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# Practical Modalities for Prevention of Fungal Infections in Cancer Patients

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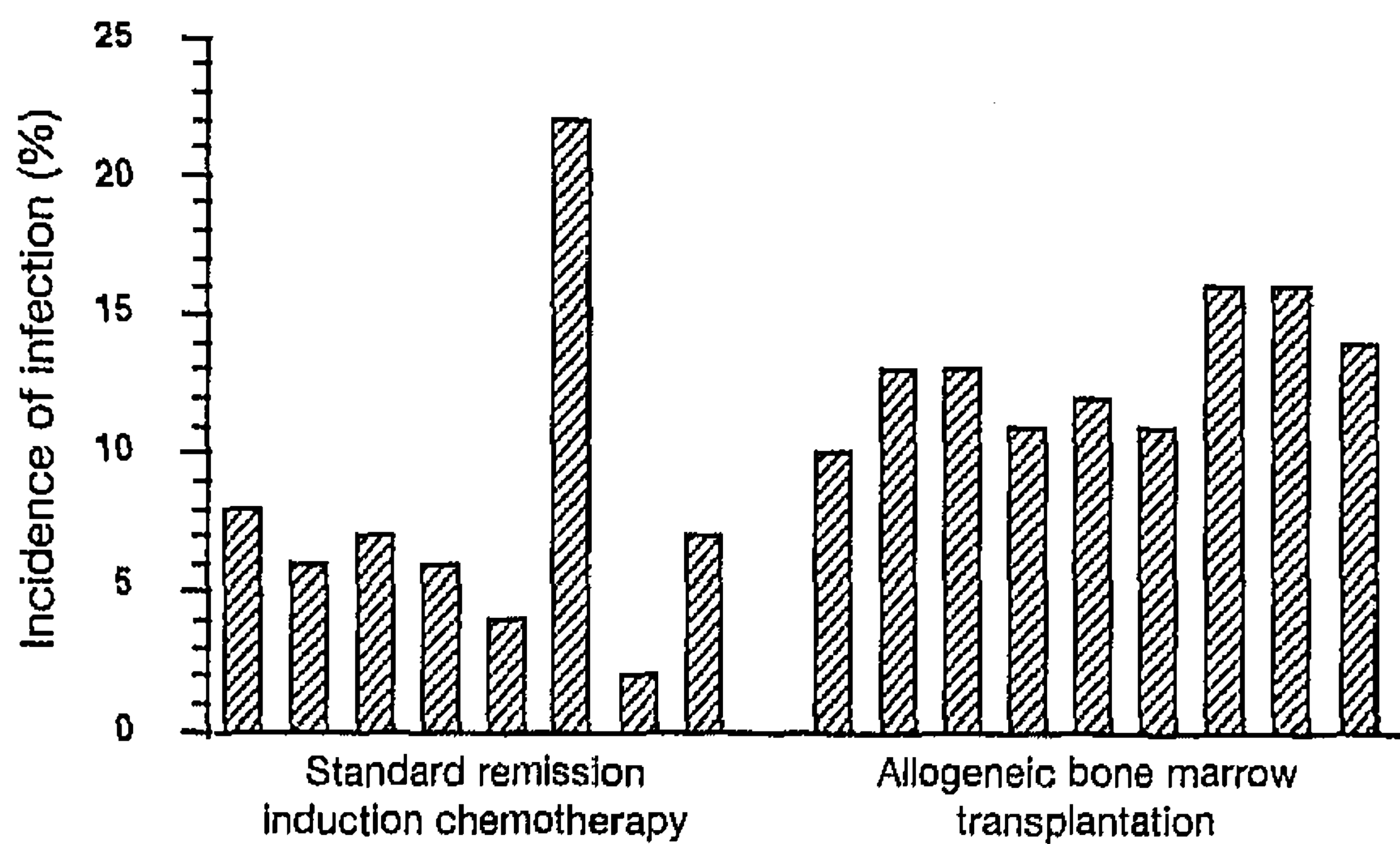
Invasive fungal infections have become a major obstacle to the treatment of patients with malignancies. *Candida* spp. and *Aspergillus* spp. now rank among the ten most prominent pathogens in these patients. Currently, there are no adequate means of detecting these infections at an early stage, and optimal hygiene and elimination of well-known sources of infection remain the most important preventive measures. Due to the lack of reliable, randomized studies, the role of antifungal drugs in the prevention of invasive fungal infections is difficult to judge. The clinical impact of the older oral antifungal agents is questionable, and compliance with therapeutic regimens of these drugs is often limited. In prospective studies in bone marrow transplant recipients, fluconazole was effective in preventing candidiasis but offered no prophylaxis against infections due to *Aspergillus* spp. and other molds. Initial trials on the use of sprays and aerosols of amphotericin B and on infusions of low doses of this drug appeared beneficial, but the number of patients included was too small to allow any definite conclusion. Itraconazole offers promise, but it can only be given orally; adequate, reliable absorption is not yet guaranteed. While the lack of data justifies a wait-and-see approach in patients at low or moderate risk of developing a fungal infection, it seems reasonable to administer prophylaxis to high-risk patients, even though there is presently no single agent suitable for all prophylactic purposes.

During the past decade, clinicians, investigators, and the pharmaceutical industry have focused more attention on fungal infections, which constitute a major cause of morbidity and mortality in patients who receive bone marrow-ablative therapy for malignant disease (1). Despite increased awareness and attempts to improve detection, the majority of fungal infections are diagnosed at autopsy (2). In up to 30% of cases of invasive fungal infections found postmortem, patients had not received any antifungal therapy. This finding indicates that the diagnostic tools for detecting disseminated fungal infection are insufficient. The incidence of documented invasive fungal infection is approximately 7% of all febrile episodes in neutropenic patients, but this incidence may be higher in some centers (Figure 1).

On the other hand, the increasing incidence of invasive fungal infections is clearly associated with

more effective antitumor strategies that induce greater mucosal damage and prolong neutropenia, as indicated by the increased incidence of fungal infections in bone marrow transplant recipients compared with patients receiving conventional cytoreductive chemotherapy (Figure 1). The availability of powerful broad-spectrum antibacterial agents is another factor that undoubtedly plays a crucial role; the use of these agents has virtually eliminated early death due to gram-negative bacillary sepsis, thereby putting the patient at risk for other, subsequent infectious complications. The incidence of invasive fungal infection may be increased by extended antibacterial coverage (R. Feld et al., 32nd ICAAC, 1990, Abstract no. 1695), possibly because the endogenous resident flora is suppressed, which seems to render the patient susceptible to ensuing fungal infection.

The extensive autopsy survey by Bodey et al. (2) revealed the presence of *Candida* spp. in 66% of cases and *Aspergillus* spp. in 30%, suggesting that many patients die either with or from a fungal infection. Indeed, *Candida* spp. and *Aspergil-*



**Figure 1:** Incidence of disseminated fungal infections in hematological malignancies versus bone marrow transplantation in various centers that use no prophylaxis or oral polyenes only. Each bar represents the incidence of proven fungal infection in a single center.

*lus* spp. now rank among the ten most prominent pathogens in patients undergoing treatment for hematological malignancies. Other fungi, such as *Cryptococcus neoformans*, *Mucor* spp., *Fusarium* spp., *Alternaria* spp., *Trichosporon* spp., and *Geotrichum candidum* are seldom encountered. *Candida albicans* prevails among *Candida* spp., but *Candida tropicalis*, *Candida glabrata*, *Candida parapsilosis*, *Candida pseudotropicalis* and *Candida krusei* are increasingly isolated, even in centers where antifungal agents are used with caution. Some of these species present problems due to their intrinsic or acquired resistance to antifungal agents, such as *Candida krusei*. Others have a clear propensity to cause invasive disease, such as *Candida tropicalis*, or to preferentially colonize central venous catheters, such as *Candida parapsilosis*. It is assumed that invasive candidiasis is preceded by colonization (3), which may be identified by surveillance cultures of the mucosal surfaces. However, colonization does not necessarily imply that a systemic infection will ensue. In marked contrast, aspergillosis is invariably acquired by inhalation of airborne *Aspergillus* spores. Infection may have been acquired before the patient became neutropenic, but exogenous contamination during neutropenia is more likely. Air ventilation systems, construction sites, medication cartons, wet and dried flowers, pigeon droppings, pepper, and tea all have been implicated in outbreaks of *Aspergillus* infections in neutropenic patients.

### General Issues and Rationale for Preventive Measures

Even with the most modern and sophisticated diagnostic tools, it is rarely possible to identify

deep-seated fungal infection at an early stage. As a result, by the time clinicians are confronted with infection it is well advanced and disseminated, and therefore difficult to cure. The mortality of culturally and/or histologically proven invasive fungal infections may exceed 90%, particularly when compounded by persistent neutropenia and underlying disease (4). Considering the limited efficacy of parenteral antifungal therapy and its high toxicity, many centers have made considerable efforts to prevent these infections.

However, before antifungal agents are used prophylactically, it is important to consider general measures to reduce the possibility of acquiring disseminated mycosis. Hand washing by visitors, nurses, doctors, and other personnel is of paramount importance; its neglect undermines all other, more sophisticated means of achieving optimal hygiene. Apart from hygiene, environments exposed to a high concentration of spores should be protected by HEPA-filtration, and well-known sources of fungi must be eliminated; this method is probably the most efficient way to reduce the number of nosocomial pulmonary aspergillosis cases in immunocompromised patients in centers with a high incidence of mold infections.

Other measures should also be considered. For instance, hemorrhagic lesions might facilitate access and growth of fungi; therefore, thrombocyte transfusions may protect profoundly thrombocytopenic patients from fungal infection. Whenever feasible, surgical excision of aspergillomas should be considered.

Reducing the duration of neutropenia to minimize the risk of developing an infection has become an attractive option, but the use of hematopoietic growth factors to prevent fungal infections requires further study. The availability of these growth factors might encourage clinicians to employ even more intensive cytoreductive chemotherapy that will cause more mucosal damage, thereby enhancing the potential for invasion by molds and yeasts. The intact mucosal barrier constitutes a reliable defense mechanisms against infection by these organisms, as demonstrated by the beneficial effects of antiviral agents that curtail mucosal damage resulting from herpes simplex infection. (R. Feld et al., 32nd ICAAC, 1992, Abstract no. 1695)

Unnecessary use of antibacterial agents and corticosteroids should be avoided, since both classes of drugs enhance the likelihood of a subsequent



invasive fungal infection. Gastric antacids should be prescribed according to strict guidelines, because a low pH protects against colonization of the small and large intestine by *Candida* spp.

### Assessment of the Prophylactic Use of Antifungal Drugs

Although there is little evidence to support this approach, antifungal drugs are often used during aggressive treatment of malignant disease. Earlier studies on the prophylactic use of the polyenes (nystatin and amphotericin B) and the imidazoles (miconazole, ketoconazole, clotrimazole) are outdated. Their findings are no longer applicable because the cytoreductive chemotherapy regimens for hematologic malignancies and solid tumors have changed substantially during the past decade. Although these drugs were somewhat effective in preventing superficial infections caused by *Candida albicans*, they were less effective in preventing disseminated mycoses (5).

It is doubtful that oral nystatin would have any beneficial effect, and there is scarce evidence that oral amphotericin B, considered the gold standard by many clinicians, is any more effective. This makes the question of whether sucking troches, pastilles, or lozenges is preferred over swallowing a suspension or tablets a trivial one. Furthermore, patient compliance with oral antifungal therapy with these agents is extremely variable, which inevitably nullifies any putative beneficial effects. Therapy with miconazole is similarly associated with problems, since tolerance of the oral preparations is generally low, especially when the patient is suffering from oral mucositis. It was thought that ketoconazole would be well tolerated and more effective because it was absorbable; however, allergic reactions and liver function disturbances have occurred with its use. Furthermore, clinical use of this drug has been associated with the selection of, and infection by, resistant *Candida* spp. as well as an increase in the rate of bacteremia (6). It must be emphasized that virtually all of the older studies as well as numerous recent ones regarding prophylaxis against fungal infections comprised a small number of mycologically or histologically proven cases of mycosis, which makes the assessment of efficacy suspect because of the large type II error.

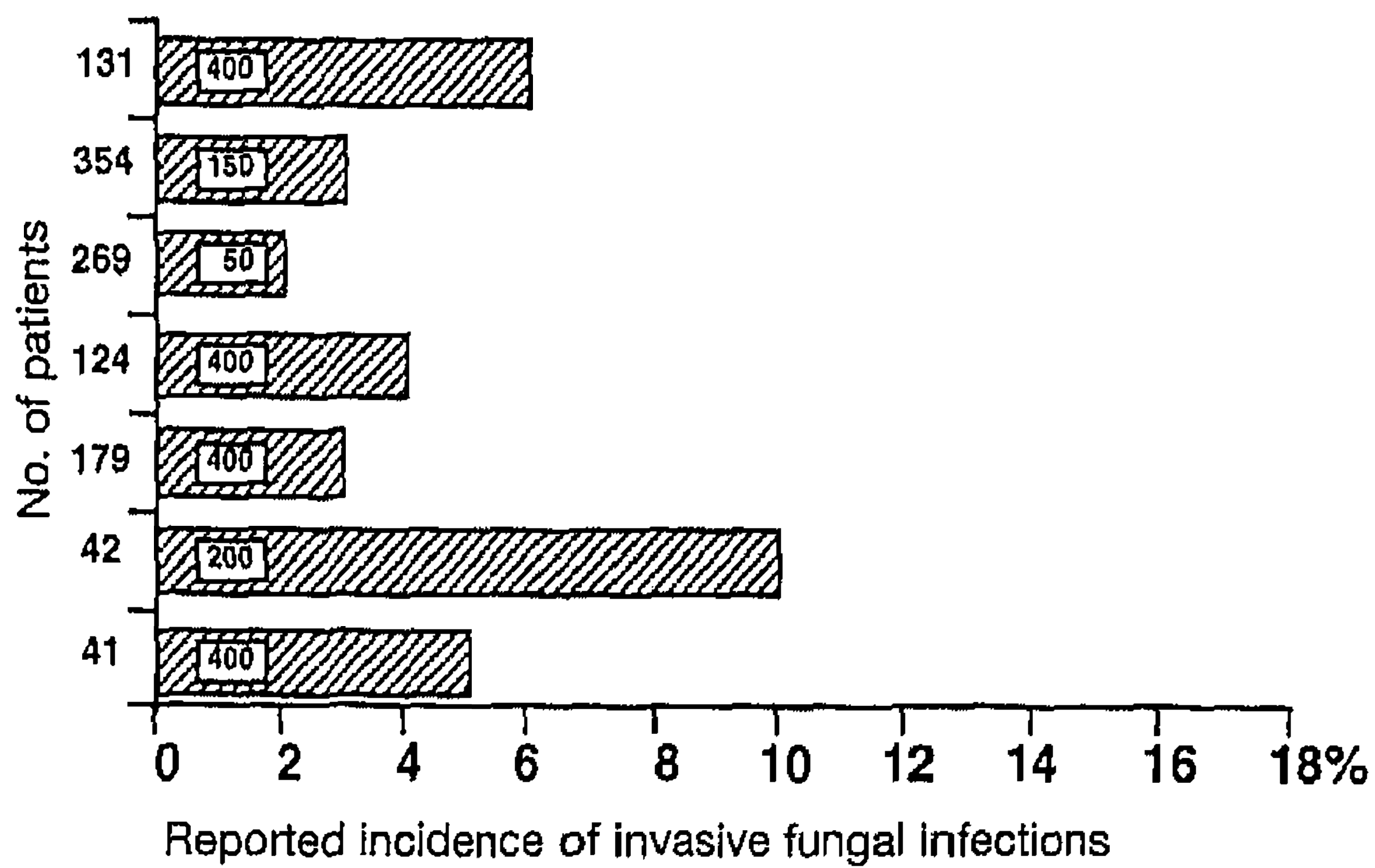
Many studies are conducted such that the results may not be generally applicable to clinical medicine. Thus, the first step in assessing any given pub-

**Table 1:** Key items in the assessment of antifungal prophylaxis studies.

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1. Were historical controls used?
    - a. Were controls case-matched?
  2. Was the study randomized?
    - a. Are statistics reliable?
    - b. Was the study conducted blindly?
  3. What were the nature and stage of the underlying disease?
  4. What was the duration of neutropenia?
  5. How was response defined?
    - a. Was the occurrence of a fungal infection reported?
      - i. If documented, was it determined whether such an infection was superficial or disseminated?
      - ii. Were probable infections reported?
      - iii. Was refractory fever the only type reported?
    - b. Was the number of deaths attributable to the fungal infection reported? Were rates of infection determined at autopsy reported?
    - c. Was perceived need for empiric systemic antifungal agents investigated?
    - d. Was overall survival reported?
  6. Was the influence of antifungal prophylaxis on colonization assessed?
  7. Were serum levels monitored (if relevant)?
  8. Were adverse events and other quality-of-life aspects mentioned?
    - a. Was patient compliance monitored?
    - b. Were interactions with other essential/unavoidable drugs determined?
  9. Was a cost-benefit analysis performed?
- 

lication is to check a number of key items (Table 1) to ensure that the study population, the type of underlying diseases, and the degree and duration of neutropenia bear some resemblance to actual clinical situations. It is also important that patients are entered consecutively and allocated their regimen at random, since historical controls are inadequate for evaluating the efficacy of an antifungal chemoprophylactic regimen.

The risk of infection varies considerably with time, due to changes in antitumor therapy regimens as well as seasonal variations and building activity and renovation. Centers that experience a high incidence of serious invasive fungal infection are those most interested in developing new prophylactic strategies; therefore, results obtained on this basis may look more impressive than they actually are, since any decrease in the incidence of mycosis is likely to be exaggerated. Moreover, the discipline involved in conducting a study often leads to better hygiene, better adherence to diagnostic protocols, and more consistent application of criteria for infections. Comparisons with historical controls will also be misleading because it is impossible to correct for these bi-



**Figure 2:** Results of various trials with fluconazole as prophylactic agent for fungal infections during neutropenia. Each bar represents a different trial; the daily dose of fluconazole is enclosed within each bar.

ases in nonrandomized studies, even when matched controls are used.

The two-part definition of the success or failure of prophylaxis deserves close attention: the direct impact of prophylaxis on the number of proven infections and the number of deaths attributable to fungal infection are crucial for the evaluation of antifungal agents, but the latter finding is seldom reported. In fact, autopsy results as regards fungal infection are virtually never reported. In contrast, surrogate measures of outcome, such as the perceived need for systemic antifungal agents and overall survival, are frequently reported. Apart from efficacy, the safety, compliance, and costs associated with prophylaxis are all relevant points that may help the physician judge the potential utility and limitations of a given strategy. It also must be underscored that many studies have a dual goal, namely to investigate infection caused by both molds and yeasts, yet each of these types of infection has a completely different epidemiology and a different portal of entry and thus requires a separate analysis. Finally, resorting to the literature is likely to be biased in favor of intervention because reports of negative findings frequently are not published.

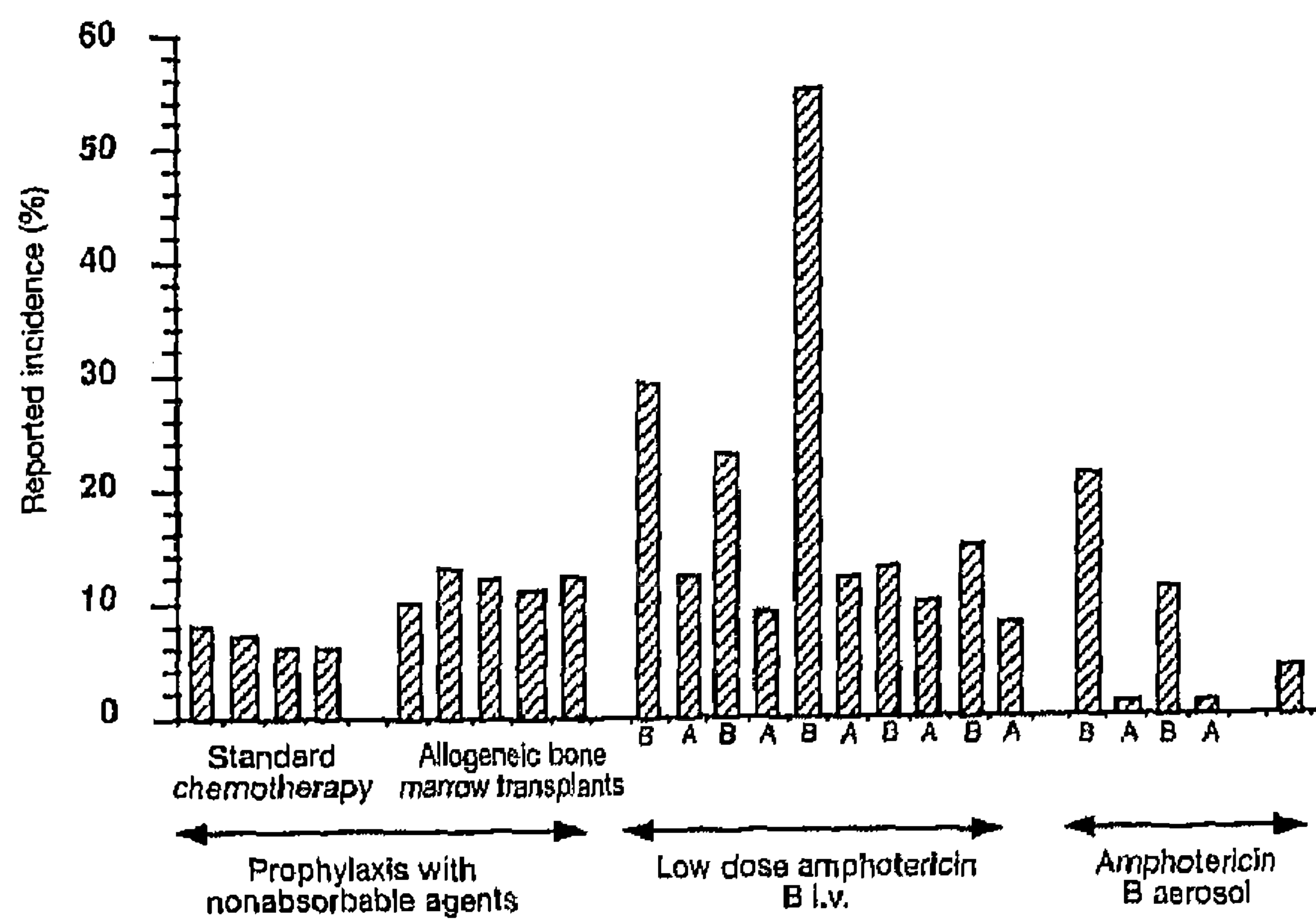
### Antifungal Drugs in the Prevention of Invasive Mycosis

**Yeast Infections.** The aim of therapy with oral antifungal agents is to reduce colonization of the gastrointestinal tract by yeasts, but there has been no consensus as to which regimen should be used. The impact of oral antifungal compounds on an invasive fungal infection remains controversial, de-

pending on the study setting. The newer triazoles are better tolerated than amphotericin B, nystatin, and ketoconazole, and they appear to be more efficacious than these older antifungal compounds. In a prospective, double-blind, placebo-controlled, multicenter study of patients undergoing bone marrow transplantation (7), prophylaxis with fluconazole at a dosage of 400 mg once daily was effective in preventing superficial and disseminated candidiasis and in lowering overall mortality. These results were confirmed in a trial by Slavin et al. (8). The same results were found in a retrospective study performed at the Detroit Medical Center (9) in which a lower dosage (100–200 mg daily) was given. Therapy with 3 mg of fluconazole per kilogram body weight appeared to be superior to oral nystatin or amphotericin B in 502 children treated for malignancies (10). However, the superiority of fluconazole was less evident when this agent was administered prophylactically to adults during remission induction therapy for acute leukemia (11–14). This finding might have been related to the various dosages used, which ranged from 50 to 400 mg daily, although there was no obvious relationship between the dosage and the ultimate results (Figure 2).

There is also a marked difference between European and North American views of the need for intravenous amphotericin B, which reflects differences in the attitude of physicians towards empiric administration of this compound. Data from the study conducted by Goodman et al. (7), in which 400 mg fluconazole was administered daily, are the most convincing, but the results from trials in which patients were treated at a lower dosage suggest that half the dose may suffice in the majority of cases (10, 14). Fluconazole was well tolerated at all dosage levels and was not associated with serious adverse effects apart from the tendency to select resistant *Candida* spp., particularly *Candida krusei* (15). Such selection of resistance may be a local phenomenon, because it was not mentioned as a problem in other prospective, randomized studies (10, 12, 13). Although fluconazole offers no protection against infections by *Aspergillus* spp., the overall prophylactic efficacy of this drug during prolonged neutropenia appeared to compare to that of low-dose intravenous amphotericin B (16). These findings underscore the limitations inherent in assessing neutropenic patients entered into a trial when the incidence of documented invasive mold infections is low, since it will be impossible to detect significant differences. Although analysis of subgroups might provide a



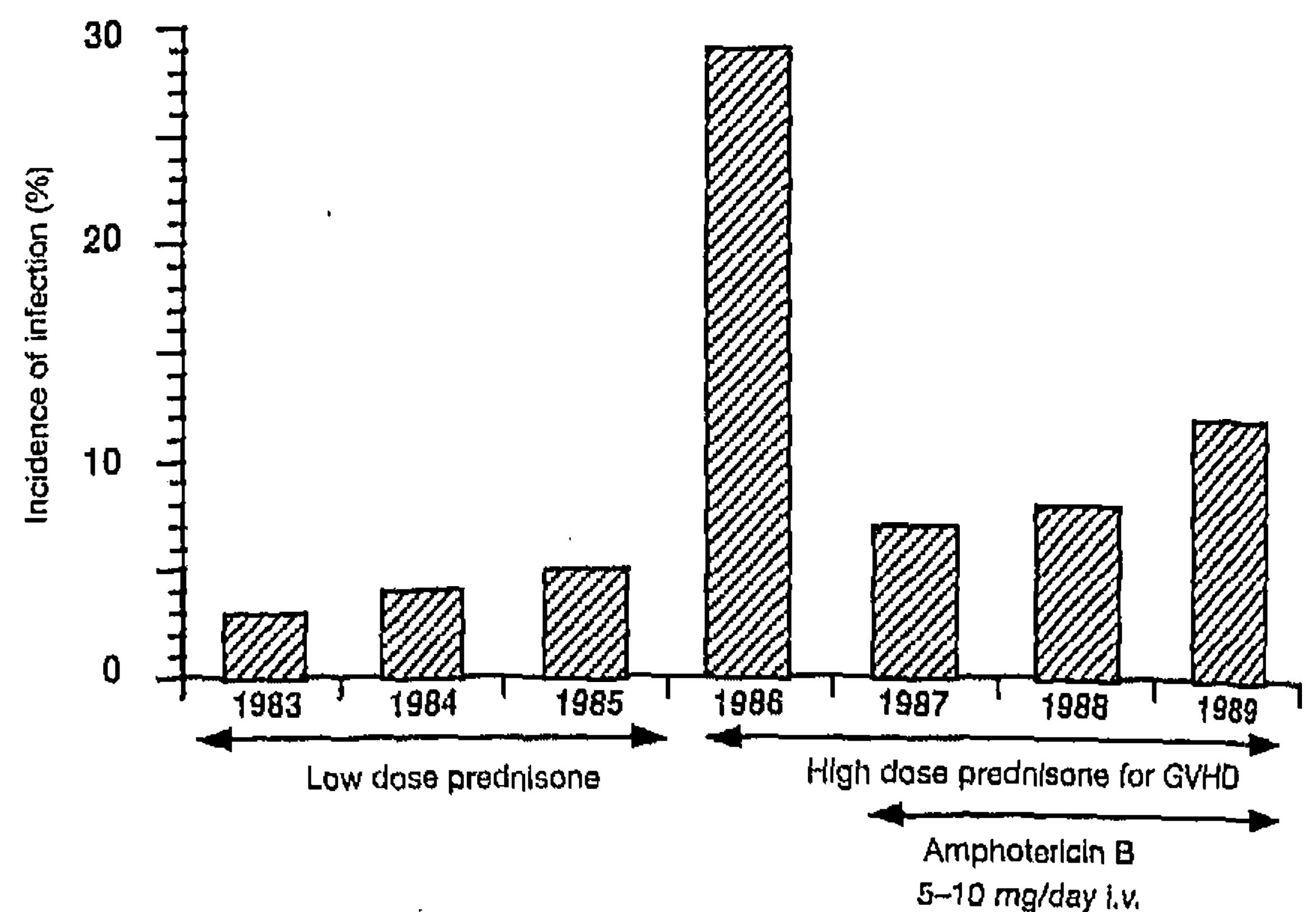


**Figure 3:** Impact of non-oral amphotericin B on the prevention of fungal infections in neutropenic patients. Each set of B/A bars represents a different study. B, incidence of fungal infections in historical controls; A, incidence of fungal infections after introduction of prophylaxis. Unmarked bars represent epidemiological surveys in various centers.

better answer, in most clinical studies the low number of suitable patients with a defined diagnosis precludes a firm conclusion.

**Mold infections.** Even though the azoles and polyenes show some promise in preventing superficial and invasive candidiasis, they afford no protection against infection due to *Aspergillus* spp. and other molds, largely because mold infections are almost always acquired by inhalation of spores into airways that are inaccessible to non-absorbable agents. Hence, other routes of administration have been explored.

In initial trials, amphotericin B sprays or inhalants (17–22) and low-dose infusions of amphotericin B (23–25) appeared to reduce the number of respiratory infections caused by *Aspergillus* spp. in patients undergoing bone marrow transplantation or remission induction therapy for hematologic malignancy. However, few patients were included in these trials, most of which were not conducted as prospective randomized studies. The rationale underlying these studies was delivery of a high concentration of aerosolized amphotericin B directly to the bronchi and bronchioli, which are considered the portal of entry in airborne infection. The incidence of pulmonary aspergillosis was lower in patients who received aerosolized amphotericin B than in historical controls, but overall mortality was not affected. Moreover, the incidence of disseminated aspergillosis was considerably higher at participating centers before the trial than that reported in other surveys (Figure 3). However, a subsequent prospective, randomized study showed that the aerosol amphotericin B offered no statistically significant advantage with re-

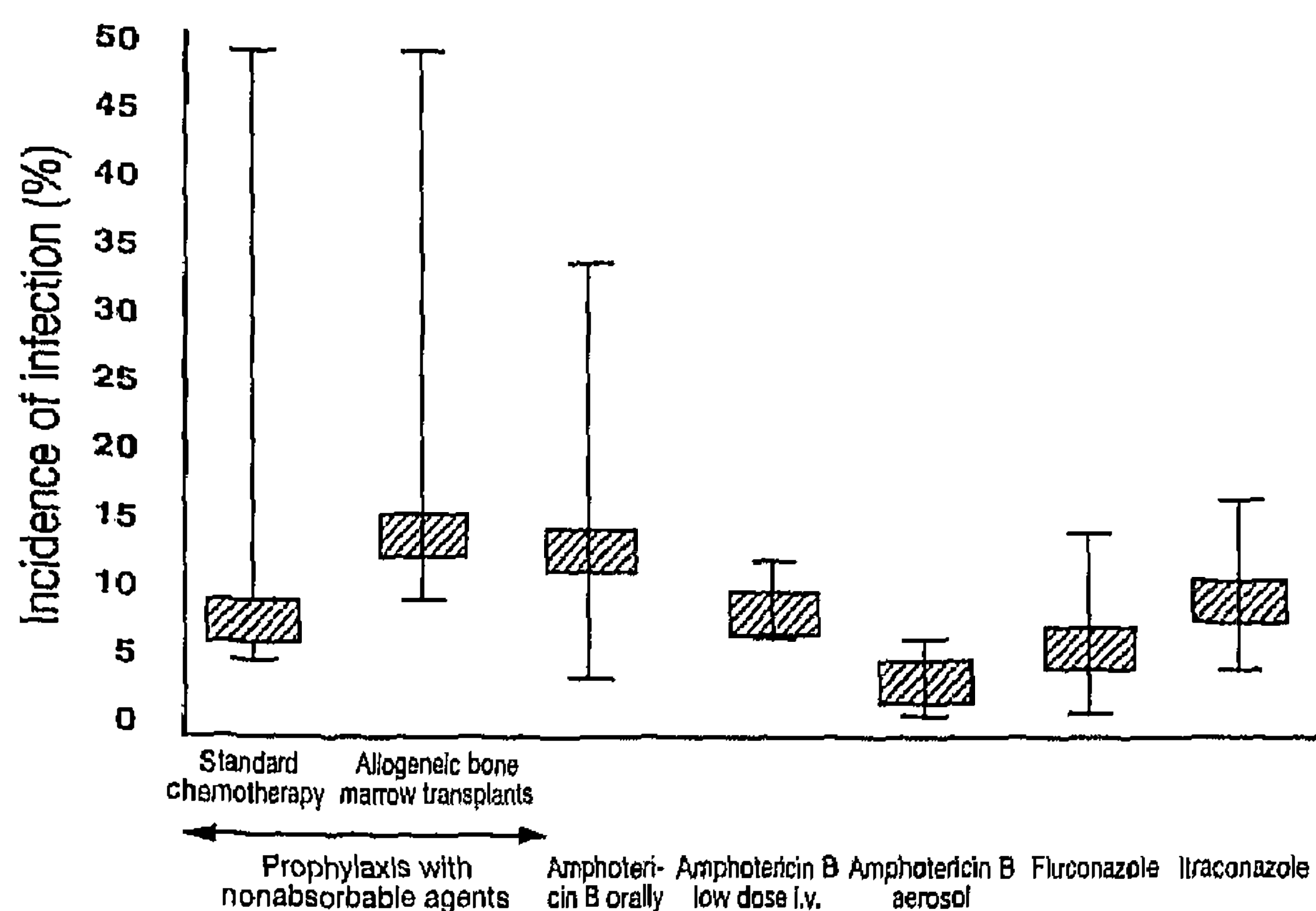


**Figure 4:** Changing incidence of fungal infections in bone marrow transplant recipients in relation to the dosage of corticosteroids for graft-versus-host disease (GVHD) and the use of antifungal prophylaxis (taken from reference 25).

spect to the number of documented infections or overall survival (26). In fact, more cases of bacteremia were documented (26) in patients who inhaled nebulized amphotericin B. Thus, until further investigations are undertaken, no firm conclusions as to the efficacy of this strategy can be drawn.

Reduced dosages of 0.1 to 0.25 mg/kg/day intravenous amphotericin B or 0.5 mg/kg 3 days/week have been tested in a prophylactic setting, principally in bone marrow transplant recipients, in an attempt to reduce the drug's toxicity while retaining its excellent antifungal activity. However, most of these studies suffer from the same flaws as those that investigated nebulized amphotericin B and have come to similar conclusions (Figure 3). The combination of amphotericin B with cyclosporine may induce renal toxicity, which necessitates adjustment of the cyclosporine dosage and increases the risk of graft-versus-host disease.

The questionable value of using historical controls for comparison was shown by O'Donnell et al. (25), who reported an increased incidence of fungal infections after high-dose corticosteroids were introduced to manage graft-versus-host disease in bone marrow transplant recipients (Figure 4). This finding was particularly worrisome to the authors because the incidence of these infections had been remarkably low during the previous years; in fact, the local incidence was far below the average for similar patients and might have been underestimated as a result of lack of awareness, lack of diagnostic facilities, or use of less intensive chemotherapy for remission induction treatment. Once confronted with the apparent epidemic, the



**Figure 5:** Mean incidence range (shown by vertical lines) of invasive fungal infections with different prophylactic antifungal regimens.

authors initiated a study that probably entailed improved clinical and microbiological surveillance, which increased the chances of detection. Implementation of the amphotericin B prophylaxis program did decrease the incidence of fungal infections, but not to the level observed before corticosteroids were introduced. After the initial decrease, however, the incidence actually rose again to those levels reported by others.

Although the liposomal formulations of amphotericin B seem to offer a safe alternative to the deoxycholate preparation, which is notorious for its toxicity, the clinical efficacy of these new compounds has not yet been proven (27). In addition, these drugs are too costly for use on a general basis.

In contrast to fluconazole, itraconazole has demonstrated clinical activity against *Aspergillus* spp. (28, 29). Even before its registration, this oral compound produced encouraging results in preventing serious fungal infections in small groups of neutropenic patients compared to historical controls (30–32). However, in a prospective, double-blind, randomized study in leukemic patients who were given oral amphotericin B, or itraconazole, 400 mg/day, neither reduced the incidence of documented and presumed *Aspergillus* infections nor influenced the perceived need for intravenous amphotericin B (33). The serum levels of the drug may have been inadequate in a substantial number of these patients, since many of them suffered mucositis induced by aggressive chemotherapy. Although itraconazole did improve suppression of *Candida* spp. in the gastrointestinal tract, these disappointing results might have been different had the drug concentration been monitored consistently during the trial and the dose of itraconazole adjusted accordingly.

The efficacy of itraconazole might also have been improved if more reliable absorption of the drug could have been achieved to ensure adequate serum levels or if higher doses were used (30, 34). With the current formulation, serum concentrations of itraconazole should be determined regularly, especially in patients suffering cytotoxic therapy-induced mucosal damage or when antacids are coadministered. At present, a new formulation of itraconazole suspended in cyclodextrin solution is being investigated and appears to be better absorbed (35). Other concerns about itraconazole have been identified: the induction of resistance to amphotericin B by previous exposure to itraconazole (36); the possible induction or inhibition of hepatic enzymes by itraconazole; the interaction of itraconazole with cyclosporine; and the propensity of itraconazole to increase intracellular levels of cytotoxic drugs such as vincristine and anthracyclines, which might enhance the toxic effects of these agents.

When fluconazole or itraconazole is used prophylactically at adequate doses, neither is likely to be of benefit in treating proven or presumed invasive fungal infection, since it must be assumed that the offending pathogen is resistant to these drugs. This is not necessarily the case for oral amphotericin B, since the negligible amounts absorbed provide no useful systemic activity, although the outcome of patients who have been treated may still be less favorable (37).

### Practical Guidelines for the Prophylactic Use of Antifungal Drugs

The efficacy of prophylactic use of antifungal drugs to prevent invasive fungal infections during episodes of prolonged and severe neutropenia is not clear because reliable, prospective, randomized studies are lacking, except for those that have investigated fluconazole in this setting. A survey of the literature showed that most strategies have produced results that differ little from those observed in patients not given prophylactic agents (Figure 5). Even for fluconazole, by far the most widely tested drug, the data are equivocal; the possible exception is that daily dosing with 400 mg of fluconazole appears to offer some protection to bone marrow transplant recipients. All other options, including amphotericin B inhalation, require further exploration before definite recommendations can be given.



Although the lack of data justifies watchful waiting, it seems reasonable to give patients at high risk of developing a life-threatening invasive fungal infection the advantage of prophylactic treatment with an antifungal drug, preferably as part of a randomized study. For example, if colonization by *Candida* spp., especially non-*albicans* strains, is encountered, prophylactic measures or early systemic antifungal therapy should be considered in a neutropenic patient (3, 38). Furthermore, patients with long-standing mucosal lesions who are being treated with broad-spectrum antibacterial agents for serious bacterial infections (39) and adult recipients of an allogeneic bone marrow transplant who are seropositive for cytomegalovirus and suffer from graft-versus-host disease (40) deserve the best antifungal prophylaxis available. Empiric parenteral amphotericin B may be a suitable alternative for neutropenic patients with persistent fever despite adequate broad-spectrum antibacterial therapy (37, 41) who have not yet developed a documented fungal infection.

Therapeutic doses of intravenous amphotericin B seem to be required to protect patients with previous aspergillosis against recrudescence during later cycles of intensive antileukemic therapy or bone marrow transplantation (42). Provided the serum levels are adequate, itraconazole could be administered as an alternative during the period between two consecutive neutropenic episodes (43–46).

## Conclusion

Considering the limited data available, there is clearly a need for thorough, well-designed clinical research regarding the epidemiology, diagnosis, treatment, and prevention of invasive fungal infections in cancer patients. Although knowledge has increased, the information is patchy and not generally applicable. If we are to establish clinically useful guidelines for treating and preventing fungal infections, cooperation between medical disciplines and medical centers is essential. The most crucial questions can be answered only by means of comprehensive clinical trials that require close cooperation between clinicians and microbiologists.

No single agent can be recommended to prevent all kinds of fungal infections under all circumstances. Most studies dealing with the prophylactic use of antifungal agents are difficult to evaluate be-

cause of methodological flaws, especially the low number of patients studied. Yet, measures for preventing fungal infections in neutropenic patients are clearly warranted because the use of more aggressive chemotherapy has led to a corresponding increase in the incidence of mycosis. In addition, timely diagnosis is seldom possible, and invasive fungal infections are associated with high mortality. Some general measures are obvious: practicing optimal hygiene, controlling the patient's environment, and avoiding clearly hazardous comedication. However, most recommendations on the prophylactic use of antifungal agents are driven by concern about the outcome of a possible invasive fungal infection rather than on hard evidence derived from published observations.

Fluconazole prophylaxis seems proper for bone marrow transplant recipients, but even in this setting its benefit is not clear because it has been associated with the selection of resistant *Candida* strains, and it offers no protection against mold infection. The use of hematopoietic growth factors (discussed elsewhere in this issue) is based on thin evidence, although it is appropriate to offer antifungal prophylaxis to patients at high risk of developing mycosis. These include patients experiencing severe mucosal damage who are also colonized with yeasts; those who are likely to experience prolonged neutropenia, particularly if it coincides with a cytomegalovirus infection and/or graft-versus-host disease; those who have undergone extensive abdominal surgery; and those receiving parenteral nutrition via a central venous catheter. The paucity of data, however, makes it impossible to achieve a consensus on the optimal prophylactic strategy. In fact, none of the presently available absorbable and nonabsorbable oral agents used for fungal chemoprophylaxis prevent infection or eradicate colonization consistently.

Fluconazole (150 to 400 mg daily) seems to be the best choice in circumstances that favor *Candida* or *Cryptococcus* infections, but it provides no protection against other frequent fungal infections in neutropenic cancer patients.

Amphotericin B administered by aerosol is a theoretically attractive option and is well-tolerated; however, promising results from clinical trials with historical controls have not been confirmed in a recent randomized trial. Hence, the value of this approach remains unproven. The usefulness of prophylaxis with intravenous amphotericin B requires further clinical investigation, but this drug



should be given at the full dose to any patient with a history of a serious invasive fungal infection to safeguard against recrudescence during subsequent neutropenic episodes. Many clinicians administer 0.1 to 0.2 mg/kg/day amphotericin B intravenously (dubbed "Ampho-lite" by its critics) for prophylactic purposes in patients at risk to circumvent the toxicity associated with the standard dose. Again, the studies that support this approach have either used historical controls or have recruited few patients. Moreover, it is unclear whether low-dose amphotericin B would eradicate infections that usually respond to much higher doses.

The erratic absorption of itraconazole discourages clinicians from using it for patients who are receiving antacids or who suffer from mucositis; its potential for interfering with the metabolism of other drugs and causing liver function disturbances deters them further. Yet, the drug still holds some promise for the future once a more reliable formulation becomes available for clinical use. Provided that adequate serum levels can be ensured, itraconazole might be used to bridge the period between consecutive neutropenic episodes in patients who have acquired an invasive fungal infection.

Until more convincing data become available, every center must devise its own method for treating life-threatening invasive fungal infections in high-risk patients, based on local circumstances and prevailing pathogens. Until the value of the presently available chemoprophylaxis has been established, a wait-and-see strategy should be adopted for patients with a low or moderate risk of developing infection. In those at high risk, early initiation of intravenous treatment with amphotericin B at a therapeutic dose is favored when fungal infection is suspected. A major goal of the Invasive Fungal Infections Cooperative Group of the European Organisation for Research and Treatment of Cancer (EORTC) is to define more effective means of preventing fungal infection through investigation and subsequent validation.

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