



Catheter-and Antibiotic-related Complications of Ambulatory Intravenous Antibiotic Therapy for Chronic Refractory Rhinosinusitis

*Jerry W. Lin, MD PhD, *Ashutosh Kacker, MD, *Vijay K. Anand, MD FACS, **Howard Levine, MD,FACS

*Department of Otorhinolaryngology - Head and Neck Surgery, Rhinology Laboratory, The New York Presbyterian Hospital- Weill Cornell Campus
Weill Medical College of Cornell University, New York, NY and

**Director, Cleveland Nasal-Sinus & Sleep Cente, Marymount Outpatient Care Center, Cleveland OH

OBJECTIVE / HYPOTHESIS: Chronic rhinosinusitis has several features of a prolonged bacterial infection including positive bacterial cultures and abnormal CT findings such as mucosal thickening and hyperostotic bone. Recent studies have suggested that chronic rhinosinusitis may be successfully treated by outpatient parenteral antibiotic treatment (OPAT). In this setting, antibiotics are administered through a peripherally inserted central catheter (PICC). This study evaluates complications arising from OPAT for chronic rhinosinusitis.

INTRODUCTION

Adult rhinosinusitis is the most commonly treated upper respiratory tract infection, afflicting nearly 16% of the US population.¹ It accounts for nearly twelve million office-based physician visits a year, resulting in direct costs of approximately 5.8 billion dollars in 1996.^{2,3} In 1997, the Task Force on Rhinosinusitis, provided a working definition of chronic rhinosinusitis in an effort to facilitate effective communication among physicians and a uniform reporting of the disease. Rhinosinusitis is clinically defined as an inflammatory response involving (1) the mucous membranes of the nasal cavity and paranasal sinuses, (2) the fluids contained within these spaces, and (3) possibly the underlying bone.⁴ Chronic rhinosinusitis, by definition, persists for twelve weeks or longer. It differs from acute rhinosinusitis not only in duration, but also in histopathology and microbiology. Histologically, it is an inflammatory process characterized by fibrosis of the lamina propria and infiltration of tissue by lymphocytes, plasma cells, and eosinophils.⁴ Bacterial pathogens found in chronic rhinosinusitis are similar to those found in acute rhinosinusitis; however, gram-negative organisms and anaerobes are more abundant.⁵

Traditionally, chronic rhinosinusitis is managed with prolonged or repeated courses of oral antibiotics, topical and/or oral steroids, and decongestants.⁶ Patients with chronic rhinosinusitis who fail maximal medical management are typically recommended to undergo endoscopic sinus surgery for enlargement of the natural ostia of the paranasal sinuses and debridement of diseased mucosa and/ or the underlying bone.⁷ Despite surgery, however, a subset of patients have persistent symptoms of rhinosinusitis. Their recalcitrant disease course is usually characterized by multiple sinus surgeries and continual changes in medical management. Medical management typically involves the administration of broad-spectrum antibiotics in various forms: oral, intravenous, and topical. In chronic recalcitrant rhinosinusitis, multiple or prolonged courses of oral antibiotics have had variable success with significant recurrence rates.⁸ Thus recent attention has been focused towards other methods of antibiotic delivery that may result in higher antibiotic concentrations in the nasal and paranasal tissues.

Since its introduction in the early 1970's, the PICC line as a method of central venous access in outpatients has become an integral component of the medical armamentarium as a means of delivering parenteral nutrition, chemotherapy, and antibiotics. Chronic rhinosinusitis, at least a subset, is presumed to be secondary to a recalcitrant bacterial infection. Therefore, physicians have taken advantage of the PICC line to administer parenteral antibiotic treatments to ambulatory patients with chronic rhinosinusitis. The success of this treatment has been reported in recent articles in the literature.^{9,10,11,12} Although PICC lines have been shown to be safe and cost-effective¹³, they are not completely devoid of complications and therefore must be used judiciously in the treatment of chronic rhinosinusitis. Complications of OPAT include PICC line-specific complications such as thrombosis, phlebitis, catheter occlusion, catheter dislodgement, and catheter disruption. Antibiotic-related complications include rash, pruritis, diarrhea, fever, neutropenia, elevated liver enzymes, and anaphylaxis. This paper examines the complications arising from OPAT for chronic rhinosinusitis in a population of patients in a tertiary care setting and compares them with those found in previous studies.

RESULTS

| PICC Line complications | # of Complications | Antibiotic Regimen |
|---------------------------------|--------------------|---|
| Thrombosis | 3 | Ceftriaxone/clindamycin (2) Linezid (1) |
| Septicemia | 1 | Vancomycin |
| Antibiotic related complication | # of Complications | Antibiotic Regimen |
| Neutropenia | 3 | Ticarcillin-clavulanate/vancomycin (2) Cefipime/imipenem-cilastin (1) |
| Elevated LFTs | 1 | Aztreonam |
| Minor Complications | # of Complications | Antibiotic Regimen |
| Rash | 11 | Aztreonam/clindamycin Ceftazidime Ceftazidime/vancomycin Ceftriaxone Ceftriaxone/clindamycin (2) Ceftriaxone/levofloxacin Ciprofloxacin/imipenem-cilastin (2) Imipenem-cilastin/vancomycin Quinupristin-dalfopristin Ticarcillin-clavulanate |
| Diarrhea | 6 | Ceftriaxone/clindamycin (2) Imipenem-cilastin/vancomycin Cefipime/vancomycin (3) |
| Fatigue | 2 | Ceftriaxone/clindamycin |
| Pruritis | 2 | Ceftriaxone Rifampin/vancomycin |
| Fever | 1 | Linezoli/vancomycin |
| Flushing | 1 | Vancomycin |
| Black tongue | 1 | Ceftriaxone/clindamycin |

METHODS: Chart review of 177 patients who underwent OPAT for chronic rhinosinusitis.

RESULTS: PICC line-related infections (4/177, 2%) included line thrombosis in three patients and septicemia in one. In the three patients with line thrombosis, the PICC lines were removed and replaced allowing for completion of the antibiotic course. Antibiotic complications (29/177, 16%) included four patients with transient neutropenia and one patient with elevated liver function tests. Of the four patients with neutropenia, only one required a change in antibiotics. The patient with elevated liver function tests did not require a change in antibiotics. Minor complications from antimicrobial treatment such as rash, itchiness, flushing, and diarrhea were reported by 25 patients, 9 of whom required a change in antibiotics. There were no permanent complications or deaths in this study.

DISCUSSION

The Task Force on Rhinosinusitis has categorized rhinosinusitis into several classifications based primarily on the time course of the disease and its response to medical management.⁴ Acute rhinosinusitis is sudden in onset, often preceded by an upper respiratory infection, and lasts up to four weeks. Within this time frame, acute rhinosinusitis resolves completely with no further symptoms after resolution. Subacute rhinosinusitis lasts longer than four weeks but not longer than twelve weeks. Like acute rhinosinusitis, subacute rhinosinusitis also resolves completely. Recurrent acute rhinosinusitis occurs four times or more in one year, but lasts no longer than 4 weeks. Between episodes, symptoms resolve completely. Chronic rhinosinusitis persists for more than twelve weeks despite medical management.

Aside from its duration, chronic rhinosinusitis differs from acute and subacute rhinosinusitis in microbiology, histopathology, and bony involvement. Although many of the same organisms are found in the various classifications of rhinosinusitis, gram-negative and anaerobic organisms are found more commonly and more abundantly in chronic rhinosinusitis.⁵ Histopathologic studies of acute rhinosinusitis demonstrate an exudative process with a predominance of neutrophils; chronic rhinosinusitis, on the other hand, shows evidence of proliferative processes, with fibrosis of the lamina propria and abundant eosinophils. All rhinosinusitis are believed to result from infection of the nasal and sinus mucosa with subsequent edema, necrosis, and epithelial desquamation. Evidence suggests that chronic rhinosinusitis arises not only from infection of the mucosa, but also from the underlying bone.¹⁴ Several studies that have induced chronic rhinosinusitis in rabbits by inoculation with pathogens have shown bony changes in the paranasal sinuses including fibrosis, bony degradation, and osteoneogenesis.^{15,16,17} Examination of the human ethmoid bones subject to chronic rhinosinusitis also shows marked increases in fibrosis and bone remodeling suggesting an elevation in rate of bone physiology.¹⁴ Consistent with these bony changes is the finding of increased hyperostosis in patients undergoing revision sinus surgery as compared with those undergoing primary sinus surgery.¹⁸

The cycle of bone resorption, osteoneogenesis, and bony fibrosis in the setting of chronic rhinosinusitis is similar to that observed in osteomyelitis. Therefore, it makes sense that chronic rhinosinusitis may respond to the medical therapy typically prescribed for cases of osteomyelitis: long-term intravenous antibiotics. In both diseases, chronically infected non-viable bone harbors and sequesters bacteria from inflammatory cells thus prolonging infectious processes. Antibiotic concentrations achieved in bone are only approximately 10-30% of serum concentrations.¹⁹ Because of this attenuation in antimicrobial efficacy in bone, eradication of bony infection necessitates long-term intravenous antibiotics to maintain a high level of serum concentration for a prolonged period of time.

The availability of PICC lines as a means of administering parenteral antimicrobial treatments to ambulatory patients has afforded otolaryngologists an opportunity to treat recalcitrant cases of chronic rhinosinusitis. Several recent retrospective studies have documented the effectiveness of OPAT for chronic rhinosinusitis as an adjunct to or independent from sinus surgery.^{9,10,11,12} They report variable success rates ranging from 29 to 89%. Importantly, they also reported complication rates of 14 to 26%.

Gross et al. evaluated 14 patients who received an average of 4.2 weeks of postoperative intravenous antibiotics following sinus surgery. They reported a 79% partial or complete response to OPAT as assessed 8 weeks after surgery, and a total complication rate of 31%: 19% of complications were catheter-related and 12% were due to drug reactions.⁹ Don et al. reviewed 70 pediatric patients who received an average of 17 days of intravenous antibiotics as an alternative to endoscopic sinus surgery. They reported resolution of symptoms in 89% of patients with a complication rate of 13% (9% catheter-related and 4% medication related).¹⁰ Fowler et al. examined 31 adult patients treated with an average of 4.8 weeks of intravenous antibiotics. They found a mere 29% success rate with 26% of patients discontinuing therapy because of a complication.¹¹ In a recent prospective case-control study, Anand et al. demonstrated significantly improved symptom-based outcomes when comparing intravenous antibiotic use in the perioperative period (two weeks preoperative plus and additional 6-8 weeks postoperative) to standard post-operative oral antibiotics alone. They reported a 20% complication rate, all related to antibiotic medication rather than the PICC line.¹² Our study reports a complication rate of 18% in a population of patients undergoing a six to eight week course of intravenous antibiotic treatment: 2% related to the PICC line per se and 16% related to the antimicrobial regimen.

Smith et al. reviewed complication rates of PICC lines versus central venous catheters (CVCs) placed for purposes of antibiotic therapy, chemotherapy, parenteral hyperalimentation, or other miscellaneous reasons.²⁰ They reported a 35% complication rate of PICC lines versus a 19% complication rate with central venous catheters. Interestingly, PICC lines placed for purposes of chemotherapy and parenteral hyperalimentation resulted in significantly more complications than CVCs (44% vs. 14% and 64% vs. 39%, respectively). Alternatively, PICC lines placed for antibiotic delivery resulted in greater, but not statistically significant rates of complications when compared with CVCs (28% vs. 19%).

The complication rate reported in this study compares quite favorably with those reported in the literature. In fact, the 2% PICC line-related complication rate is lower than any of the studies reporting OPAT as a feasible medical management for chronic sinusitis. It is also lower than studies of general PICC line-related complications reported in the literature.

CONCLUSIONS:

Intravenous antimicrobial treatment administered through a PICC line in an outpatient setting is well-tolerated for chronic rhinosinusitis. Although PICC line and antibiotic-related complications are relatively infrequent, the physician should be aware of these complications and consider them in selecting patients for OPAT

REFERENCES

- 1 Pleis JR, Coles R. Summary health statistics for U.S. Adults: National Health Interview Survey. National Center for Health Statistics. Vital Health Stat 10(209): 1-113, 2002.
- 2 Cherry DK, Woodwell, DA. National Ambulatory Medical Care Survey: 2000 summary. Advance data from vital and health statistics: No. 208. Hyattsville, Maryland: National Center for Health Statistics, 2002.
- 3 Ray NF, Baraniuk JN, Thamer M, et al. Healthcare expenditures for sinusitis in 1996: contributions of asthma, rhinitis, and other airway disorders. *J Allergy Clin Immunol* 103(3 Pt 1): 408-414, 1999.
- 4 Lanza DC, Kennedy DW. Adult rhinosinusitis defined. *Otolaryngol Head Neck Surg* 117: S1-S7, 1997.
- 5 Brook I. Acute and chronic frontal sinusitis. *Curr Opin Pulm Med* 9: 171-174, 2003.
- 6 Gwaltney JM Jr, Jones JG, Kennedy DW. Medical management of sinusitis: educational goals and management guidelines. The International Conference on Sinus Disease. *Ann Otol Rhinol Laryngol Suppl* 167: 22-30, 1995.
- 7 Anand VK, Osguthorpe JD, Rice D. Surgical management of adult rhinosinusitis. *Otolaryngol Head Neck Surg* 117(3): S50-S52, 1997.
- 8 Tanner SB, Keitel DL, Foutch RE, et al. Recurrence rate of sphenoid sinusitis after medical therapy. *J Allergy Clin Immunol* 111: S125, 2003.
- 9 Gross, ND, McInnes RJA, Hwang PH. Outpatient intravenous antibiotics for chronic rhinosinusitis. *Laryngoscope* 112: 1758-1761, 2002.
- 10 Don DM, Yellon FR, Casselbrant ML, et al. Efficacy of a stepwise protocol that includes intravenous antibiotic therapy for the management of chronic sinusitis in children and adolescents. *Arch Otolaryngol Head Neck Surg* 127: 1093-1098, 2001.
- 11 Fowler KC, Duncavage JA, Murray JJ, et al. Chronic sinusitis and intravenous antibiotic therapy: resolution, recurrent and adverse events. *J Allergy Clin Immunol* 111: s85, 2003.
- 12 Anand V, Levine H, Friedman M, et al. Intravenous antibiotics for refractory rhinosinusitis in nonsurgical patients: preliminary findings of a prospective study. *Am J Rhinol* 17(6): 363-368, 2003.
- 13 Balinsky W, Nesbitt S. Cost-effectiveness of outpatient parenteral antibiotics: a review of the literature. *Am J Med* 87: 301-305, 1989.
- 14 Kennedy DW, Senior BA, Gannon FH, et al. Histology and histomorphometry of ethmoid bone in chronic rhinosinusitis. *Laryngoscope* 108: 502-507, 1998.
- 15 Norlander T, Westrin KM, Stierna P. The inflammatory response of the sinus and nasal mucosa during sinusitis: implications for research and therapy. *Acta Otolaryngol Suppl (Stockh)* 515: 38-44, 1994.
- 16 Westrin KM, Norlander T, Stierna P, et al. Experimental maxillary sinusitis induced by *Bacteroides Fragilis*. A bacteriological and histological study in rabbits. *Acta Otolaryngol (Stockh)* 112: 107-114, 1992.
- 17 Bolger W, Leonard D, Dick E, et al. Gram negative sinusitis: a bacteriologic and histological study in rabbits. *Am J Rhinol* 11(1): 15-25, 1997.
- 18 Kacker A, Huang C, Anand V. Incidence of chronic hyperostotic rhinosinusitis in patients undergoing sinus surgery compared to revision surgery. *Rhinology* 40: 80-82, 2002.
- 19 Salvati E, Small R, Brause B, et al. Infections associated with orthopedic devices. Sugarman B, Young E, eds. *Infections Associated with Prosthetic Devices*. Boca Raton, Florida: CRC Press: 181-218, 1984.
- 20 Smith JR, Friedell ML, Cheatham ML, et al. Peripherally inserted central catheters revisited. *Am J Surg* 176: 208-211, 1998.