuthy, R. a, Chalmers, J. M., & Damiano, P. C. (2010). Preventive dental utilization for Medicaid-enrolled children in lowa identified with intellectual and/or developmental disability. *Journal of Public Health Dentistry*, 70(1), 35–44. doi:10.1111/j. 1752-7325.2009.00141.x
- Chi, D. L., Rossitch, K. C., & Beeles, E. M. (2013). Developmental delays and dental caries in low-income preschoolers in the USA: a pilot cross-sectional study and preliminary explanatory model. *BMC Oral Health*, *13*, 53. doi:10.1186/1472-6831-13-53
- Children's Health Insurance Program. (2012).
- Cua, F. T. (1991). Calcium and phosphorous in teeth from children with and without cystic fibrosis. *Biological Trace Element Research*, 30(3), 277–89.
- Cystic Fibrosis Foundation. (2012). Cystic Fibrosis Foundation 2011 Patient Registry Annual Data Report. Bethesda, MD.
- Dabrowska, E., Błahuszewska, K., Minarowska, A., Kaczmarski, M., Niedźwiecka-Andrzejewicz, I., & Stokowska, W. (2006). Assessment of dental status and oral hygiene in the study population of cystic fibrosis patients in the Podlasie province. Advances in Medica, 51 Suppl 1, 100–103.
- Farrell, P. M. (2008). The prevalence of cystic fibrosis in the European Union. *Journal of Cystic Fibrosis : Official Journal of the European Cystic Fibrosis Society*, 7(5), 450–3. doi:10.1016/j.jcf.2008.03.007
- Feranchak, A. P. (2004). Hepatobiliary complications of cystic fibrosis. Current Gastroenterology Reports, 6(3), 231-9.
- Ferrazzano, G. F., Orlando, S., Sangianantoni, G., Cantile, T., & Ingenito, a. (2009). Dental and periodontal health status in children affected by cystic fibrosis in a southern Italian region. *European Journal of Paediatric Dentistry : Official Journal of European Academy of Paediatric Dentistry*, 10(2), 65–8.
- Ferrazzano, G., & Sangianantoni, G. (2012). Dental enamel defects in Italian children with cystic fibrosis: an observational study. *Community Dental* 29(1), 106–109.
- Flume, P. a, O'Sullivan, B. P., Robinson, K. a, Goss, C. H., Mogayzel, P. J., Willey-Courand, D. B., ... Marshall, B. (2007). Cystic fibrosis pulmonary guidelines: chronic medications for maintenance of lung health. *American Journal of Respiratory and Critical Care Medicine*, 176(10), 957–69. doi:10.1164/rccm.200705-664OC
- Halfhide, C., Hj, E., & Couriel, J. (2011). Inhaled bronchodilators for cystic fibrosis (Review), (5).
- Jagels, A. E., & Sweeney, E. A. (1976). Oral health of patients with cystic fibrosis and their siblings. Journal of Dental Research, 55(6), 991–6.
- Kargul, B., Tanboga, I., Ergeneli, S., Karakoc, F., & Dagli, E. (1998). Inhaler medicament effects on saliva and plaque pH in asthmatic children. *The Journal of Clinical Pediatric Dentistry*, 22(2), 137–40.
- Kaye, C. I., Accurso, F., La Franchi, S., Lane, P. a, Hope, N., Sonya, P., Michele A, L.-P. (2006). Newborn screening fact sheets. *Pediatrics*, 118(3), e934–63. doi:10.1542/peds.2006-1783







Selected References

- Kinirons, M. J. (1983). Increased salivary buffering in association with a low caries experience in children suffering from cystic fibrosis. Journal of Dental Research, 62(7), 815–7.
- Kinirons, M. J. (1985). Dental Health of Children with Cystic Fibrosis: An interim report. Journal of Paediatric Dentistry, 1(1), 3–7.
- Kinirons, M. J. (1989). Dental health of patients suffering from cystic fibrosis in Northern Ireland. Community Dental Health, 6(2), 113–20.
- Kinirons, M. J. (1992). The effect of antibiotic therapy on the oral health of cystic fibrosis children. International Journal of Paediatric
 Dentistry / the British Paedodontic Society [and] the International Association of Dentistry for Children, 2(3), 139–43.
- Linnett, V., Seow, W. K., Connor, F., & Shepherd, R. (2002). Oral health of children with gastro-esophageal reflux disease: a controlled study. *Australian Dental Journal*, *47*(2), 156–62.
- Milano, M., Lee, J. Y., Donovan, K., & Chen, J.-W. (2006). A cross-sectional study of medication-related factors and caries experience in asthmatic children. *Pediatric Dentistry*, 28(5), 415–9.
- Moffitt, J. M., Cooley, R. O., Olsen, N. H., & Hefferren, J. J. (1974). Prediction of tetracycline-induced tooth discoloration. *Journal of the American Dental Association (1939), 88*(3), 547–52.
- Moran, a, Hardin, D., Rodman, D., Allen, H. F., Beall, R. J., Borowitz, D., ... Zipf, W. B. (1999). Diagnosis, screening and management of cystic fibrosis related diabetes mellitus: a consensus conference report. Diabetes Research and Clinical Practice, 45(1), 61–73.
- Moursi, A. M., Fernandez, J. B., Daronch, M., Zee, L., & Jones, C. L. (2010). Nutrition and oral health considerations in children with special health care needs: implications for oral health care providers. *Pediatric Dentistry*, 32(4), 333–42.
- Mousa, H. M., & Woodley, F. W. (2012). Gastroesophageal reflux in cystic fibrosis: current understandings of mechanisms and management.
 Current Gastroenterology Reports, 14(3), 226–35. doi:10.1007/s11894-012-0261-9
- Narang, a, Maguire, A., Nunn, J., & Bush, A. (2003). Oral health and related factors in cystic fibrosis and other chronic respiratory disorders. *Archives of Disease in Childhood, 88*(8), 702–707.
- Primosch, R. (1980). Dental and skeletal maturation in patients with cystic fibrosis. Journal of Oral Medicine, 35(1), 7–13.
- Primosch, R. E. (1980). Tetracycline discoloration, enamel defects, and dental caries in patients with cystic fibrosis. *Oral Surgery, Oral Medicine*, and *Oral Pathology*, 50(4), 301–8.
- Ratjen, F., & Döring, G. (2003). Cystic fibrosis. Lancet, 361(9358), 681–9. doi:10.1016/S0140-6736(03)12567-6
- Robinson, P. (2001). Cystic fibrosis. *Thorax*, 56(3), 237–41.
- Rommens, J. M., lannuzzi, M. C., Kerem, B., Drumm, M. L., Melmer, G., Dean, M., Hidaka, N. (1989). Identification of the cystic fibrosis gene: chromosome walking and jumping. *Science (New York, N.Y.)*, 245(4922), 1059–65.
- Rowe, S. M., Miller, S., & Sorscher, E. J. (2005). Cystic fibrosis. The New England Journal of Medicine, 352(19), 1992–2001. doi:10.1056/ NEJMra043184







Selected references

- Salvatore, D., Buzzetti, R., Baldo, E., Furnari, M. L., Lucidi, V., Manunza, D., ... Mastella, G. (2012). An overview of international literature from cystic fibrosis registries. Part 4: update 2011. *Journal of Cystic Fibrosis : Official Journal of the European Cystic Fibrosis Society*, 11(6), 480–93. doi:10.1016/j.jcf.2012.07.005
- Siracusa, C. M., Weiland, J. L., Acton, J. D., Chima, A. K., Chini, B. A., Hoberman, A. J., McPhail, G. L. (2014). The impact of transforming healthcare delivery on cystic fibrosis outcomes: a decade of quality improvement at Cincinnati Children's Hospital. *BMJ Quality & Safety*, 23 Suppl 1, i56–i63. doi:10.1136/bmigs-2013-002361
- Smyth, A. R., Bell, S. C., Bojcin, S., Bryon, M., Duff, A., Flume, P., Wolfe, S. (2014). European Cystic Fibrosis Society Standards of Care: Best Practice guidelines. *Journal of Cystic Fibrosis: Official Journal of the European Cystic Fibrosis Society*, 13S1, S23–S42. doi:10.1016/j.jcf. 2014.03.010
- Sokol, R. J., & Durie, P. R. (1999). Recommendations for management of liver and biliary tract disease in cystic fibrosis. Cystic Fibrosis Foundation Hepatobiliary Disease Consensus Group. *Journal of Pediatric Gastroenterology and Nutrition*, 28 Suppl 1(9), S1–13.
- Storhaug, K. (1985). Caries experience in disabled pre-school children. Acta Odontologica Scandinavica, 43(4), 241–8.
- Storhaug, K., & Holst, D. (1987). Caries experience of disabled school-age children. *Community Dentistry and Oral Epidemiology*, 15(3), 144–9.
- Strausbaugh, S. D., & Davis, P. B. (2007). Cystic fibrosis: a review of epidemiology and pathobiology. *Clinics in Chest Medicine*, 28(2), 279–88. doi:10.1016/j.ccm.2007.02.011
- Swallow, J. N., De Haller, J., & Young, W. F. (1967). Side-effects to antibiotics in cystic fibrosis: dental changes in relation to antibiotic administration. *Archives of Disease in Childhood*, 42(223), 311–8.
- Sweeney, E. A., & Shaw, J. H. (1965). The effect of dietary pancreatin supplements on dental caries and on the composition of saliva in caries-susceptible rats. *Journal of Dental Research*, 44(5), 973–6.
- Vic, P., Tassin, E., Turck, D., Gottrand, F., Launay, V., & Farriaux, J. P. (1995). Frequency of gastroesophageal reflux in infants and in young children with cystic fibrosis. *Archives of Pediatrics*, 2, 742–746.
- Waldman HB, Ackerman MB, P. S. (2014). Increasing use of dental services by children, but many are unable to secure needed care. *J Clin Pediatr Dent*, 39(1), 9–11.
- Williams, B. J., Dehnbostel, J., & Blackwell, T. S. (2010). Pseudomonas aeruginosa: host defense in lung diseases. Respirology (Carlton, Vic.), 15(7), 1037–56. doi:10.1111/j.1440-1843.2010.01819.x
- Woestenenk, J. W., Castelijns, S. J. a M., van der Ent, C. K., & Houwen, R. H. J. (2012). Nutritional intervention in patients with Cystic Fibrosis: A systematic review. *Journal of Cystic Fibrosis : Official Journal of the European Cystic Fibrosis Society*, 12(2), 102–115. doi:10.1016/j.jcf. 2012.11.005













