Most patients with cystic fibrosis may receive insufficient antibiotics to fight lung infections

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Andrea Hahn, M.D., MS, an infectious disease specialist at Children's National Health System and the study's lead author Credit: Children's National Health System

The majority of patients with cystic fibrosis may not achieve blood concentrations of antibiotics sufficiently high enough to effectively fight bacteria responsible for pulmonary exacerbations, leading to worsening pulmonary function, indicates a study led by researchers at Children's National Health System. Additionally, the study findings show that it's impossible to predict solely from dosing regimens which patients will achieve therapeutically meaningful antibiotic concentrations in their blood.

The findings, published online in the *Journal of Pediatric Pharmacology and Therapeutics*, suggest that closely monitoring blood antibiotic concentrations could prove key to improving clinical outcomes.

Cystic fibrosis, a genetic condition that affects about 70,000 people worldwide, is characterized by a buildup of thick, sticky mucus in patients' lungs. There, the mucus traps bacteria, causing patients to develop frequent lung infections that progressively damage these vital organs and impair patients' ability to breathe.

These infections, which cause a host of symptoms collectively known as pulmonary exacerbations, are typically treated with a combination of at least two antibiotics with unique mechanisms. One of these drugs is typically a Beta-lactam antibiotic, a member of a family of antibiotics that includes penicillin derivatives, cephalosporins, monobactams and carbapenems.

Although all antibiotics have a minimum concentration threshold necessary to treat infections, Beta-lactam antibiotics are time-dependent in their bactericidal activity. Their concentrations must exceed a minimum inhibitory concentration for a certain period. However, explains study lead author Andrea Hahn, M.D., MS, an infectious

disease specialist at Children's National, blood concentrations of Beta-lactam antibiotics aren't typically tracked while patients receive them.

Since antibiotic dosing often doesn't correlate with cystic fibrosis patients' clinical outcomes, Dr. Hahn and colleagues examined whether patients actually achieved serum antibiotic concentrations that are therapeutically effective.

The researchers collected data from 19 patients seen at Children's Cystic Fibrosis Center. For each patient, the researchers collected respiratory secretions on four different occasions:

- When they were at the clinic for a well-visit
- At the beginning of an acute pulmonary exacerbation that required intravenous antibiotic therapy
- After treating that acute pulmonary exacerbation and
- More than 30 days after the patient completed the treatment course.

The researchers also checked plasma drug concentrations of Beta-lactam antibiotics during each patient's treatment course. They collected samples at a minimum of four time points:

- A trough of fewer than 30 minutes before a dose
- A peak one hour after a dose was infused
- A sample three to four hours after the dose was infused and
- A repeat trough fewer than 30 minutes before another dose.

In addition, all the patients underwent pulmonary function tests at the start of their exacerbations and about once weekly until their antibiotic therapy ended.

Using these data points, the researchers constructed a model to

determine which patients had achieved therapeutic concentrations for the bacteria found in their respiratory secretions. They then correlated these findings with the results of patients' pulmonary function tests. Just 47 percent of patients had achieved therapeutic concentrations. Those who achieved significantly high antibiotic exposure had more improvement on their pulmonary function tests compared with patients who didn't.

Paradoxically, they discovered that although each patient received recommended antibiotic doses, some patients had adequately high serum antibiotic concentrations while others did not.

Dr. Hahn notes that real-time monitoring of antibiotic blood concentrations could help doctors stay on top of whether patients are being adequately dosed. The research team is investigating this in a new study.

Another way to ensure patients receive therapeutically meaningful levels of antibiotics is to develop new models that incorporate variables such as age, gender and creatinine clearance—a measure of kidney function that can be a valuable predictor of metabolism—to predict drug pharmacokinetics. Using findings from this research, Dr. Hahn adds, Children's National already has implemented an algorithm using different variables to determine antibiotic dosing for patients treated at the hospital.

"Getting adequate treatment is crucial for getting better," she says. "At Children's National, we are implementing policies to make sure that happens for our patients with cystic fibrosis, infusing new research insights into patients' ongoing clinical care."

More information: Andrea Hahn et al, Relationship of Pulmonary Outcomes, Microbiology, and Serum Antibiotic Concentrations in Cystic

Fibrosis Patients, *The Journal of Pediatric Pharmacology and Therapeutics* (2018). DOI: 10.5863/1551-6776-23.5.379