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Improving Case Finding of Invasive Aspergillosis in Children using String Searches

Sruti Nadimpalli, MD MPH^a, Elizabeth Salsgiver, MPH^a, Dana O'Toole^a, Lisa Saiman, MD MPH^{a,b}, Alla Babina, MS^c, Philip Graham III, MD MSc^{a,b}, and Marc Foca, MD^a

^aDivision of Pediatric Infectious Diseases, Department of Pediatrics, Columbia University Medical Center, New York, NY 10032

^bDepartment of Infection Prevention and Control, New York-Presbyterian Hospital, New York, NY 10032

^cDepartment of Biomedical Informatics, Columbia University Medical Center, New York, NY 10032

Abstract

Surveillance for invasive *Aspergillus* (IA) in children is complex. We performed a retrospective study (2004–2013) using string searches of relevant terms within histopathology and radiology reports in efforts to improve detection of IA. Overall, 22 children met IA criteria of whom five (23%) were only identified by string searches.

Keywords

aspergillus; immunocompromised; epidemiology; surveillance; string search

INTRODUCTION

Invasive *Aspergillus* (IA) is well described in immunosuppressed children, but accurately diagnosing IA is challenging. *Aspergillus* is difficult to grow from clinical specimens; histopathologic and radiographic studies may lack specificity; serum galactomannan has suboptimal sensitivity (71%) and specificity (82%)¹; and invasive diagnostic procedures carry potential morbidity. Thus, diagnosing IA has relied on a combination of these studies² as reflected in international consensus guidelines with case definitions for proven, probable, and possible IA³. These case definitions have been employed in clinical trials and for clinical management,^{4,5} but have not been extensively utilized for epidemiologic surveillance.

Corresponding Author: Sruti S. Nadimpalli, MD MPH, Present address: Stanford University Medical Center, Department of Pediatrics, Division of Pediatric Infectious Diseases, 300 Pasteur Drive, Room G312, Stanford, CA 94305, sruti@stanford.edu.

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String searches, combinations of words or phrases used to retrieve specific information from a data source, allow for rapid retrieval of information from documents or databases. The objective of the current study was to determine if string searches of relevant terms within subjects' histopathology and radiology reports improved surveillance for IA. We hypothesized that the use of string searches applied to histopathology and radiology reports would improve epidemiologic surveillance for IA in children.

METHODS

A retrospective case series of children 18 years of age diagnosed with IA from 2004-2013 at a tertiary care children's hospital in New York City was performed. The institutional review board of Columbia University Medical Center approved the conduct of this study with a waiver of informed consent.

As previously described^{2,3}, proven cases had positive cultures from a sterile body site, histopathologic findings of hyphae with tissue damage, or both. Probable cases had relevant host factors (e.g., prolonged neutropenia or corticosteroid therapy), laboratory findings (e.g., positive cultures from non-sterile body site or detection of galactomannan), and clinical factors (e.g., consistent radiographic findings or nasal ulcer with black eschar). Possible cases had relevant host factors and laboratory findings.

Case finding for IA utilized several sources. (1) Positive laboratory studies including *Aspergillus* cultures and serum galactomannan results were collected⁶. Excluded cases included instances of *Aspergillus* isolated from sputum of children with cystic fibrosis, from superficial skin cultures without histopathologic evidence of angioinvasion or clinical or radiologic evidence of disseminated disease; *Aspergillus* from the external ear canal; and allergic bronchopulmonary aspergillosis. (2) Department of Infection Prevention and Control surveillance records during the study period were reviewed. (3) String searches of relevant terms including "wildcard" characters (e.g., "%spergil%") were applied to histopathology reports from biopsies, autopsies, and radiology to detect cases of IA. A wildcard character such as "*" or "%" can represent any character within a search term, such that the string search would detect minor variations on the primary search term.

In histopathology reports, search terms included: septated hyphae, hyaline hyphae, septated hyaline hyphae, acute angle branching, forty-five degree branching, vascular invasion, angioinvasion, local invasion, *Aspergillus*, aspergillosis, consistent with *Aspergillus*, and consistent with aspergillosis. In radiology reports, search terms included: nodule, halo, cavity, consistent with *Aspergillus*, consistent with aspergillosis, and air-crescent sign.

Descriptive analysis was used to determine (i) the number of additional cases of IA detected by string searches, (ii) the number of IA cases for which the categories of proven, probable, or possible were changed by string searches, and (iii) the relative contribution of string searches of histopathology versus radiology reports for detection of IA.

RESULTS

Clinical Characteristics of Subjects with IA

Twenty-two subjects were identified with proven, possible or probable IA, of whom 13 (59%) were male. The average age of subjects was 11.2 years (range 0.6-18 years). Nine (41%), 2 (9%), 2 (9%) and 1 (4.5%) of subjects had undergone hematopoietic stem cell transplant (HSCT), cardiac transplant, liver transplant, or HSCT and cardiac transplant, respectively. The others were receiving immunosuppressive treatment for cancer (n=4), severe systemic lupus erythematosus (n=2), hemophagocytic lymphohistiocytosis (n=1) and Wegener's granulomatosis (n=1).

Seventeen (77%) subjects had neutropenia within 30 days of diagnosis of IA, of whom 13 (59%) had neutropenia for 10 days. Eleven (50%) had received high-dose corticosteroids (0.3mg/kg/day of prednisone, or equivalent) prior to IA diagnosis. Other immunosuppressive agents included tacrolimus (n=10, 46%), cyclophosphamide (n=4, 18%), mycophenolate (n=3, 14%), and rituximab (n=1, 4%).

Diagnosis of IA

Overall, 15 (68%) of 22 subjects met criteria for proven IA, 4 (18%) for probable IA, and 3 (14%) for possible IA. The most common sites of infection were pulmonary (n=13), sinuses (n=3), and cardiac (n=3); 6 subjects had multi-site infections and none had central nervous system infection. Six subjects (27%) had positive cultures from a sterile site, 14 (64%) had histopathologic findings consistent with *Aspergillus*, and 5 had both positive cultures and histopathology. Serum galactomannan EIA was positive in 13 (81%) of 16 tested subjects. Fourteen (64%) had radiographic studies within the 30 days prior to IA diagnosis of whom 11 had CT or magnetic resonance imaging. The most common pulmonary abnormalities were nodules (n=7), pleural effusions (n=6), and consolidation (n=4). No halos or air-crescents were reported.

String searches

String searches of histopathology reports detected 5 additional cases of IA and all met criteria for proven IA (Table). String searches of pathology reports also changed the classification of 4 subjects from possible to proven IA. String searches of radiology reports did not detect additional IA cases, but changed the classification of 2 subjects from possible to probable.

DISCUSSION

To our knowledge, this is the first study to apply string searches to improve case-finding for invasive aspergillosis. This method increased overall IA detection by 29%, proven IA detection by 36%, and probable IA detection by 100%. Additionally, we found that string searches of histopathology reports were more useful than string searches of radiology reports.

We also found that some IA criteria were more common in this pediatric population. Nearly all proven IA cases had positive histopathology results, but only 6 had positive cultures. All probable and possible IA cases had positive serum galactomannan results.

This single-center study was limited by a small sample size. Not all cases had cultures, histopathology, or galactomannan obtained. Histopathologic findings may represent infections with molds other than *Aspergillus*.

In conclusion, prospectively performed string searches have the potential to improve surveillance for IA and is relatively easy to implement. While natural language processing (NLP) might offer even better detection of IA, NLP is not widely available. Future studies should assess the utility of automated string searches to improve surveillance for IA in other patient populations.

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HIGHLIGHTS

- Accurate diagnosis of invasive aspergillosis (IA) is challenging.
- String searches for IA terms were performed on histopathology and radiology reports.
- String searches improved IA case detection by 29%.
- Automated string searches for specific terms may aid in IA surveillance.

Table 1

Case definition assessment for children with proven, probable, and possible IA

Subject	Proven IA		Probable IA					Host Factor
	Mycological Factor (1)		Mycological Factor (1)		Radiographic/Clinical Factor	Host Factor		
	Sterile Site Culture	Positive Histopathology	Non-Sterile Site Culture	Positive Serum GM				
Proven								
1	X	X						
2 [*]		X						
3 [*]		X						
4	X							
5	X	X						
6 [†]		X						
7 [*]		X						
8 [*]		X						
9 [*]		X						
10 [†]		X						
11 [†]		X						
12	X	X						
13 [†]		X						
14	X	X						
15	X	X						
Probable								
16 [‡]			X	X	X	X		
17			X		X	X		
18			X		X	X		
19 [‡]			X		X	X		
Possible								
20							X	

Subject	Proven IA		Probable IA				Host Factor		
	Mycological Factor (1)		Host Factor	Mycological Factor (1)		Radiographic/Clinical Factor			
	Sterile Site Culture	Positive Histopathology		Non-Sterile Site Culture	Positive Serum GM				
21							X		
22							X		

GM = galactomannan

* Detected by NLP alone.

[†] NLP changed these subjects' IA classification from possible to proven.

[‡] NLP changed these subjects' IA classification from possible to probable.