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Benefits of set length antibiotic treatment for pulmonary exacerbations

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Pulmonary exacerbations (PEx) in patients with cystic fibrosis (CF) continue to be important clinical events that are associated with significant morbidity and risk of diminished survival. (1) There are no validated diagnostic criteria to define PEx; however patients tend to present with increasing sputum production, reduction in lung function, diminished appetite, and weight loss.(1)

PEx are also associated with more rapid lung function decline, poorer quality of life, and increased healthcare costs.(2) Studies that have focused on clinical outcomes after PEx have noted poorer short-term outcomes, including reduced recovery of lung function in a substantial fraction of events (up to 50%).(3, 4) It is possible that some PEx treatment decisions may account for poorer outcomes. (5) For example, in the US, treatment with intravenous (IV) antibiotics for less than 9 days and treatment entirely as an outpatient have both been associated with an increased risk of retreatment with IV antibiotics within 30 days of PEx treatment completion, despite similar patient characteristics at IV antibiotic initiation.(5)

A systematic review performed to develop treatment guidelines for the management of PEx found insufficient evidence for most treatment decisions (6) but treatment with antibiotics (including oral, inhaled and intravenous formulations in various combinations) are considered standard of care.(6) Based on the 2016 US CF Foundation Patient Registry (CFFPR), more than 17,000 PEx events treated with IV antibiotics were recorded. Examination of the median IV antibiotic duration reveals dramatic variation in duration of

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IV antibiotic use by center. Consistent with when there is an absence of high quality evidence to guide care, clinical practice often devolves to dramatic variation in care. It is difficult to presume that all of the patients were treated with the optimal duration of antibiotics, and it is more likely that there are durations that are too short, resulting in insufficient treatment (5) or too long, adding cost and increasing risk of adverse effects. This implies there is a duration that would be considered optimal. Although this could be determined by achievement of a specific measure (e.g. biomarker or clinical outcome), there are no such measures that have yet been identified and daily assessment is impractical. The other option is to identify a standard duration that is appropriate for the large majority of patients.

Other disease settings have benefitted from carefully studying the appropriate duration of antibiotic use, enabling guidelines to clearly delineate standard durations of treatment. For instance, by conducting high quality clinical trials, guidelines by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases have been able to make strong recommendations regarding the duration of treatment for uncomplicated cystitis and pyelonephritis (oral trimethoprim-sulfamethoxazole for 3 days and oral ciprofloxacin for 7 days respectively).(7) Based on high quality evidence, duration of treatment can be standardized, leading to cost reductions and reduction in complications related to inappropriate antibiotic use including changes in bacterial resistance patterns in populations.(8) In fact, data regarding duration of antibiotic treatment for ventilator associated pneumonia, community acquired pneumonia and soft tissue infections have all supported standardized shorter durations of treatments than had been widely adopted decades ago.(9) Having quality evidence to establish an optimal duration of treatment is central to any use of a therapeutic including and especially antimicrobial agents. Although there will be treatment failures and treatment complications even with standard dosing durations, we must strive to optimize our understanding of treatment duration using high quality data to minimize these occurrences, balancing the cost and benefits of antibiotic duration. We acknowledge that there may be multiple etiologies and duration of symptoms when our patients are offered IV therapy, but this does not mean that there should be multiple treatment regimens or durations. The same could be argued for all other pulmonary infections (COPD exacerbation, pneumonia, chronic bronchitis) and yet a standardized duration was indeed possible.

Given the strong evidence and successful implementation in other diseases, it is very possible for an optimal standard duration of IV antibiotic therapy to be defined in CF. For this reason, the Standardized Treatment of Pulmonary Exacerbations (STOP) study (clinicaltrials.gov NCT02109822) was conducted to refine key clinical endpoints and variance for treatment response for an IV exacerbation in CF.(10) This study led to the initiation of the STOP2 study (NCT02781610).(11) The STOP2 trial is a divergent trial design that evaluates subjects' interim improvement in lung function as measured by forced expiratory volume in one second (FEV₁) and symptoms as measured by a CF specific respiratory symptom diary to tailor randomization to IV treatment duration (10 vs. 14 days for early responders, 14 vs. 21 days for delayed responders). While one could have envisioned a treatment arm in this trial based solely on symptomatic response, several key challenges arise from such a trial design. First, although patients may be willing to end

antibiotics at a point when their symptoms had hit an asymptote at 5 days, physicians would unlikely be willing to stop early; we found sites unwilling to participate in the STOP2 study merely because we had a treatment arm that included only 10 days of treatment in a population that would have already had a robust symptom and lung function response. S Next, no baseline standardized symptom collection (when the patient is well) is routinely available thus making symptom response as an endpoint challenging. Last, we found that the symptom score was highly sensitive to treatment, but the large symptom improvement observed across the population regardless of treatment duration raises questions about the treatment-associated specificity of symptom changes.(12) Data from this large-scale randomized controlled trial (RCT) (STOP2 trial will have over 850 CF patients) will provide clear evidence regarding the optimal duration of IV antibiotics for adults with CF who present with a physician-defined PEx. Equally important, in conjunction with the RCT, there are ancillary studies including a detailed cost benefit analysis to fully understand the implications of the trial results.

A new era for evidence for the treatment for acute pulmonary exacerbation in CF has begun. The goal is to develop a standardized protocol for the management of acute pulmonary exacerbation in CF – this has the potential to reduce practice variability, optimize care and better understand the risks and benefits for specific durations of IV antibiotics for exacerbation. It is time to create order from chaos and improve the lives of our patients.

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