Infectious Diseases Pharmacotherapy for Children With Cystic Fibrosis CE

Leah Molloy, PharmD, & Kristen Nichols, PharmD, BCPS

Leah Molloy, Clinical Pharmacist Specialist, Pediatric Infectious Diseases, Department of Pharmacy, Children's Hospital of Michigan, Detroit Medical Center, Detroit, MI.

Kristen Nichols, Assistant Professor of Pharmacy Practice, Butler University College of Pharmacy and Health Sciences, Indianapolis, IN; Clinical Pharmacist Specialist, Pediatric Infectious Diseases, Riley Hospital for Children at Indiana University Health, Indianapolis, IN; and Co-Director, Pediatric Antimicrobial Stewardship Program, Department of Pediatrics, Ryan White Center for Pediatric Infectious Diseases, Indiana University School of Medicine, Indianapolis, IN.

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Correspondence: Leah Molloy, PharmD, Department of Pharmacy, Children's Hospital of Michigan, 3901 Beaubien, Detroit, MI 48322; e-mail: LMolloy@DMC.org.

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ABSTRACT

Cystic fibrosis (CF) affects several organs, most notably the lungs, which become predisposed to infections with potentially severe consequences. Because of physiologic changes and infection characteristics, unique approaches to antimicrobial agent selection, dosing, and administration are needed. To provide optimal acute and long-term care, pediatric health care providers must be aware of these patient features and common approaches to antimicrobial therapy in CF, which can differ significantly from those of other infectious diseases. The purpose of this article is to review common respiratory pathogens, pharmacology of commonly used antimicrobial agents, and unique pharmacokinetics and dosing strategies often used when treating children with CF. J Pediatr Health Care. (2015) *29*, 565-578.

KEY WORDS

CF, Cystic Fibrosis ID Pharmacotherapy, Cystic Fibrosis ID Pharmacology

OBJECTIVES

1. Identify common respiratory tract pathogens in cystic fibrosis.
2. Describe basic pharmacology of antimicrobial agents commonly used in cystic fibrosis.
3. Explain how altered pharmacokinetics in children with cystic fibrosis warrant unique dosing strategies.
4. Recommend appropriate antimicrobial regimens for acute pulmonary exacerbations.
5. Describe the approach to chronic infection for children with cystic fibrosis.

Cystic fibrosis (CF), the most common deadly genetic disease, is primarily described among White patients. Because of alterations of the CF transmembrane regulator (CFTR) gene, dysfunctional chloride and bicarbonate transfer across cell membranes results in significantly more viscous mucus. This abnormality affects a number of organs, including the intestine,

pancreas, and vas deferens in males. The most notably affected organ is the lungs, wherein this increased mucus viscosity substantially impairs mucociliary function (Stoltz, Meyerholz, & Welsh, 2015). These physiologic changes reduce patients' ability to clear sputum and subsequently predispose them to respiratory infections, which can lead to acute pulmonary exacerbations (APEs).

APEs manifest as a group of respiratory symptoms such as cough, shortness of breath, positive findings on chest examination through auscultation or imaging, and decline in respiratory function as measured by forced expiratory volume in 1 second (FEV-1; Flume et al., 2009; Stenbit & Flume, 2011). Although APEs are common and important complications of CF, a standardized definition for diagnosis does not exist. Proposed criteria have additionally included hemoptysis, decreased oxygen saturation, weight loss, and reduced exercise tolerance (Anstead et al., 2014).

In addition to patient discomfort and the need for medical intervention, APEs can have a detrimental impact on long-term lung function. In two different studies, about one quarter of patients failed to recover an FEV-1 of at least 90% to 95% of baseline within 3 months of treatment for an APE, and most of these had still had not recovered lung function within 6 months after treatment (Sanders et al., 2010a; Sanders et al., 2010b). Severity and frequency of APEs also impact outcomes. Patients presenting with greater declines in FEV-1 are less likely to recover baseline lung function within 3 months, and the occurrence of three or more APEs in adults (or any number of APEs in children) is associated with a greater rate of lung function decline compared with patients without APEs (Sanders, Bittner, Rosenfeld, Redding, & Goss, 2011). Additionally, patients who experience more frequent APEs are at an increased risk for lung transplant and mortality (deBoer et al., 2011). Thus, prompt and effective antimicrobial therapy is important to the appropriate management and potential prevention of APEs.

Numerous pathogens have been implicated in CF lung disease. Among the most common are *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Haemophilus influenzae*, *Stenotrophomonas maltophilia*, *Achromobacter xylosoxidans,* and *Burkholderia cepacia* complex (Ciofu, Hansen, & Hoiby, 2013; Razvi et al., 2009). Reported data from the CF Foundation (CFF) indicate that *H. influenzae* and *S. aureus* are more common in children, while the prevalence of *P. aeruginosa* increases with age and is greater among patients older than 18 years (Saiman et al., 2014). Although certain pathogens may be predicted to some degree per patient age, respiratory CF infections are largely polymicrobial (Sibley & Surette, 2011). As such, the selection of antibiotic agents is multifactorial, especially in the empiric setting when current culture results are not yet known. In addition to considering common pathogens, clinicians must also review patient-specific cultures from previous infections and determine whether identified organisms are colonizers or true pathogens. Finally, once current respiratory culture and susceptibility data become available, the antimicrobial regimen should be tailored carefully to target currently isolated causative pathogens, while still acknowledging other organisms isolated on recent past cultures. Additionally, unrecognized pathogens can lessen the predictability of clinical outcomes on the basis of in vitro culture and susceptibility results (Aaron et al., 2005; Sibley & Surette, 2011).

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PHARMACOKINETIC CONSIDERATIONS

Pharmacokinetics (PK) and pharmacodynamics (PD) are integral to managing infectious diseases in patients with CF. PK describes the way medications are absorbed, distributed in the body, metabolized, and eliminated; some of these parameters are known to be altered in patients with CF, requiring an individualized approach to drug dosing (McKinnon & Davis, 2004; Rey, Treluyer, & Pons, 1998; Touw, 1998; Zobell et al., 2013).

Absorption

CF-related changes to the gastrointestinal tract such as chronic inflammation, fat malabsorption, nausea, and vomiting impair adequate nutritional intake and may also result in variable drug absorption, although the impact of these factors alone on antimicrobial therapy appears to be minimal. However, patients with significant nutrient malabsorption causing inadequate weight gain commonly require enteral feeding tubes, which can affect antibiotic absorption. For example, fluoroquinolone drugs are best absorbed from an acidic environment. Therefore, administration through a gastric tube terminating in the stomach is preferred over a jejunostomy tube terminating in the less acidic small intestine, where higher doses may be considered to overcome this barrier. Additionally, co-administration of antibiotics with enteral feedings can impair drug absorption and often need to be given