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Workload Due to *Aspergillus fumigatus* and Significance of the Organism in the Microbiology Laboratory of a General Hospital

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The increase in the immunocompromised population and the incidence of invasive aspergillosis (IA) are leading to an overinterpretation of the potential clinical significance of many isolates of *Aspergillus fumigatus*. Our work prospectively assesses the workload of the isolation of *A. fumigatus* and its clinical significance in the microbiology laboratory of a large teaching hospital. During a 3-year period, all patients from whom *A. fumigatus* was isolated were prospectively monitored and classified as having IA or "nonsignificant" disease. A point score based on the prediction of five easily obtained laboratory and clinical parameters was applied. We found 404 *A. fumigatus* isolates in 260 patients (1/1,000 microbiology laboratory samples; 2.1 patients/10,000 admissions). A total of 90 isolates (22.3%) were from patients with IA. Of the 260 patients, 31 (12%) had invasive disease (IA), and the remaining 229 had "nonsignificant" disease. A score based on points for five parameters was applied to our population. It was constructed as follows: "sample obtained by invasive procedures" (1 point), "presence of two or more positive samples from the same patient" (1 point), "leukemia" (2 points), "neutropenia" (5 points), and "corticosteroid treatment" (2 points). Patients with a score of 0 had only a 2.5% probability of IA. Those with a score of 1 or 2 had an increased probability of 10.3%. The probabilities rose to 40% and 70%, respectively, for patients with a score of 3 or 4 or a score of ≥5. A simple score based on five easily available parameters may be of help to microbiologists and clinicians to predict the risk of IA.

An increase in invasive fungal infections has been observed in recent years in developed countries (2, 16, 18). This increase is due mainly to the widespread use of antibiotics and the large number of immunodepressed patients (4, 7, 14, 17). Invasive aspergillosis (IA) is a particularly severe disease which is traditionally reported in patients with hematological malignancy or neutropenia (8), those undergoing bone marrow (10, 31) or solid organ (28) transplantation, or those receiving corticosteroid therapy (3).

In patients with these underlying conditions, the isolation of *Aspergillus fumigatus* by a microbiology laboratory, even from nonsterile samples, is generally regarded as potentially significant. Unfortunately, this concept is being extrapolated to other populations, thus increasing the workload of the microbiology laboratory and producing, in our opinion, an overinterpretation of the potential clinical significance of *A. fumigatus* isolates.

The aim of our prospective study was to determine the workload created by the isolation of *Aspergillus fumigatus* and its overall clinical significance in the microbiology laboratory of a large general teaching hospital.

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MATERIALS AND METHODS

Study period and institutional information. This prospective study was carried out from November 1999 to October 2002 in a large tertiary teaching hospital which serves a population of approximately 650,000 inhabitants in the area south of Madrid. The hospital has approximately 1,750 beds, and there were 188,374 hospital admissions during the study period. The hospital includes all medical and surgical specialties, in addition to pediatric, psychiatric, obstetric-gynecologic, and oncology services. The hospital has an intensive solid organ transplant program (heart, liver, and kidney) and an infectious disease unit for the care of AIDS patients.

Our institution attends to all types of patients at risk of acquiring IA, including solid organ and bone marrow transplant recipients and patients with hematological malignancies or human immunodeficiency virus (HIV) infections.

During the study period there were no outbreaks of IA.

Patients included in the study. We excluded patients from whom species other than *A. fumigatus* were isolated, as they were not responsible for IA at our institution.

Patients with one or more isolates of *Aspergillus fumigatus* were prospectively monitored by at least one trained infectious disease physician from our department. For every case there was an individual data collection form, and every case was monitored from the moment the fungus was identified. Several parameters were recorded, including demographic, clinical, microbiological, and epidemiological data. We also recorded, when present, the major risk factors for acquiring IA, the underlying disease, granulocytopenia, transplantation, active neoplastic process, HIV status, chronic liver disease, chronic obstructive pulmonary disease (COPD)/asthma, diabetes, chronic renal insufficiency, corticosteroid therapy, broad-spectrum antibacterial therapy, antifungal and anticancer therapy, and other parameters. Patients were grouped according to their underlying diseases.

Each patient included in the study was classified according to the probability of having IA, in accordance with international consensus criteria (1). According to these criteria, the final interpretation of any case was included in the following groups: "proven case," "probable case," "possible case," "colonization" (cases

not fulfilling the former criteria and representing sample colonization, in the opinion of the principal investigator) (21), and "laboratory contamination" (growth of the fungus outside the streak on the culture medium plate). Cases with allergic bronchopulmonary aspergillosis were considered colonizations in the statistical analysis. We shall now refer only to patients with proven or probable criteria as patients with IA.

Microbiological culturing and other diagnostic procedures. Samples were obtained on the basis of clinical indications. All specimens were cultured in both fungal and conventional media. Fungal media included Sabouraud dextrose agar with chloramphenicol, brain heart infusion agar with antibacterial agents, and potato dextrose agar. Conventional media included sheep blood agar and chocolate agar. Fungal cultures were incubated at 32 to 37°C for no fewer than 7 days (19).

We performed rapid fungal staining (calcofluor stain) or determination of galactomannan (Platelia enzyme-linked immunosorbent assay) as needed.

Species were identified on the basis of culture characteristics and morphology of conidiophores and conidia.

Microbiological and clinical parameters obtained. For all patients with one or more isolates of *A. fumigatus*, we prospectively obtained the following parameters: "presence of two or more correlative positive samples for *A. fumigatus*" (when a patient had a sample positive for *A. fumigatus* and the next sample obtained from the same origin and processed in the laboratory yielded *A. fumigatus* again), "respiratory or extrarespiratory origin of the sample," "sample obtained by invasive procedures" (samples which were collected by means of invasive procedures, such as bronchoscopy, biopsy, sterile fluid sampling, and prosthetic material), "sex" and "age" of the patient, "service of admission," "transplantation (kidney, heart, liver, and bone marrow)," "neoplastic process (general, leukemia, and lymphoma)," "chemotherapy," "neutropenia" (<500 μl during the preceding 15 days), "corticosteroid treatment" (≥15 mg per day of prednisone or equivalent for 15 or more days), "HIV infection," "antibiotic treatment" (≥72 h), "chronic liver disease," "COPD/asthma," "chronic renal insufficiency," "mechanical ventilation," "diabetes," "congestive heart failure" and "antifungal prophylactic treatment." These data were made available to the microbiology department immediately.

Calculation of the laboratory workload. With the information regarding the total number of fungal isolates, the total number of samples processed in the microbiology laboratory, and the total hospital admissions at our institution during the 3-year study period, we calculated the numbers of fungi isolated per 10,000 patients admitted and per 10,000 samples processed.

Predictive model of invasive disease. All data were collected and entered into an Access database. For analysis, only proven and probable cases of invasive disease were considered IA. The possible aspergillosis and allergic bronchopulmonary aspergillosis cases were classified as "nonsignificant."

We determined the probability of infection by analyzing the seven groups of patients with IA and classified according to underlying diseases. We also calculated the probability of IA when the different samples and the number of positive samples per patient were evaluated. The statistical significance of the variable "age" was obtained by Student's *t* test.

The prediction of infection from a positive culture was obtained by multivariate logistic regression analysis with SPSS version 11.5. Before that analysis, univariate logistic regression analysis has been performed on every individual variable, and only those with a statistical *P* value of <0.1 were included. We used the adjusted odds ratio and the 95% confidence interval (CI) to estimate the relative risk (RR). We developed a score by assigning a proportional value to the odds ratio adjusted in the logistic regression model. A receiver operating characteristic curve was generated to evaluate the predictive potential of the score. The area under the curve and its 95% CI are presented. We evaluated the linear increase in the probability of infection by using the chi-square test for trend. The null hypothesis was rejected in every contrast of hypothesis for an alpha error of <0.05.

RESULTS

Fungal isolation and workload. During the study period, there were 188,374 hospital admissions, and the microbiology laboratory processed 412,375 samples. From these, we obtained 7,160 clinical isolates of fungi (yeasts and molds) from 6,144 samples which were positive for fungi; these samples were obtained from 3,615 different patients. Of these isolates, 1,073 were filamentous fungi, 588 were *Aspergillus* spp., and 404 were *A. fumigatus*. *A. fumigatus* was isolated 2.1 times per 1,000 admissions and 1 time per 1,000 microbiology samples and represented 5.6% of the total fungal isolations. The 404 isolates of *A. fumigatus* from 260 patients constituted the basis of our study. Most isolates were recovered from respiratory samples (334; 82.7%); 70 isolates (17.3%) were obtained from extrarespiratory samples.

Patients with isolates of *A. fumigatus* were located in high-risk units, including intensive care units and hematology wards (36.9%); internal medicine wards (49.2%); surgery wards (10.8%); and low-risk units, including psychiatry and obstetrics wards (3.1%).

Of the 260 patients with one or more *A. fumigatus* isolates, 9 patients had proven aspergillosis (3.5%), 22 had probable aspergillosis (8.5%), 14 had possible aspergillosis (5.4%), and 3 had allergic bronchopulmonary aspergillosis (1%). Colonization was diagnosed in 126 cases (48.5%), and 86 patients were considered to have plain laboratory contaminants (33.1%). Proven or probable cases of IA caused by *A. fumigatus* occurred in 1.6 cases/10,000 admissions. Regarding the incidence throughout the study period, 18 cases occurred during the first year (3 cases/10,000 admissions), 6 occurred during the second year (1 case/10,000 admissions), and 7 occurred during the third year (1.3 cases/10,000 admissions). Males (n = 21; 67.7%) predominated over females (n = 10; 32.3%), and their underlying diseases in order of frequency included the following: COPD/asthma with corticosteroid treatment (10; 32.2%); hematological malignancies, such as leukemia and lymphoma (7; 22.5%); advanced HIV infections (4; 12.9%); solid organ transplantation (3; 9.7%); and miscellaneous conditions (5; 16.2%).

As far as clinical manifestations were concerned, 22 of our patients had IA limited to the respiratory tract, 5 had extrarespiratory single-organ invasive infections, and 4 had disseminated disease (lung and extrarespiratory involvement).

Of the 31 patients with IA, 19 (61%) died: 7 with proven IA (78%) and 12 with probable IA (54.5%).

Probability of infection in the case of a positive culture. Of the 404 isolates (260 patients) of *A. fumigatus*, only 90 (22.3%) were from the 31 patients with proven or probable IA. Therefore, the overall probability that a positive *A. fumigatus* culture represented a case of IA was 22.3%.

The probability of IA in patients with a single *A. fumigatus* isolate (5.85%) was lower than that in patients with two isolates (18.42%) or with three or more isolates (38.23%) (χ^2 trend, $P < 0.001$). The mean numbers of positive cultures in patients classified with IA, colonization, and laboratory contamination (95% CI) were, respectively, 3 (3.85 to 2.15), 1.56 (1.72 to 1.40), and 1.10 (1.23 to 0.98). The comparison was statistically significant ($P < 0.001$).

When the underlying conditions of the patients with one or more isolates of *A. fumigatus* were analyzed, the probabilities of IA were found to be remarkably different depending on the risk group; however, we only found statistical differences in patients with leukemia: 6 of these 10 patients had IA (χ^2 trend, $P < 0.001$).

A culture with *A. fumigatus* was potentially more representative when obtained from a biopsy or from prosthetic material than when obtained from nonsterile samples or sterile fluids (χ^2 trend, $P < 0.001$).

To identify the prediction of infection from a positive cul-

TABLE 1. Variables that were included in the univariate logistic regression analysis and that showed statistical significance and their associated *P* values

Variable	*P*
Correlative positive samples	<0.001
Deep samples	0.017
Bone marrow transplant	0.026
General neoplastic process	0.023
Leukemia	<0.001
Chemotherapy	0.082
Neutropenia	<0.001
Steroid therapy	<0.001

ture, we applied a logistic regression analysis. We selected only those parameters that demonstrated a *P* value of <0.1 in the univariate analysis, i.e., "presence of two or more correlative positive samples," "sample obtained by invasive procedures," "bone marrow transplantation," "general neoplastic process," "leukemia," "chemotherapy," "neutropenia," and "corticosteroid treatment" (Table 1). When these eight variables were included, the model selected only five with statistical significance: "sample obtained by invasive procedures" ($P = 0.009$), "two or more correlative positive samples" ($P = 0.038$), "leukemia" ($P = 0.033$), "neutropenia" ($P = 0.003$), and "corticosteroid treatment" ($P < 0.001$). Table 2 shows in detail the values of Wald's coefficient, the level of statistical significance, and the RR, along with the 95% CI.

The multivariate logistic regression analysis was performed with a cutoff of 0.3, because in this way, the model showed improved values for specificity (92.1%) and sensitivity (54.8%). We obtained a positive predictive value (PPV) for the model of 48.6% and a negative predictive value (NPV) of 94.0%.

We obtained a score with the five variables selected by the multivariate model. A proportional value was assigned to each variable according to the RR values: "sample obtained by invasive procedures" was assigned a value of 1 (RR, 3.85), "two or more correlative positive samples" was assigned a value of 1 (RR, 3.07), "leukemia" was assigned a value of 2 (RR, 6.38), "corticosteroid treatment" was assigned a value of 2 (RR, 5.45), and "neutropenia" was assigned a value of 5 (RR, 16.21). The model presented an area under the curve of 0.809, with a *P* value, determined by the chi-square test, of <0.001. We grouped the final score of the patients according to whether they had 0, 1 or 2, 3 or 4, or ≥5 points. These groupings had a *P* value of <0.001. When we applied the score (range, 0 to 10 points) to our population with one or more isolates of *A. fumigatus*, the score was predictive of the probability of IA. Patients with a score of 0 had only a 2.5% probability of IA. In those with a score of 1 or 2, the probability rose to 10.3%, and in those with a score of 3 or 4 or a score of ≥5, the probabilities rose to 40% and 70%, respectively (Table 3). The sensitivity, specificity, PPV, and NPV of the model at each scoring level for the whole population are shown in Table 4.

TABLE 2. Variables selected for prediction of infection in the multivariate logistic regression analysis

Variable	Wald's coefficient	*P*	RR	95.0% CI for RR	
				Lower	Upper
Invasive samples	6.828	0.009	3.849	1.401	10.578
Correlative cultures	4.300	0.038	3.077	1.064	8.904
Leukemia	4.547	0.033	6.381	1.162	35.051
Neutropenia	8.902	0.003	16.215	2.601	101.100
Corticosteroid treatment	12.743	<0.001	5.452	2.149	13.834
Constant	67.354	<0.001	0.000		

TABLE 3. Number of patients classified in each group by the model, number of isolates, and cases of IA per group

Score	No. of:		No. (%) of cases of IA (proven or probable)
	Patients	Isolates	
0	119	136	3 (2.52)
1 or 2	106	189	11 (10.37)
3 or 4	25	56	10 (40.0)
≥5	10	23	7 (70.0)
Total	260	404	31

DISCUSSION

A rise in the number of cases of IA with very high rates of mortality has been reported during the last 20 years (5, 7, 9, 14). The disease is mainly caused by *A. fumigatus* (6, 22), occurs almost exclusively in humans with different degrees of immunodeficiency, and produces a wide range of clinical manifestations (6, 15, 25). Our series, however, shows an increasing number of patients with severe COPD treated with corticosteroids, which represented the most frequent underlying condition of IA in our institution during the study period. Meersseman and colleagues recently reported that this particular group is growing (16).

The isolation of *A. fumigatus* in the microbiology laboratory from patients with the usual underlying conditions should be regarded as potentially predictive of IA, although it must be stressed that this alarm is leading to an overinterpretation of the significance of these cultures in different populations (32). We were unable to find recent references addressing the workload involved in isolating *A. fumigatus* in the microbiology laboratory of a large general hospital or addressing the unbiased significance of those isolates.

In our study, *Aspergillus fumigatus* represented 5.6% of all fungal isolates in the clinical microbiology laboratory, and it

TABLE 4. Sensitivity, specificity, PPV, and NPV of the model at each scoring level for the whole population

Scoring level	%			
	Sensitivity	Specificity	PPV[a]	NPV[a]
0	100	0	12	
1	90.3	50.65	19.9	97.5
2	67.7	74.7	26.6	94.5
3	54.8	92.1	48.6	93.8
4	32.3	98.7	77.0	91.5
5	22.6	98.7	70.0	90.4
7	16.1	99.6	83.3	89.8
9	6.5	99.6	66.7	88.7
10	3.2	100	100	88.4

[a] These predictive values are valid for institutions with incidences of IA similar to ours.

was isolated 21 times per 10,000 hospital admissions but from only 4 of 10,000 patients with IA. If no other variables are considered, this value is very low, and most isolates of *A. fumigatus* do not represent proven or probable IA (21).

IA in our study occurred in 31 out of 260 patients (12%; 1.6 episodes/10,000 admissions) and involved 22% of all *A. fumigatus* isolates (90/404 isolates). This proportion of patients has been estimated very differently in the literature, depending on the bias of the selection of cases, from 9% to 90% (8, 21, 26, 27, 30).

These data give rise to the question of how to help clinicians interpret and treat patients with clinical samples from which *Aspergillus fumigatus* is obtained. The underlying conditions of the patients, together with imaging techniques and nonculture methods, are of unquestionable help; however, they are often not immediately obtainable, are difficult to interpret, or are too costly for general use, with the result that clinicians are confronted with a clinical situation involving one or more isolates of *Aspergillus* in different samples (6, 11, 12, 23, 24, 29).

When a culture turned positive in the microbiology laboratory, Horvarth and Dummer, using risk stratification, found a high PPV for a positive culture of *A. fumigatus* in patients with granulocytopenia or bone marrow transplant (13). However, there are no studies which have determined the value of a positive culture in an unselected population using not only clinical and epidemiological data in the prediction but also easily available laboratory data. We observed that the probability of IA increased considerably when the patient had two or more correlative cultures for *A. fumigatus*. We determined that the probability of having IA was higher when the sample was a biopsy or included prosthetic material. In another study by our group, the growth of *A. fumigatus* in two different fungal culture media on the first day of incubation was found to assist in the diagnosis of a true IA episode (20).

We used a prediction score to try to simplify the interpretation of laboratory results for clinicians when one or more *A. fumigatus* strains are isolated in clinical samples. This score allowed us to differentiate among a high-risk population (score of ≥ 5; risk of 70%), a low-risk population (score of ≤ 1; risk of 10%), and an intermediate population.

We conclude that our model is an easy and cost-effective tool which may help to rule out the probability of proven or probable IA in a large institution. It enables us to rapidly identify a group of patients for whom more sophisticated imaging or nonculture techniques should be used. Our score combines easily obtainable clinical and microbiological information, enabling us to predict the clinical significance of *A. fumigatus* isolates and to define a population which could benefit from a more aggressive examination for the confirmation of IA. The score should be validated by other groups.

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REFERENCES

1. **Ascioglu, S., J. H. Rex, B. de Pauw, J. E. Bennett, J. Bille, F. Crokaert, D. W. Denning, J. P. Donnelly, J. E. Edwards, Z. Erjavec, D. Fiere, O. Lortholary, J. Maertens, J. F. Meis, T. F. Patterson, J. Ritter, D. Selleslag, P. M. Shah, D. A. Stevens, T. J. Walsh, et al.** 2002. Defining opportunistic invasive fungal infections in immunocompromised patients with cancer and hematopoietic stem cell transplants: an international consensus. Clin. Infect. Dis. **34:**7–14.
2. **Bodey, G., B. Bueltmann, W. Duguid, D. Gibbs, H. Hanak, M. Hotchi, G. Mall, P. Martino, F. Meunier, S. Milliken, et al.** 1992. Fungal infections in cancer patients: an international autopsy survey. Eur. J. Clin. Microbiol. Infect. Dis. **11:**99–109.
3. **Bodey, G. P., and S. Vartivarian.** 1989. Aspergillosis. Eur. J. Clin. Microbiol. Infect. Dis. **8:**413–437.
4. **Boon, A. P., D. O'Brien, and D. H. Adams.** 1991. 10 year review of invasive aspergillosis detected at necropsy. J. Clin. Pathol. **44:**452–454.
5. **Caillot, D., O. Casasnovas, A. Bernard, J. F. Couaillier, C. Durand, B. Cuisenier, E. Solary, F. Piard, T. Petrella, A. Bonnin, G. Couillault, M. Dumas, and H. Guy.** 1997. Improved management of invasive pulmonary aspergillosis in neutropenic patients using early thoracic computed tomographic scan and surgery. J. Clin. Oncol. **15:**139–147.
6. **Denning, D. W.** 1998. Invasive aspergillosis. Clin. Infect. Dis. **26:**781–805.
7. **Denning, D. W., and D. A. Stevens.** 1990. Antifungal and surgical treatment of invasive aspergillosis: review of 2,121 published cases. Rev. Infect. Dis. **12:**1147–1201.
8. **Fisher, B. D., D. Armstrong, B. Yu, and J. W. Gold.** 1981. Invasive aspergillosis. Progress in early diagnosis and treatment. Am. J. Med. **71:**571–577.
9. **Groll, A. H., P. M. Shah, C. Mentzel, M. Schneider, G. Just-Nuebling, and K. Huebner.** 1996. Trends in the postmortem epidemiology of invasive fungal infections at a university hospital. J. Infect. **33:**23–32.
10. **Gurwith, M. J., E. B. Stinson, and J. S. Remington.** 1971. *Aspergillus* infection complicating cardiac transplantation. Report of five cases. Arch. Intern. Med. **128:**541–545.
11. **Gustafson, T. L., W. Schaffner, G. B. Lavely, C. W. Stratton, H. K. Johnson, and R. H. Hutcheson, Jr.** 1983. Invasive aspergillosis in renal transplant recipients: correlation with corticosteroid therapy. J Infect. Dis. **148:**230–238.
12. **Hope, W. W., and D. W. Denning.** 2004. Invasive aspergillosis: current and future challenges in diagnosis and therapy. Clin. Microbiol. Infect. **10:**2–4.
13. **Horvath, J. A., and S. Dummer.** 1996. The use of respiratory-tract cultures in the diagnosis of invasive pulmonary aspergillosis. Am. J. Med. **100:**171–178.
14. **Iwen, P. C., E. C. Reed, J. O. Armitage, P. J. Bierman, A. Kessinger, J. M. Vose, M. A. Arneson, B. A. Winfield, and G. L. Woods.** 1993. Nosocomial invasive aspergillosis in lymphoma patients treated with bone marrow or peripheral stem cell transplants. Infect. Control Hosp. Epidemiol. **14:**131–139.
15. **Kaiser, L., T. Huguenin, P. D. Lew, B. Chapuis, and D. Pittet.** 1998. Invasive aspergillosis. Clinical features of 35 proven cases at a single institution. Medicine (Baltimore) **77:**188–194.
16. **Meersseman, W., S. J. Vandecasteele, A. Wilmer, E. Verbeken, W. E. Peetermans, and E. Wijngaerden.** 2004. Invasive aspergillosis in critically ill patients without malignancy. Am. J. Respir. Crit. Care Med. **170:**621–625.
17. **Morrison, V. A., R. J. Haake, and D. J. Weisdorf.** 1994. Non-Candida fungal infections after bone marrow transplantation: risk factors and outcome. Am. J. Med. **96:**497–503.
18. **Morrison, V. A., R. J. Haake, and D. J. Weisdorf.** 1993. The spectrum of non-Candida fungal infections following bone marrow transplantation. Medicine (Baltimore) **72:**78–89.
19. **Murray, P., E. Baron, M. Pfaller, F. Tenover, and R. Yolken.** 1999. Manual of clinical microbiology. American Society for Microbiology, Washington, D.C.
20. **Peláez, T. M.-A. J., L. Alcalá, J. Guinea, P. Muñoz, J. M. García-Lechuz, J. Gómez-Rodríguez, V. García-Arias, and E. Bouza.** 2003. *Aspergillus fumigatus*: is time of growth and number of positive media an indication of invasiveness? Abstr. 43rd Intersci. Conf. Antimicrob. Agents Chemother., abstr. M-1032.
21. **Perfect, J. R., G. M. Cox, J. Y. Lee, C. A. Kauffman, L. de Repentigny, S. W. Chapman, V. A. Morrison, P. Pappas, J. W. Hiemenz, and D. A. Stevens.** 2001. The impact of culture isolation of *Aspergillus* species: a hospital-based survey of aspergillosis. Clin. Infect. Dis. **33:**1824–1833.
22. **Rinaldi, M. G.** 1983. Invasive aspergillosis. Rev. Infect. Dis. **5:**1061–1077.
23. **Roilides, E., C. Blake, A. Holmes, P. A. Pizzo, and T. J. Walsh.** 1996. Granulocyte-macrophage colony-stimulating factor and interferon-gamma prevent dexamethasone-induced immunosuppression of antifungal monocyte activity against *Aspergillus fumigatus* hyphae. J. Med. Vet. Mycol. **34:**63–69.
24. **Roilides, E., A. Holmes, C. Blake, P. A. Pizzo, and T. J. Walsh.** 1993. Impairment of neutrophil antifungal activity against hyphae of *Aspergillus fumigatus* in children infected with human immunodeficiency virus. J. Infect. Dis. **167:**905–911.
25. **Soubani, A. O., and P. H. Chandrasekar.** 2002. The clinical spectrum of pulmonary aspergillosis. Chest **121:**1988–1999.
26. **Sridhar, H., R. S. Jayshree, P. P. Bapsy, L. Appaji, M. Navin Kumar, M. Shafiulla, and B. R. Vijay Kumar.** 2002. Invasive aspergillosis in cancer. Mycoses **45:**358–363.
27. **Stevens, D. A., V. L. Kan, M. A. Judson, V. A. Morrison, S. Dummer, D. W. Denning, J. E. Bennett, T. J. Walsh, T. F. Patterson, and G. A. Pankey.** 2000.

Practice guidelines for diseases caused by *Aspergillus*. Clin. Infect. Dis. **30:** 696–709.
28. **Weiland, D., R. M. Ferguson, P. K. Peterson, D. C. Snover, R. L. Simmons, and J. S. Najarian.** 1983. Aspergillosis in 25 renal transplant patients. Epidemiology, clinical presentation, diagnosis, and management. Ann. Surg. **198:**622–629.
29. **Wheat, L.** 2003. Rapid diagnosis of invasive aspergillosis by antigen detection. Transpl. Infect. Dis. **5:**158–166.
30. **Williamson, E. C., D. A. Oliver, E. M. Johnson, A. B. Foot, D. I. Marks, and D. W. Warnock.** 2000. *Aspergillus* antigen testing in bone marrow transplant recipients. J. Clin. Pathol. **53:**362–366.
31. **Wingard, J. R., S. U. Beals, G. W. Santos, W. G. Merz, and R. Saral.** 1987. *Aspergillus* infections in bone marrow transplant recipients. Bone Marrow Transplant. **2:**175–181.
32. **Yu, V. L., R. R. Muder, and A. Poorsattar.** 1986. Significance of isolation of *Aspergillus* from the respiratory tract in diagnosis of invasive pulmonary aspergillosis. Results from a three-year prospective study. Am. J. Med. **81:** 249–254.