

Oral antifungal therapy for *Fusarium*-associated chronic rhinosinusitis

Annie S. Lee, MD¹, Barbara Przybyszewski, BS², Kathleen Montone, MD³, Donald C. Lanza, MD¹

Background: *Fusarium* is commonly reported as an organism found in fungus-associated chronic rhinosinusitis (CRS) yet it is known to be resistant to commonly used antifungal therapies. The goals of this work are to report the incidence of *Fusarium*-associated CRS in fungal cultures and to describe the treatment experience with oral antifungal agent aimed at this problem.

Methods: Patients with sinus cultures obtained from 2005 through 2008 were retrospectively identified and their medical records were evaluated. Cultures were obtained in patients with recalcitrant rhinosinusitis when purulent discharge was observed. Patient response to the therapy was measured upon the basis of self reported symptom improvements and endoscopic examination.

Results: In this 4-year period 2,570 outpatient fungal cultures were obtained and 194 (7.5%) were positive for *Fusarium*. These 194 positive cultures appeared in 94 individuals. Thirty-four tested positive multiple times. Twenty-three (24.5%) had severe recalcitrant CRS poorly responsive to standard therapies warranting antifungal therapy aimed at *Fusarium*. Fifteen individuals were treated with voriconazole, 5 with posaconazole, and 3 with both at separate

times. Endoscopic evidence of initial improvement on therapy was evident in 16 of 23 patients (69.6%). Of 18 patients who could comment on their experience with the antifungal treatments, nearly 90% of them reported substantial improvement with the therapy. Nine (9/23; 39.1%) were forced to discontinue oral antifungal therapy due to untoward effects.

Conclusion: *Fusarium* appears in 7.55% of outpatient cultures of CRS. Of the patients testing positive for *Fusarium*, 25% received oral antifungal therapy. A positive response was seen in 16 of 23 (69.6%) while receiving other standard therapies. Since *Fusarium* is not routinely sensitive to commonly used antifungal agents, it warrants special attention. © 2011 ARS-AAOA, LLC.

Key Words:

Fusarium; chronic rhinosinusitis; voriconazole; posaconazole; fungal sinusitis; antifungal therapy

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Rhinosinusitis is a common cause of illness and although it affects an estimated 31 million Americans annually it remains poorly understood.^{1,2} It can be associated with many etiologic factors and comorbidities.^{2,3} Some forms of rhinosinusitis are known to be associated with fungus.^{2,3} The nature of this fungal association may vary based upon several factors but it is perhaps most importantly related

to the integrity and reactivity of the host's immune system (adaptive and innate). Recently, a consensus panel published their recommendations on the proper classification of fungal rhinosinusitis.⁴

Independent of this classification it is suggested that fungus, without host fungal allergy, is causative or a contributor to the inflammation in chronic rhinosinusitis (CRS) with polyps.^{2,5} Thus topical and even systemic antifungal agents have been used to improve CRS with polyps.⁶ Conflicting data on the efficacy of topical antifungal therapy for CRS with polyps exists.⁷ To date, there are no prospective clinical trials studying the efficacy of systemic antifungal therapy in refractory chronic rhinosinusitis. Several retrospective studies looking at the effectiveness systemic itraconazole (Sporanox®) exist,^{8,9} but the correlation between the fungal species being treated and the choice of antifungal is not clearly elucidated in those studies.

Fusarium is a filamentous mold that is commonly found in soil. It is known to cause disease in plants, animals and in

¹ Sinus and Nasal Institute of Florida Foundation, St. Petersburg, FL;

² Department of Microbiology, BayCare Health Systems, Clearwater, FL;

³ Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia, PA

Correspondence to: Donald C. Lanza, MD, Sinus and Nasal Institute of Florida Foundation, 550 94th Ave. North, St. Petersburg, FL 33702; e-mail: dclanza@sniflmd.com

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humans causing keratitis, cutaneous infections, onychomycosis, rhinosinusitis, and infections of burns and wounds.¹⁰ *Fusarium* infections in the immunocompromised state are often lethal.¹⁰ This is related in part to its antifungal resistance. Using standardized methods, *Fusarium* is known to be variably sensitive to common antifungal agents like amphotericin B, terbinafine (Lamasil®), fluconazole (Diflucan®), or itraconazole.¹¹ Prior to the availability of posaconazole (Noxafil®) in 2005, voriconazole (Vfend®) was advised to have clinical effect against this genus of fungus.¹² The goals of this retrospective chart review are to report the incidence of *Fusarium*-associated CRS in fungal cultures from a tertiary rhinology practice and to describe its treatment experience with systemic voriconazole and/or posaconazole.

Patients and methods

As part of an ongoing quality assessment and practice improvement program for the Sinus and Nasal Institute of Florida, P.A. (SNI), retrospective chart review was employed to characterize an experience with systemic antifungal therapy for *Fusarium*-associated CRS. Informed consent for patient participation was obtained for this program and for purposes of medical research. All endoscopically directed sinus culture data originating from SNI from January 2005 through December 2008 were retrieved from the BayCare Health Systems Laboratory. Telephone interview using a standardized question format was attempted for all study patients.

Inclusion criteria were patients who had CRS with cultures positive for *Fusarium* and received either voriconazole or posaconazole as treatment for these findings. Patients who were treated with those agents for acute or chronic invasive fungal rhinosinusitis were excluded as well as those not complaint with treatment recommendations. Patient chart review was performed to characterize their rhinosinusitis and past medical histories. The duration of their oral antifungal use and any side effects to the medications were noted. Findings of the endoscopic examination in the office just prior to the initiation of the antifungal treatment were compared to the examination 1 month into antifungal treatment.

Endoscopically-directed culture

Patients with CRS exhibiting purulent nasal discharge at the time of their office visits had endoscopically directed cultures performed. Purulence was defined as opaque yellow, green, or brown discharge that may or may not have had an eosinophilic mucin consistency.¹³ Any purulent discharge seen at exams was aspirated under endoscopic visualization. The culturing technique utilized was discussed previously.¹⁴ All culture specimens were sent to BayCare Health Systems Laboratory for Gram stain, aerobic and fungal growth, and antibiotic susceptibility testing. All cul-

TABLE 1. *Fusarium* in fungal culture

Year	Fungal cultures taken, n	Cultures positive for <i>Fusarium</i> , n (%)	Patients with positive <i>Fusarium</i> , n
2005	129	8 (6.20)	8
2006	555	37 (6.67)	20
2007	730	60 (8.22)	35
2008	1156	89 (7.70)	52
Total	2570	194 (7.55)	

ture data for patients meeting inclusion criteria were reviewed. For the purposes of this work, *Fusarium*-associated chronic rhinosinusitis is intended to describe the condition whereby purulent material from CRS patients grew *Fusarium* using standard mycology.

Telephone survey

In March 2010, a telephone survey to assess patients' experiences with voriconazole and posaconazole was undertaken. Each patient treated with those antifungal agents was contacted for a brief 6-question survey that asked them to rate their sinus symptoms at the time of survey compared to when they first presented to SNI. If they recalled using the oral antifungal, they were asked to evaluate if the medication offered any improvement of their symptoms. Finally, using a 5-point scale system patients were asked to rate the effectiveness of oral antifungal medications and various other treatment modalities such as systemic steroids, irrigations, culture-directed antibacterial therapy, and surgery.

Results

Between 2005 and 2008, a total of 2570 outpatient fungal cultures were obtained and 194 were positive for *Fusarium*, giving the overall incidence of *Fusarium* of 7.55% in this tertiary rhinology practice setting (Table 1). These 194 positive cultures appeared in 94 individuals, and 34 of the patients had multiple cultures positive for *Fusarium* during the 4-year period.

Twenty-three (23) patients with CRS fulfilled study criteria. Fifteen patients were treated with voriconazole and 5 patients were treated with posaconazole, while 3 patients were treated with both medications at separate times. Patient demographics as well as the nature and treatment history of their chronic rhinosinusitis are seen in Table 2. Incidentally, 17 of the 23 patients (73.9%) were also found to have *Staphylococcus aureus* in their cultures at one point. Eight of these patients grew methicillin-resistant *Staphylococcus aureus* (MRSA) in their culture.

Prior to initiating the antifungal therapy, all 23 patients had refractory CRS with extensive prior experiences with various standard treatments geared toward CRS. Specifically, all patients had been previously treated with multiple courses of systemic steroids, sinonasal irrigation, and

TABLE 2. Demographics and antifungal treatments

Patient	Sex	Age, years	Disease	Surgeries prior to antifungal Tx, n, total (SNI)	Surgeries after initiation of antifungal Tx, n	Mold allergy	Relative contraindication for conventional Tx	Fusarium positive cultures, n		Associated <i>Staphylococcus aureus</i>	Antifungal	Total Tx duration, months (number of courses)
								Before initiation of antifungal	After initiation of antifungal			
1	F	74	P	6 (0)	2	N	Glaucoma	0	3	Y (MRSA)	Vori	7.5 (2)
2	M	72	P	6 (1)	0	N	None	1	1	Y (MRSA)	Vori	1 (1)
3	M	55	CRS	5 (1)	0	N	None	1	1	Y	Vori	2.5 (1)
4	M	64	CRS	4 (2)	0	N	None	1	1	Y (MRSA)	Vori	3 (1)
5	F	45	P	2 (1)	0	Y	None	1	0	Y (MRSA)	Vori	3.5 (1)
6	M	52	P	3 (0)	2	Y	Osteoporosis, depression	0	3	Y	Vori	29 (2)
7	F	39	P	5 (2)	1	Y	None	3	4	Y	Vori, Posa	20.5 (2) ^a
8	F	50	P	3 (1)	1	Y	None	1	1	Y	Vori	23 (2)
9	M	20	P	4 (2)	0	N	None	1	0	Y	Vori	7 (1)
10	M	57	P	6 (2)	0	Y	None	1	0	Y (MRSA)	Vori	8 (1)
11	F	48	P	6 (0)	0	Y	None	0	2	Y (MRSA)	Vori	15 (2)
12	F	46	P	4 (0)	2	Y	None	0	2	Y (MRSA)	Vori	2 (1)
13	F	51	P	1 (0)	0	Y	Multiple Abx allergies	2	0	Y (MRSA)	Vori	4 (1)
14	F	40	P	2 (0)	1	Y	None	2	0	N	Vori, Posa	17 (2) ^a
15	M	49	P	4 (2)	0	Y	Depression	1	0	N	Posa, Vori	6 (2)
16	F	57	P	3 (1)	1	Y	Osteoporosis	1	0	Y	Vori	11 (1)
17	F	43	P	1 (0)	0	Y	None	1	0	N	Vori	11 (1)
18	F	42	P	2 (0)	0	N	Osteopenia	1	0	Y	Vori	4 (1)
19	F	27	P	2 (1)	1	Y	None	1	0	N	Posa	1.5 (1)
20	F	59	P	2 (1)	1	Y	Osteoporosis, CSCR	1	0	Y	Posa	2.5 (1)
21	F	46	P	4 (2)	1	Y	Depression	4	1	N	Posa	18 (1) ^a
22	F	58	P	5 (1)	0	Y	Osteoporosis	1	1	N	Posa	0.75 (1)
23	M	21	P	7 (2)	1	Y	None	3	0	Y	Posa	17 (1) ^a
Mean		48.5		3.78 (0.96)	0.61			1.22	0.87			9.92

^aPatient still on the antifungal as of January 1, 2010.Abx = antibiotic; CSCR = central serous chorioretinopathy; CRS = chronic rhinosinusitis; F = female; M = male; MRSA = methicillin-resistant *S. aureus*; N = no; P = chronic rhinosinusitis with polyps; Posa = posaconazole; SNI = Sinus and Nasal Institute of Florida; Tx = treatment; Vori = voriconazole; Y = yes.

culture-directed antimicrobial therapy, and all had endoscopic sinus surgeries prior to initiating of either voriconazole or posaconazole. On average, these patients had 3.78 sinus surgeries prior to the antifungal therapies (2.83 surgeries at outside facilities and 0.96 surgeries at SNI). All patients continued other standard CRS therapies aimed at reduction of inflammation of the sinus lining during antifungal therapy, including culture-directed antimicrobial therapies whenever the cultures yielded bacterial involvement.

Telephone survey

Twenty out of 23 (87%) patients were successfully reached by telephone and agreed to participate in the survey. Sixteen of the 20 patients reported greater than 80% improvement in their overall sinonasal symptoms since they were first seen at our facility. Two patients reported 50% improvement and 1 patient reported 20% improvement.

Of the 20 patients who participated in the survey, 18 patients recalled being on voriconazole or posaconazole. Twelve patients believed that the antifungal agent had lasting positive effect on their symptoms. Four patients had the impression that the agents had temporary positive effect, while 2 patients thought that the agents did not help their sinusitis symptoms.

Using a 5-point scale system with 1 being “not helpful” and 5 being “very helpful,” 16 of the 18 (89%) patients found the azole targeting *Fusarium* helpful to some degree (scale value ≥ 3) (Table 3).

Endoscopic examination 1 month into therapy

The patients' clinical response to the azole targeting *Fusarium* was also measured by their endoscopic examination approximately 1 month into therapy. Patients exhibiting decreased eosinophilic mucin, fungal debris, mucosal inflammation, and polypoid swelling on exam were considered to have responded to the treatment. Ten of the

15 patients who were treated with voriconazole had endoscopic evidence of improvement in the first month. Three of the 5 patients who were treated with posaconazole showed improvement on their endoscopic examination. All 3 patients who were treated with both voriconazole and posaconazole showed no evidence of improvement with the first agent, but demonstrated improvement 1 month into treatment when they were switched to the second agent. Overall, 16 of the 23 patients showed endoscopic evidence of a positive response to azole targeting *Fusarium*, giving a response rate of 69.6%.

Side effect profile

Adverse effects experienced by the patients with voriconazole and posaconazole are listed in Table 4. The most common side effects experienced by the patients were dermatologic symptoms such as rash or erythema. One patient experienced epidermal lysis on voriconazole. Many patients experienced temporary visual symptoms such as photosensitivity or vision with amber hue. With posaconazole, patients experienced various sporadic and nonspecific symptoms such as nausea, myalgia, and increased blood pressure. On the whole, 12 of the 23 patients (52.2%) experienced some form of adverse effects with the use of oral antifungals, voriconazole, or posaconazole. Nine patients (39.1%) had to discontinue the medication because of the side effects.

Discussion

“*Fusarium*-associated chronic rhinosinusitis” is the authors' term to indicate the poorly characterized relationship between the presence of *Fusarium* in endoscopically aspirated purulence and the treatment response to fungal-specific antimicrobial therapy. All patients identified in this retrospective chart review had severe refractory CRS and all had used standard therapies that gave prior substantial symptom relief. However, the results of these treatments were deemed insufficient. This was either because they gave only temporary benefit, incomplete effect, or because of associated side effects. The addition of antifungal therapy aimed at *Fusarium* culture results gave additional improvements in many study subjects. Endoscopic evidence of initial improvement on therapy was evident in 69.6%. Of the 18 patients who were able to comment on their antifungal experience, nearly 90% reported substantial improvement from antifungal therapy with 12 reporting some sustained benefit. Despite multiple concurrent therapies, no patient was cured of their CRS and *Fusarium* persisted in some despite antifungal therapy. More than 50% experienced some form of adverse effects with the use of these oral antifungal therapies, requiring 40% of patients to discontinue treatment.

Identifying the specific fungi involved any form of fungus-associated rhinosinusitis can be very important to choosing

TABLE 3. Patient perception of treatment efficacy*

Treatments	Patients
Oral antifungals	16/18
5	9/18
4	3/18
3	4/18
Systemic steroids	18/18
Sinonasal irrigation	18/18
Surgery	16/18 ^a
Culture-directed therapy	17/18

*Patients answering “3” or greater on a 5-point scale telephone survey questionnaire.

^aTwo of the 18 patients did not have surgery at SNI.

SNI = Sinus and Nasal Institute of Florida.

TABLE 4. Side effects

Voriconazole (n = 15)		Posaconazole (n = 8)	
Side effect	Number of patients	Side effect	Number of patients
Erythema	3	Increased liver function tests	1
Rash	3	Increased blood pressure	1
Photosensitivity	3	Nausea	1
Temporary visual changes	2	Ankle swelling	1
Alopecia	1	Myalgia	1
Joint pain	1		

effective antifungal therapy. Yet proper identification can be challenging with routine mycology and histopathology. Mycology can take weeks to produce useful information and does not always yield results. Moreover, using routine histopathology, *Fusarium* is extremely difficult to distinguish from *Aspergillus*.¹⁵ Unfortunately, in vitro testing results for antifungal drug sensitivities are not widely available either, because this testing is fraught with difficulties. However, some standardized antifungal sensitivity information is available in the form of published antibiograms.¹¹ The most common *Fusarium* species to cause human infection is *F. solani* (50%), followed by *F. oxysporum* (20%), and *F. verticillioides* (20%).¹⁰ According to one source, the drug of choice based upon antimicrobial susceptibility testing of *F. solani* is posaconazole. The problem of antifungal resistance may help explain incomplete treatment responses reported in fungal rhinosinusitis with systemic antifungal therapy despite the appearance of proper patient selection.¹⁶ Thus, fungus-specific antimicrobial therapy of severe chronic rhinosinusitis is an advanced concept that warrants further investigation. Interestingly, topical ophthalmic antibacterial preparations used for *Fusarium* keratitis have shown in vitro activity of tobramycin, moxifloxacin, chloramphenicol, and benzalkonium chloride.¹⁷ Theoretically, this could suggest unanticipated benefits in CRS with antibacterial rinses aimed primarily at bacteria.

Regarding the etiology of CRS with polyps, there is much debate. Although it is widely recognized that fungus can be found in 100% of normal individuals' nasal passages,⁵ the mere presence of mold does not implicate a diseased state or causality. Nonetheless, in vitro evidence has shown that fungus can serve as a potent source for eosinophilic chemotaxis.¹⁸ Eosinophils are associated with refractory chronic rhinosinusitis with polyps through degranulation. Alternately, *Staphylococcus aureus* superantigen inducing eosinophil chemotaxis is another mechanism described by researchers to explain polyp formation in CRS.^{2,19,20} Data from this chart review indicate a higher than expected co-existence of *Fusarium* and *Staphylococcus*. Nearly 74% of these patients had cultures that were positive at one point in time for *Staphylococcus aureus* and *Fusarium*. The significance of this is difficult to determine but it is appealing to conceive that perhaps the severity of these patients dis-

orders are related an abnormal immune response to both organisms.

There are obvious limitations to this report because of its retrospective nature and lack of controls and randomization. The telephone survey conducted posttreatment is subject to recall bias, as the time lapse between the treatment and the telephone contact ranged between 0 and 49 months. Also, it was a nonvalidated questionnaire, which poses further challenges in data analysis. The patients were frequently treated with antifungal and antimicrobials concurrently based on their culture results, which makes it difficult to discern if the patients responded to one or the other modality. It should be noted that the patients all failed antimicrobial therapy alone prior to being put on antifungal medications.

It is important to emphasize that the following criteria had to be met before systemic antifungal therapy with voriconazole or posaconazole was considered: (1) fungal culture positive for *Fusarium*; (2) either persistent or worsening symptoms despite standard therapy aimed at CRS; or adverse effects from the therapy commonly used for CRS; and (3) patient capable of understanding the risk associated with the therapy. It should also be noted that these antifungal therapies are very expensive (>\$2000/month) and multiple positive fungal cultures with or without fungal elements documented in pathologic specimens were typically required for insurance coverage of the medications. Although infectious disease consultation was not typically sought out for this patient population, this could be of value in disease management and monitoring therapy.

Conclusion

Due to the retrospective nature of this report it is difficult to draw firm conclusions regarding efficacy of antifungal therapy for *Fusarium*-associated CRS. The data supports that *Fusarium* is present in 7.5% of fungal cultures of purulence from patients with CRS. Of the patients testing positive for *Fusarium*, 25% received oral antifungal therapy. It is well known that *Fusarium* is typically resistant to antifungal therapies that are commonly used for fungal rhinosinusitis. From this experience it appears as though targeted systemic antifungal therapy in carefully selected patients can

give benefit based upon endoscopic findings (69.7%) and patient self-reported improvements (90%). However, given the high side effect profile (50%) of systemic voriconazole

and posaconazole, patients need to be informed of the serious potential risks of treatment before considering this as a reasonable treatment option for severe refractory CRS. ④

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