

Hospitalization for COPD Exacerbation: An Opportunity for Azithromycin?

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Abstract

Hospital admission for COPD exacerbation is a frequent and costly event. Although preventing hospitalization is a key goal for patients and healthcare systems, the hospital admission represents an opportunity to optimize care. Daily azithromycin therapy has been shown to reduce COPD exacerbations, yet this therapy remains underutilized amid concerns for cardiac toxicity. We sought to evaluate the potential impact of initiating chronic azithromycin in appropriate patients during hospitalization for COPD exacerbation. We reviewed medical records from 808 patients admitted with COPD exacerbation who were currently receiving optimal inhaler therapy. To determine the potential impact of initiating azithromycin at hospital discharge, we recorded the number of hospital readmissions within the following year. We quantified the proportion of patients who were free of any of the contraindications proffered for chronic azithromycin therapy.

Results: Two patients were already receiving chronic azithromycin. Of 806 remaining patients, 51.4% of patients were readmitted to the same hospital within 1 year, and 7.4% had ≥ 5 readmissions. Only 17.5% of the patients did not have any cardiac contraindications to azithromycin therapy and only 7.9% were free of contraindications and non-smokers. With regard to specific risk factors, 10.2% had baseline QTc prolongation, 65% were taking concurrent QTc prolonging medications, 32.8% had comorbid cardiovascular disease and 13.4% had a resting heart rate > 100 beats per minute.

Conclusion: Patients hospitalized for COPD exacerbation have a high rate of readmission within the following year, and could potentially benefit from the exacerbation-reduction effects of chronic azithromycin therapy. Unfortunately, an intervention designed to promote azithromycin initiation is likely to be low-yield, because the majority of hospitalized patients in our sample had a contraindication predisposing them to cardiac toxicity.

Keywords : COPD; Acute exacerbation of COPD; Azithromycin; QT prolongation

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Introduction

Hospital admission for acute exacerbation of COPD (AECOPD) is a frequent event, with 606,000 admissions in the U.S. in 2010, [1] and 22% of these patients will experience readmission within 30 days [2]. The stakes are high during and after an exacerbation. The in-hospital mortality for AECOPD is approximately 10% [3].

A European study reported that admission for AECOPD was associated with a four-year mortality of 45% [4]. Exacerbations leading to hypercapnic respiratory failure have a mortality rate of almost 50% at two years [3]. Repeated exacerbations are independently associated with increased mortality: patients with three or more exacerbations requiring emergency department treatment had a five-year survival rate of 30% compared to a

survival rate of 80% in those without an exacerbation [5].

Although preventing hospitalization is a key goal for patients and healthcare systems, the hospital admission represents an opportunity to optimize care. Quality measures include optimal bronchodilator and corticosteroid therapy, administration of influenza and pneumococcal vaccinations, referral to pulmonary rehabilitation, and counseling on smoking cessation. Another therapy recommended by the American College of Chest physicians and Canadian Thoracic Society for patients with moderate to severe COPD who have had at least one exacerbation of moderate or greater severity in the previous year, despite optimal maintenance inhaler therapy is the use of chronic macrolide treatment [6]. A large randomized controlled trial of COPD patients who had an exacerbation within the last year showed that daily azithromycin decreased the frequency of exacerbations from 1.83 to 1.48 per patient-year and increased the time between exacerbations from 174 to 266 days [7]. Although this recommendation is not universally endorsed [8] and azithromycin does not currently have a Federal Drug Administration indication for this use, the potential impact of reducing AECOPD on patient health status and healthcare utilization is sizeable. Despite good evidence for the efficacy of azithromycin in reducing AECOPD, concerns regarding its potential for cardiovascular toxicity have limited its widespread use.

Although all macrolides pose a risk of QT prolongation, azithromycin demonstrates minimal interference with cytochrome p450 and the least inhibition of the rapid component of the delayed rectifier current, thus imparting the lowest risk of ventricular arrhythmias [9]. However, a large retrospective cohort study showed that acute use of azithromycin was associated with approximately 47 additional cardiovascular deaths causes per 1 million antibiotic courses, as compared with the cardio-safe drug amoxicillin [10].

Acknowledging both the clinically important decrease in COPD exacerbations and excess cardiovascular risk, experts have proposed that azithromycin be used judiciously in a population restricted to avoid cardiovascular risk [11]. Specifically, Wenzel and colleagues propose excluding patients with any of the following: 1) QTc interval ≥ 450 milliseconds, 2) co-administration of QT-prolonging medication, 3) comorbid cardiovascular disease including heart failure, peripheral vascular disease, or cerebrovascular disease, or 4) heart rate > 100 beats per minute [11]. Although this is a responsible approach, we anticipate that many patients who could potentially benefit from azithromycin prophylaxis would be excluded based on potential for harm. COPD is commonly comorbid with cardiovascular disease, [12, 13] as well other conditions such as depression [14-16] and gastroesophageal reflux disease [17] that are frequently managed with medications well known to cause QT prolongation.

The objective of this study was to determine what proportion of patients hospitalized for AECOPD might be eligible for initiation of chronic azithromycin therapy because this therapy could potentially decrease the risk of recurrent exacerbations and subsequent healthcare utilization.

Methods

The study was approved by the Institutional Review Board of University of South Florida. We selected patients admitted in Tampa General Hospital from January 2012 to January 2014 with a primary or secondary diagnosis of AECOPD (*International Classification of Diseases* [ICD]-9 code 491.21) coded on the discharge summary and clinical evidence of exacerbation (an acute event characterized by a change in the patient's symptoms that is beyond normal day-to-day variations and may warrant a change in regular medication) [18]. Patients were excluded if they were already receiving long-term azithromycin. If a patient was admitted more than once during the study period, only the first admission was used. The electronic medical record (Epicare; EPIC, Verona WI) was searched to determine whether patients met the following contraindications for azithromycin treatment: 1) QTc interval ≥ 450 milliseconds, 2) co-administration of QT-prolonging medications, 3) comorbid cardiovascular disease including heart failure, peripheral vascular disease, or cerebrovascular disease, or 4) heart rate at time of discharge > 100 beats per minute. We standardized the classification of QT-prolonging medications by screening the patients' medications using an online database (www.crediblemeds.com). We recorded whether hearing loss was documented at admission, as well as current smoking status for each patient. We reviewed the complete chart to quantify the number of readmissions, including observation and inpatient status, to Tampa General Hospital in the subsequent twelve months after the index admission.

Descriptive statistics were used to determine the frequency of readmissions, the proportion of patients with each contraindication, and the number of patients with no contraindications who would be eligible for chronic azithromycin therapy. Analyses were performed using SPSS software, version 16.0 (SPSS Inc., Chicago, IL, USA).

Results

Two patients were excluded because they were already receiving chronic azithromycin, and 8 were excluded because. Of 806 remaining patients, 44.9% were female, and the average age was 62.6 (range 34 - 90). 414 (51.4%) patients were readmitted to the same hospital within 1 year, and 60 (7.4%) had ≥ 5 readmissions. Only 141 (17.5%) patients did not have any cardiac

Table 1 Frequency of contraindications to azithromycin in patients.

Hospitalized for AECOPD (n = 806)	
Cardiovascular contraindications	
QTc interval ≥ 450 ms	82 (10.2%)
QT-prolonging medications	524 (65%)
Cardiovascular comorbidity	264 (32.8%)
Heart rate > 100 beats per minute	108 (13.4%)
Free of all cardiac contraindications	141 (17.5%)
Smoking status	
Active tobacco smoker	396 (49.1%)
Free of cardiac contraindications and non-smoker	64 (7.9%)

AECOPD: Acute Exacerbation of Chronic Obstructive Pulmonary Disease; QTc: Corrected QT Interval; ms: milliseconds

contraindications to azithromycin therapy. The occurrence of individual risk factors is shown in **(Table 1)**. Specifically, 82 (10.2%) had baseline QTc prolongation ≥ 450 milliseconds, 524 (65%) were taking concurrent QTc-prolonging medications, 264 (32.8%) had cardiovascular conditions and 108 (13.4%) had a resting heart rate > 100 beats per minute. The most common concurrent QTc-prolonging medications were selective serotonin reuptake inhibitors (26.5%), antibiotics (17.7%), diuretics (17.5%) and proton-pump inhibitors (12.7%). Hearing loss was documented in 12 (1.5%) patients. 396 (49.1%) patients were active tobacco smokers. Only 7.9% of patients were non-smokers and free of contraindications.

Discussion

Patients hospitalized for COPD exacerbation have a high rate of readmission within the following year, and could potentially benefit from the exacerbation-reduction effects of chronic azithromycin therapy. We found the baseline use of this therapy to be very uncommon in patients presenting to the hospital. Unfortunately, initiating azithromycin in eligible patients at discharge may be a low-yield intervention, because the majority of hospitalized patients in our sample had a contraindication predisposing them to cardiac toxicity. Additionally, over half of our patients were active tobacco smokers, and a subgroup analysis showed that the exacerbation reduction effects of azithromycin were absent in current smokers [18]. The percentage of patients with no contraindications and who were non-smokers was strikingly low.

The limitations of our study include restriction to a single center and the limitations inherent in retrospective research including potentially inaccurate documentation. The incidence of hearing loss was likely underestimated because it was rarely specifically mentioned in the acute care setting. We could only measure hospital readmissions that occurred to our own institution, which almost certainly underestimated the total number of readmissions from an overall healthcare utilization standpoint. However, same-center readmission is a highly valued outcome in the setting of reimbursement reform.

This is the first study to our knowledge to evaluate the frequency of contraindications to long-term azithromycin use in COPD patients. Although our findings apply specifically to hospitalized patients who are more likely to have comorbidities and be acutely ill, the extremely high incidence of cardiovascular contraindications suggest that this may partially explain the poor uptake of chronic azithromycin therapy in the outpatient setting as well. Future research should determine the true risk associated with various factors in order to maximize the proportion of patients most likely to benefit and least likely to harm.

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