Examination of Antibiotic Dosing Practices for Refractory Rhinosinusitis in Relation to Body Weight

Timothy R. Boyle, MD, FACS; Emmalee A. Boyle

ABSTRACT

Objective: Rhinosinusitis is a common condition that is frequently treated as an infectious disease with antibiotics. In general, antibiotic dosing in adults follows a flat scheme with no regard for body size. Wide variability in body weight raises concern whether this dosing scheme results in efficacious dosing for patients of various sizes. If not, larger patients with chronic rhinosinusitis may have avoidable morbidity from their disease, and surgery may be prematurely recommended. Our goal was to better understand the possible treatment implications of varying body size when prescribing antibiotics for chronic rhinosinusitis.

Design: Retrospective chart review.

Setting: Otolaryngology referral center at a multispecialty medical center.

Participants: Patients (N=180) with refractory chronic rhinosinusitis referred to an otolaryngologist for consideration of sinus surgery.

Methods: Main outcome measures included antibiotic usage, dosing, and body size metrics.

Results: There was wide variation in patient weight and body mass index. However, treatment guidelines for adults do not recommend dosage adjustments for variation in weight, and there was little variation in dosing strategies for each antibiotic prescribed. Therefore, per kilogram dosing varied widely between patients. Of the 9 antibiotics prescribed for chronic rhinosinusitis, the median per kilogram dose of only 1 antibiotic exceeded the minimum recommended per kilogram dose for children.

Conclusion: In the absence of weight-based guidelines for antibiotic administration, the potential for suboptimal dosing in patients seeking relief for chronic rhinosinusitis or other infectious diseases is great, and further study is needed to examine dosing practices.

INTRODUCTION

Rhinosinusitis is a common medical condition that affects as many as 14% of adults in the United States each year[1] and generally is treated in practice as an infectious disease. Chronic rhinosinusitis is defined as rhinosinusitis that persists for 12 weeks or longer without resolution.[2] Following acute rhinosinusitis, chronic rhinosinusitis develops within 4 years in approximately 5.5% of patients.[1] The pathophysiology of chronic rhinosinusitis is not well-defined, but it is generally accepted to be an inflammatory disease in which bacterial colonization may contribute to pathogenesis.[3] In the United States, the cost of disease management for chronic rhinosinusitis is estimated to be between $4.3 billion and $5.8 billion per year,[4,5] with the average patient spending nearly $2500 on disease management, including antibiotics, in the year preceding endoscopic sinus surgery.[1] There are currently no FDA-approved antibiotics for the treatment of chronic rhinosinusitis and in a 2011 Cochrane review, Piromchai et al[6] found only 1 randomized controlled trial examining the efficacy of antibiotic treatment for chronic rhinosinusitis. Based on lack of strong evidence, current guidelines recommend antibiotics as an option for the treatment of chronic rhinosinusitis in conjunction with other steroidal or decongestant therapies.[3,7] Regardless, antibiotics frequently are prescribed.[8] It is estimated that 94% of otolaryngologists in the United States prescribe prolonged courses of oral antibiotics for the treatment of chronic rhinosinusitis,[9] and that more than 1 in 5 antibiotics prescribed in adults are for rhinosinusitis.[10] Dosing strategies are based on standard guidelines with modification for relevant disease, perceived severity, and recent antibiotic use.[10,11] However, while dosing varies with body size in children up to 40 kg, there are no accepted recommendations for varying dose in relation to body size in adults. Adults who weight 70 kg are routinely prescribed the same dose as those who weight 150 kg.

The influence of body size on drug distribution is well-recognized. Body size is an important consideration for optimizing drug therapy in pediatrics, hematology, oncology, anesthesia and critical care, and evidence suggests that the physiological

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Author Affiliation: Department of Otolaryngology–Head and Neck Surgery, Marshfield Clinic, Marshfield, Wis (Boyle).

Corresponding Author: Timothy R. Boyle, MD, Department of Otolaryngology – Head and Neck Surgery, Marshfield Clinic, 1000 N Oak Ave, Marshfield, WI 54449; phone 715.387.5245; fax 715.389.5757; e-mail boyle.timothy@marshfieldclinic.org.

Table 1. Patient Demographics (N = 180)

Gender	**n (%)**
Male	85 (47.2)
Female	95 (52.8)
Median age (range)	
Male	53 (21 – 83)
Female	53 (21 – 88)
Median body weight (range)	
Male (kg)	92 (55.1 – 160)
Female (kg)	77 (45 – 126)
Median body mass index (BMI) (range)	
Male	29.1 (18.8 – 47.6)
Female	28.6 (16.7 – 45)
Obese (BMI ≥ 30), n (%)	
Male	36 (42.3)
Female	40 (42.1)

changes associated with obesity can alter important pharmacokinetic properties, including distribution and clearance.[12] However, body size is not considered in dosing for antimicrobial therapy in adults.[13] In general, pharmacodynamics studies are lacking for antibiotic use in adult patients of varying body size, and it is unknown whether equal dosing in patients with widely variable weights or body compositions is equally efficacious, although there is some evidence to the contrary.[12] In the case of chronic rhinosinusitis, suboptimal dosing may mean avoidable morbidity and the premature recommendation for surgical intervention. This study was designed to review antibiotic choices and dosing regimens before referral for evaluation of surgical treatment for refractory rhinosinusitis and to consider the possible treatment implications of varying body size among our patient population.

METHODS

This study was performed in the Department of Otolaryngology at Marshfield Clinic, a large, multispecialty group practice located in central Wisconsin. It was approved by the Marshfield Clinic Research Foundation Institutional Review Board. A retrospective review was performed on the electronic medical record (EMR) of adults aged 19 years and older who were referred by their primary medical provider to a single otolaryngologist for surgical treatment of refractory rhinosinusitis between January 2006 and June 2009. All patients were considered to have failed antibiotic and other "maximal" medical therapy including nasal steroids, systemic steroids, antihistamines, and saline irrigations. Upon referral, nearly all patients considered themselves to have chronic sinusitis and met symptom length criteria; however, many were not formally designated as such. Study subjects underwent a detailed otolaryngic evaluation including endoscopic examination of the nose and/or computed tomography scan of the sinuses. All patient physical examination and radiographic data were retrieved from the Marshfield Clinic EMR. Age, sex, symptoms, ear, nose and throat examination findings, antibiotic and dosage, weight, body mass index, radiographic results, and surgical intervention were recorded. Patients with primary noninfectious diagnoses including nasal polyps, allergic rhinitis, tumors, or septal obstructions were excluded. Patients with cystic fibrosis or allergic fungal sinusitis also were excluded.

Recommended dosing strategies for all antibiotics examined were obtained from the Physicians' Desk Reference (PDR) Network.[14] Recommended doses for amoxicillin-clavulanate, levofloxacin, azithromycin, ciprofloxacin, and clarithromycin are specific for acute bacterial rhinosinusitis. The recommended dose of amoxicillin is for infections of the ear, nose, and throat. The recommended dose of cephalexin is described as the "usual" amount. The recommended dose of trimethoprim-sulfamethoxazole is the standard dose recommended for other indications, and that for clindamycin is the standard dose for "serious infection." Because adult dosing, unlike pediatric dosing, is flat and not based on weight, the per kg dose recommended for children weighing less than 40 kg was used as a weight-based comparator for the purposes of this study. The primary analyses in this report are descriptive and based on standard summary statistics.

RESULTS

Between January 2006 and July 2009, 180 (47.2% male) patients met inclusion criteria for chart review (Table 1). All patients had been treated multiple times for sinusitis, although few were specifically designated as "chronic" by their primary care providers. All patients received multiple courses of antibiotics. The most recent antibiotic course likely would have been chosen considering the environment of recent antibiotic use and a higher likelihood of resistant organisms.

All patients were referred to the otolaryngologist in the midst of a course of or immediately after completing a course of antibiotics. Antibiotic therapy used at the time of referral is shown in Table 2. The most frequently prescribed antibiotic was amoxicillin-clavulanate (37.8%), followed by levofloxacin (18.3%), azithromycin (16.1%), and amoxicillin (12.2%). Cephalexin, clarithromycin, trimethoprim-sulfamethoxazole, and clindamycin were each prescribed to 5% of patients or fewer. Antibiotic dosing was relatively consistent. For each antibiotic, the majority of patients received the same daily dose. Adult dosing recommendations for the antibiotics commonly prescribed for rhinosinusitis were obtained from the PDR Network[14] and are also shown in Table 2. The median daily dose coincided with PDR Network guidelines for levofloxacin, ciprofloxacin, clarithromycin, and trimethoprim-sulfamethoxazole, but was higher for amoxicillin-clavulanate, amoxicillin, and cephalexin and lower for azithromycin and clindamycin (Table 3).

Patient body weight varied widely, resulting in large variation in the median per kilogram dose prescribed for each antibiotic (Table 4). Based on body weight, few patients received what would be considered the minimum therapeutic dose in

children. The median per kilogram dose was less than the recommended pediatric per kilogram dose for all but one of the antibiotics examined (Table 4). There was no evidence of any patient receiving a larger dose of a previously prescribed antibiotic. All patients either received the doses described or lower doses of the same or other antibiotics in previous treatment failures.

DISCUSSION

Acute and chronic rhinosinusitis are conditions that are commonly diagnosed and treated.[1] When acute bacterial rhinosinusitis is suspected, antibiotics generally are administered in order to return the sinuses to health, decrease symptom duration, prevent severe complications, and decrease development of chronic disease.[11] Many studies have demonstrated significant clinical benefit from the use of antibiotics in acute bacterial rhinosinusitis.[15] The efficacy of antibiotics in chronic rhinosinusitis is unclear,[15] and no antibiotic is currently FDA-approved for the treatment of chronic sinusitis, although they are routinely prescribed.[8,9]

Adequate antibiotic dosing for chronic rhinosinusitis is unclear and difficult to define. Even some antibiotics that are commonly used for acute bacterial sinusitis have no approved indication in their literature, including cephalexin, trimethoprim-sulfamethoxazole, and clindamycin. Antibiotic efficacy is dependent on several factors, including antibiotic chosen, dose and duration of antibiotic therapy, and appropriate diagnosis.[15] Dosing for these antibiotics tends to follow otitis media guidelines. For previously untreated patients, standard dose amoxicillin is recommended as a first line antibiotic intervention.[10] *The Physicians' Desk Reference* recommends amoxicillin for infections caused by susceptible (β-lactamase negative) strains of *Streptococcus pneumoniae, Staphylococcus* spp., or *Haemophilus influenzae,*[16] which account for approximately 40% to 90% of acute bacterial rhinosinusitis cases in adults.[11] There is no specific mention of *Moraxella catarrhalis*, which accounts for an additional 2% to 10% of cases in adults.[11] Adult dosing is recommended for children weighing more than 40 kg.[14] In the amoxicillin-treated group, patient weights ranged from 69 kg to 128 kg, but following the flat dosing scheme, the majority of patients were treated with 1500 mg per day, resulting in a wide range of per kilogram doses. All of these patients, whether

Table 2. Antibiotic Use and Dosing

Antibiotic	N (%)	Recommended Daily Dose (mg)[14]	Median Daily Dose (mg) (range)	Received Median Daily Dose, n (%)
Amoxicillin-clavulanate	68 (37.8)	1000[a]	1750 (1000 – 1750)	59 (86.8)
Levofloxacin	33 (18.3)	500[a]	500 (250 – 750)	26 (78.8)
Azithromycin	29 (16.1)	500[a]	250 (250 – 500)	25 (86.2)
Amoxicillin	22 (12.2)	1000[b]	1500 (500 – 3000)	15 (68.2)
Ciprofloxacin	9 (5.0)	1000[a]	1000 (500 – 1000)	8 (88.9)
Cephalexin	7 (3.9)	1000[c]	2000 (1500 – 2000)	6 (85.7)
Clarithromycin	6 (3.8)	1000[a]	1000 (1000 – 1000)	6 (100.0)
Trimethoprim-sulfamethoxazole	5 (2.8)	320[d]	320 (160 – 320)	4 (80.0)
Clindamycin	1 (0.6)	1200[e]	900	1

[a] Physician's desk reference (PDR)-recommended dose for acute bacterial rhinosinusitis.
[b]PDR-recommended dose for infections of the ear, nose, and throat.
[c]PDR-recommended "usual" amount.
[d]PDR-recommended amount for other indications.
[e]PDR-recommended dose for "serious infection."

Table 3. Recommended and Actual Antibiotic Dosing

Antibiotic	N (%)	Recommended Regimen	Recommended Daily Dose (mg)[14]	Median Daily Dose (mg) (range)
Amoxicillin-clavulanate	68 (37.8)	500 mg q12h	1000[a]	1750 (1000 – 1750)
Levofloxacin	33 (18.3)	500 mg qd	500[a]	500 (250 – 750)
Azithromycin	29 (16.1)	500 mg qd	500[a]	250 (250 – 500)
Amoxicillin	22 (12.2)	500 mg q12h	1000[b]	1500 (500 – 3000)
Ciprofloxacin	9 (5.0)	500 mg q12h	1000[a]	1000 (500 – 1000)
Cephalexin	7 (3.9)	500 mg q12h	1000[c]	2000 (1500 – 2000)
Clarithromycin	6 (3.8)	500 mg q12h	1000[a]	1000 (1000 – 1000)
Trimethoprim-sulfamethoxazole	5 (2.8)	160 mg q12h	320[d]	320 (160 – 320)
Clindamycin	1 (0.6)	600 mg q12h	1200[e]	900

[a]PDR-recommended dose for acute bacterial rhinosinusitis.
[b]PDR-recommended dose for infections of the ear, nose, and throat.
[c]PDR-recommended "usual" amount.
[d]PDR-recommended amount for other indications.
[e]PDR-recommended dose for "serious infection."

Table 4. Per Kilogram Antibiotic Dosing

Antibiotic	N (%)	Median Body Weight (kg) (range)	Median Per Kilogram Dose (mg/kg) (range)	Pediatric Minimum Therapeutic Dose (mg/kg)[a]
Amoxicillin-clavulanate	68 (37.8)	86 (58 – 126)	19.3 (10.4 – 30.2)	30
Levofloxacin	33 (18.3)	81 (47 – 160)	6.2 (3.1 – 13.9)	8
Azithromycin	29 (16.1)	83 (45 – 128)	3.0 (1.9 – 8.5)	10
Amoxicillin	22 (12.2)	89 (48 – 128)	16.9 (10.4 – 34.1)	30
Ciprofloxacin	9 (5.0)	88 (46 – 108)	11.4 (5.4 – 21.7)	10
Cephalexin	7 (3.9)	108 (57 – 122)	18.5 (16.4 – 35.1)	25
Clarithromycin	6 (3.8)	84 (79 – 86)	11.9 (11.6 – 12.7)	15
Trimethoprim-sulfamethoxazole	5 (2.8)	84 (55 – 87)	3.8 (2.0 – 5.8)	8
Clindamycin	1 (0.6)	108	8.3	16

[a]PDR-recommended per kg dose for children weighing less than 40 kg.[14]

they received the minimum 10.4 mg/kg dose or the maximum 34.1 mg/kg dose, were considered treatment failures upon referral to otolaryngology. However, many may not have received a therapeutic dose, as only one of the 22 patients who received amoxicillin was dosed at a level higher than the 30 mg/kg recommended in pediatric populations. Findings were similar for most of the antibiotics examined (Table 4).

The activity of most antibiotics ultimately depends on concentration at the site of infection; in this case, the sinus cavity. β-lactam antibiotics, such as amoxicillin, are time-dependent killers, and bacterial eradication is dependent on maintenance of concentrations at the site of infection above the minimum inhibitory concentration (MIC) of the organism for as much of the dosing period as possible.[11] The activity of macrolides, such as azithromycin, are similar except that these antibiotics exhibit persistent activity, and thus, effective bacterial eradication is dependent on the ratio of the antibiotic concentration at the site of infection over to MIC.[11] Fluoroquinolones, such as levofloxacin, are concentration-dependent killers, functioning best when concentrations are appreciably above the MIC of the pathogen, and dosing regimens are designed to maximize drug concentration at the site of infection.[11] Thus, in order to optimize efficacy, antibiotic concentrations at the site of infection must be maintained above the bacterial MIC for as long as possible during the antibiotic regimen.

Despite the high frequency of obesity in the United States,[17] few studies have examined drug distribution in obese patients, and even nonobese adults vary widely in body size and composition.[12,18] Several physiological changes occur in obesity that can alter pharmacodynamics by altering the processes of distribution, protein binding, metabolism, and clearance of antimicrobial agents.[13] While drug absorption does not appear to be altered in obesity, drug distribution into the tissue can be altered by body composition, regional blood flow, drug lipophilicity, and plasma protein binding.[12] Obesity also has been shown to alter glomerular filtration rate (GFR), which can affect clearance of antibiotics through the kidney.[12] Available data suggest that many antimicrobial agents, including β-lactams, vancomycin, fluoroquinolones, macrolides, linezolid, sulphonamides, and fluconazole, should be given in higher doses to patients with larger body size.[12] However, alteration of dose based on body weight is highly dependent on antibiotic of interest and in a 2000 review of the literature, Cheymol[18] noted major differences in determining appropriate dosages of vancomycin, ciprofloxacin, aminoglycosides, and gentamicin in morbidly obese patients. Conducting pharmacokinetic studies in subjects of varying size and composition is challenging, and while some progress has been made,[19,20] there is still no clear answer as to which size descriptor is best for studying pharmacokinetics in obese subjects.[18,21]

CONCLUSION

Despite wide variability of body size and composition among adults and the tremendous increase in obesity in the past 30 years,[22] adult antibiotic recommendations are not based upon body weight or composition. Appropriate dosing of antibiotics not only improves drug efficacy, but also may reduce risk for the development of antimicrobial resistance.[17] As most antibiotics routinely prescribed for the treatment of rhinosinusitis are administered to adults as flat dosing regimens, we question whether it is reasonable to expect curative doses in patients of larger size. The data presented here demonstrate that there is wide variation in per kilogram dosing among chronic rhinosinusitis sufferers referred to an otolaryngologist, and that very few patients are treated at the per kilogram levels considered therapeutic in pediatric patients. We hypothesize that basing antibiotic administration on a flat dosing regimen without regard for body size or composition could result in misdosing, significantly affecting treatment outcome. Treatment with a nontherapeutic dose of antibiotics may result in treatment failure for patients with chronic rhinosinusitis, leading to unnecessary morbidity and premature referral for surgery.

The retrospective design of the present study is a major limitation. Although antibiotic therapy was used for the treatment of chronic rhinosinusitis in all cases, it is unlikely that antibiotic therapy was provided as the sole therapy, and the role of prescribed or over-the-counter steroidal or decongestant therapies was not examined. Future prospective studies should be designed to sample antibiotic concentrations in the blood and/or at the site of infection and determine bacterial MICs from sinus cultures in patients with different body sizes to determine whether suboptimal antibiotic dosing truly occurs in larger individuals with chronic rhinosinusitis. Additionally, future antibiotic pharmacodynamics studies should stratify by body size or take per kilogram dosing into account to evaluate the efficacy of flat versus variable dosing strategies in adults.

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