

Economic considerations of antifungal prophylaxis in patients undergoing surgical procedures

Maria Adriana Cataldo
Nicola Petrosillo

Second Infectious Diseases Division,
National Institute for Infectious
Diseases, "Lazzaro Spallanzani",
Rome, Italy

Abstract: Fungi are a frequent cause of nosocomial infections, with an incidence that has increased significantly in recent years, especially among critically ill patients who require intensive care unit (ICU) admission. Among ICU patients, postsurgical patients have a higher risk of *Candida* infections in the bloodstream. In consideration of the high incidence of fungal infections in these patients, their strong impact on mortality rate, and of the difficulties in *Candida* diagnosis, some experts suggest the use of antifungal prophylaxis in critically ill surgical patients. A clinical benefit from this strategy has been demonstrated, but the economic impact of the use of antifungal prophylaxis in surgical patients has not been systematically evaluated, and its cost–benefit ratio has not been defined. Whereas the costs associated with treating fungal infections are very high, the cost of antifungal drugs varies from affordable (ie, the older azoles) to expensive (ie, echinocandins, polyenes, and the newer azoles). Adverse drug-related effects and the possibly increased incidence of fluconazole resistance and of isolates other than *Candida albicans* must also be taken into account. From the published studies of antifungal prophylaxis in surgical patients, a likely economic benefit of this strategy could be inferred, but its usefulness and cost–benefits should be evaluated in light of local data, because the available evidence does not permit general recommendations.

Keywords: antifungal prophylaxis, cost-effectiveness, economics, surgery, fungal infection

Introduction

Fungi are a frequent cause of nosocomial infections, with an incidence that has significantly increased in recent years.¹ It has been reported that *Candida* is responsible for 9% of all nosocomial bloodstream infections in the US² and that it is the most common cause of invasive mycoses.³ *Aspergillus* species and other emerging fungi, such as *Fusarium* and *Rhizopus* species, are less frequently isolated, but may cause infections in immunocompromised surgical patients. Regarding *Candida* infections, *C. albicans* accounts for most nosocomial infections, although in some units up to 50% of *Candida* infections are due to species other than *C. albicans*.^{4,5}

In the past, fungi were considered to be etiologic agents of infections essentially occurring in neutropenic patients, such as transplant recipients or those with cancer. More recently, a role for fungi has been recognized also in infections affecting critically ill patients, especially those who require intensive care unit (ICU) admission. Among ICU patients, surgical ones have a higher risk of *Candida* bloodstream infections.⁶ It has been reported that about two-thirds of all episodes of candidemia occur in ICUs and in surgical wards,¹ and that *Candida* is the third most common isolate from blood in these wards.² According to data from the National Epidemiology of Mycosis Survey,

Correspondence: Maria Adriana Cataldo
Second Infectious Diseases Division,
National Institute for Infectious
Diseases, "Lazzaro Spallanzani",
Via Portuense, 292 00149 Rome, Italy
Tel +39 065 517 0432
Fax +39 065 517 0486
Email adriana.cataldo@inmi.it

the overall rate of *Candida* bloodstream infections was 0.98 per 1000 surgical ICU patient-days and 1.42 per 1000 surgical ICU patient-days when a central venous catheter is in place.⁷ The higher incidence of fungal infections among surgical patients is due to the severity of their underlying diseases, impaired gastrointestinal mucosal integrity, frequency of treatment with broad-spectrum antibiotics, and parenteral nutrition.^{3,4}

The crude mortality rate for *Candida* bloodstream infection ranges from 40% to 60%,^{8–10} and the mortality rate attributable to candidemia has been estimated at 25%–38%.^{11,12} However, the impact of *Candida* infections on mortality is still controversial. In a matched case-control study carefully adjusted for age, severity of illness, and underlying disease, it was demonstrated that candidemia did not significantly affect mortality in the ICU.¹³ In contrast, the results of a systematic review of studies examining the mortality rate related to candidemia suggest that most of the mortality is attributable to the infection itself.¹⁴

Surgical patients who develop *Candida* bloodstream infections have a mortality rate significantly higher than patients in surgical ICUs without this infection.⁷ Moreover, invasive candidiasis is associated with prolonged hospital stays.^{8–10} In a large cohort of ICU patients, it was calculated that nosocomial *Candida* infections were associated with an increase of 17 days and 8 days in length of hospital stay and ICU stay, respectively.¹⁵

A major problem affecting the management of fungal infection is the difficulty in making an early diagnosis, given the poor sensitivity of diagnostic tests. On the other hand, several efficacious antifungal agents are now available with a good safety profile.

The high incidence of fungal infections in surgical patients, impact on mortality rate, and abovementioned diagnostic difficulties have led some experts to suggest the use of antifungal prophylaxis in these patients. However, there is a lack of clear evidence of benefit from this strategy on the incidence of fungal infections and on mortality rates.

Although fungal infections, due to their high associated morbidity and mortality, have a strong impact on hospital costs and on health economic balances, the cost–benefit ratio of fungal prophylaxis strategy is not well defined. This review summarizes the available evidence for the economic impact of antifungal prophylaxis among surgical patients, and briefly reports the relevant efficacy data in light of the potential cost–benefit ratio.

Which surgical patients are at greater risk for fungal infection?

In spite of the identification of several risk factors associated with fungal infection among surgical patients, it is not possible to define a particular group of high-risk patients.

The probability of infection differs according to the type of surgical procedure. Patients who undergo abdominal surgery are at highest risk. Patients who undergo neurosurgical or ear, nose, and throat procedures are at the lowest risk, followed by orthopedic and gynecologic patients.⁷

A multicenter study including 4276 surgical patients identified previous surgery, acute renal failure, and receipt of parenteral nutrition as factors independently associated with increased risk of *Candida* bloodstream infections.⁷ Other risk factors for fungal infections in surgical patients are the severity of the underlying condition,¹⁶ duration of stay in the ICU, receipt of antibacterial agents, and use of a central venous catheter.

Colonization with *Candida* is another important risk factor for subsequent invasive infection. The role of *Candida* colonization on the development of subsequent infection has been specifically investigated in surgical patients, revealing that the intensity and duration of colonization are determining factors.¹⁷ Several risk-predictive models for invasive candidiasis among critically ill patients have been published. However, they showed suboptimal performance and were not validated in independent ICU cohorts.¹⁸

Is antifungal prophylaxis efficacious in preventing infections in surgical patients?

The effectiveness of antifungal prophylaxis is still debated in several patient categories. A number of studies on this topic have been published, and five meta-analyses have been done to reassess the effectiveness and safety of this strategy in surgical patients. The characteristics of the patients included and the prophylactic strategies analyzed differed between the published meta-analyses, but there was some overlap of the studies included. Here we report the main findings regarding the efficacy of antifungal prophylaxis in surgical patients.

A meta-analysis by Vardakas et al included six randomized, placebo-controlled trials containing 43–292 patients assessing the role of azoles in antifungal prophylaxis among high-risk surgical ICU patients.¹⁹ High-risk patients were defined as those having three or more risk factors associated with fungal infection, and patients undergoing transplantation were also

included if they were expected to stay in the ICU for more than five days following surgery. Antifungal agents used in the studies were fluconazole 100–400 mg with or without a loading dose and administered orally or intravenously, itraconazole 5 mg/kg orally, and ketoconazole 200 mg orally, and with a variable duration of prophylaxis. A pooled analysis showed that patients receiving azole prophylaxis developed significantly fewer fungal infections, including candidemia, invasive fungal infections outside the bloodstream, and non-invasive fungal infections compared with placebo recipients. Mortality was significantly lower neither in patients undergoing antifungal prophylaxis, nor in the subgroup analysis conducted including only surgical patients.¹⁹

The meta-analysis by Cruciani et al included nine randomized controlled trials with 43–292 patients comparing systemic antifungal agents with controls in nonneutropenic adult ICU surgical or trauma patients.²⁰ Antifungal agents used in the included studies were fluconazole 100–400 mg with or without a loading dose, administered orally or intravenously and ketoconazole 200 mg administered orally or parenterally compared with placebo or with no treatment/nystatin/clotrimazole. The length of prophylaxis differed among the studies. This pooled analysis also showed that the probability of *Candida* infection in patients who received antifungal prophylaxis was significantly lower. Interestingly, the metaregression showed that neither the azole prescribed nor the Acute Physiology and Chronic Health Evaluation (APACHE) II score influenced treatment effects. Moreover, this meta-analysis demonstrated a 79% reduction in mortality attributable to *Candida* infection in azole-treated patients. Overall mortality was also significantly reduced.²⁰

The meta-analysis by Playford et al included 12 randomized controlled trials including 38–292 patients and evaluated the effect of any antifungal regimen in nonneutropenic critically ill patients.²¹ This meta-analysis also included nonsurgical patients, but the majority of those included were postsurgical ICU patients. Eight trials compared fluconazole 100–400 mg with or without a loading dose administered orally or intravenously, with no antifungal therapy, and four compared ketoconazole 200–400 mg administered orally with no antifungal treatment or a nonadsorbable agent. The duration of prophylaxis differed among the studies. The fluconazole and ketoconazole trials analyzed separately did not show a significant reduction of mortality risk. Fluconazole significantly reduced the incidence of proven invasive fungal infections. When the trials were analyzed together, fluconazole and ketoconazole were found to reduce

total mortality and invasive infections. Subgroup analysis of postsurgical patients demonstrated a significant reduction of proven invasive infections and mortality in the fluconazole and ketoconazole prophylaxis groups.²¹

The meta-analysis by Shorr et al included four randomized trials with 43–260 patients comparing fluconazole with placebo in critically ill surgical patients. There was heterogeneity among the trials with respect to fluconazole dosing (100–400 mg/day, with or without a loading dose), route of administration (orally or intravenously or both), and duration of the prophylactic regimen. The authors of this meta-analysis reported that prophylaxis significantly reduced the incidence of fungal infections but was not associated with a lower mortality rate. The incidence of candidemia was not significantly reduced in the fluconazole group.²²

The meta-analysis by Ho et al included seven randomized controlled trials of fluconazole prophylaxis involving immunocompetent critically ill or high-risk surgical patients, excluding studies that included liver transplanted or neutropenic cancer patients.²³ The numbers of patients included in the trials ranged from 43 to 260, doses of fluconazole ranged from 100 to 800 mg/day, and the duration of the prophylactic regimen varied between the studies. Candidemia was significantly less frequent in the fluconazole group, but hospital mortality and total length of hospital stay did not differ between the two groups.²³

In conclusion, these meta-analyses showed a clinical benefit of antifungal prophylaxis in patients at different degrees of risk. Only two pooled analyses showed significantly lower mortality rates. However, due to the inadequate sample size of the trials and the heterogeneity in type and dosage of antifungal agent, duration of prophylaxis, and patient characteristics, it is not possible to identify a clear indication for a prophylactic antifungal strategy from these studies.

Costs of antifungal prophylaxis

When considering the economic balance of antifungal prophylaxis, it is necessary to take into account several cost components. First, the economic consequences of fungal infection must be considered. A multicenter Spanish study assessed the economic impact of *Candida* colonization and *Candida* infection in critically ill patients admitted to an ICU. *Candida* colonization resulted in an additional €8000 and *Candida* infection in almost €16,000 in direct costs, respectively.²⁴

A prospective cohort study of *Candida* infections conducted in the medical and surgical ICUs of a large US hospital

reported an unadjusted median cost of \$41,832 for patients with *Candida* infections and of \$19,252 for those without *Candida* infections.¹⁵ A cost per ICU patient-day of \$230 was also calculated.¹⁵

A multiple linear regression model was used to determine the cost of an ICU admission attributable to *Candida* infection and to verify if clinical factors other than fungal infection have an impact on the cost of an ICU admission. *Candida* infections were associated with a median increase in the cost of \$21,590 per patient and, in particular, with significantly increased costs in the service categories of room and board (\$16,549), pharmacy (\$5501), laboratory (\$8216), supplies (\$3289), and physical and occupational therapy (\$2677). The variable that most strongly affected cost was the length of stay in the ICU.¹⁵ The results of a random effects model revealed that the daily ICU cost did not change after patients became infected with *Candida*, confirming that the increase in ICU cost is probably due to the increased length of stay rather than increased daily ICU cost.¹⁵

Another US study specifically assessed the estimated costs of care associated with candidemia over an entire hospital stay.¹⁰ The increase in cost of care during hospitalization was \$44,536 and \$34,123 in patients receiving private insurance and Medicare, respectively.¹⁰ The total cost included expenditure for diagnostic procedures, antifungal therapy, hospital stay, adverse drug reactions, and switch therapy because of adverse drug reactions.¹⁰ The largest component of total cost was due to protracted hospital stays. The results of a regression analysis performed to control for

factors that may influence length of hospitalization showed that candidemia had the most impact.¹⁰

The acquisition cost of antifungal agent is also an important component of prophylaxis expenditure. Table 1 summarizes the costs of commercial available antifungal agents. Economic cost widely varies depending on the drug, the dosage used, route of administration, and total duration of prophylactic treatment. For example, published trials have reported fluconazole dosages of 100–400 mg/day preceded by a loading dose of 800 mg and administration by the parenteral or enteral route, with different costs. Costs of antifungal agents vary between countries and hospitals, and may differ if the drug is administered during hospitalization, at a long-term care facility, or in an outpatient setting. Fluconazole is the drug most frequently used in prophylactic regimens. It is inexpensive and its pricing is expected to be reduced following the expiration of its patented life. The guidelines from the Infectious Diseases Society of America recommend fluconazole 6 mg/kg/day as an antifungal agent for prophylaxis in high-risk ICU patients.²⁵

The antifungal profile and pharmacokinetic parameters of the echinocandins (caspofungin, micafungin, anidulafungin) could make them good choices for antifungal prophylaxis. However, these agents are expensive and need to be administered intravenously. Similarly, the high cost and need for parenteral infusion limits the use of lipid formulations of amphotericin B.

The economic cost of the side effects associated with antifungal agents must also be considered. The costs

Table 1 Costs of antifungal agents

Antifungal agent (usual dosage)	Product cost (US\$)	Estimated daily cost*
Amphotericin B 0.5–1.0 mg/kg/IV/day	\$12/50 mg vial	\$12–24
L-Amphotericin B 1–5 mg/kg/IV/day	\$188/50 mg vial	\$263–1316
Fluconazole 400 mg/day orally or IV	\$8/200 mg tablet \$88/400 mg IV	\$16 for oral administration \$88 for IV administration
Itraconazole 200 mg/day orally or 200 mg/day IV	\$10/100 mg capsules \$158/200 mg vial	\$20 for oral administration \$158 for IV administration
Ketoconazole 400 mg/day orally	\$5/200 mg tab	\$10
Posaconazole 600–800 mg/day orally	\$576/105 mL susp (40 mg/mL)	\$82–110
Voriconazole 6 mg/kg/IV q12h first day, then 3 mg/kg/IV q12h or 400 mg orally q12h on day 1 followed by 200 mg orally q12h	\$121/200 mg vial \$39/200 mg tab	\$508 first day then \$255 for IV administration \$156 first day then \$78 for oral administration
Anidulafungin 100–200 mg/IV first day followed by 50–100 mg/IV/day	\$112/50 mg vial	\$224–448 first day then \$112–224
Caspofungin 70 mg/IV first day followed by 50 mg/day IV	\$395/70 mg vial \$395/50 mg vial	\$395
Micafungin 50–150 mg/day IV	\$112/50 mg vial	\$112–336

Notes: *For a 70 kg patient. All cost data were extracted from the 2007 Drug Topics Redbook, Thomson Healthcare, Inc.

Abbreviations: L, liposomal; IV, intravenous; q, quondam; h, hours; cps, capsule; tab, tablet; susp, suspension.

associated with drug-related adverse events depend on their incidence and severity, and are calculated taking into account the costs of several components, including loss of life-years, loss of quality life-years, long-term morbidity of selected adverse events, and an extended hospital stay due to an adverse event.

Fluconazole is generally well tolerated, with a very low incidence of serious adverse effects, and the new azoles and echinocandins have low toxicity rates. On the other hand, administration of amphotericin B or liposomal amphotericin is frequently associated with nephrotoxicity.

Some of the aforementioned meta-analyses explored the incidence of toxicity due to antifungal prophylaxis. Comparing azoles with placebo, there was no significant difference in the incidence of side effects.¹⁹ The pooled analysis that included trials comparing fluconazole or ketoconazole with no antifungal therapy or with nonadsorbable agents showed no difference in the occurrence of severe adverse events. Shorr et al, reviewing the safety of fluconazole prophylaxis, reported that rates of laboratory abnormalities were similar across all the studies that presented safety data, and did not differ between the intervention and placebo arms. No deaths were attributed to fluconazole administration, and intervention was stopped in only five patients (two on fluconazole and three on placebo) because of toxicity concerns.²²

Another important economic consequence is the potential impact of prophylaxis on the emergence of antifungal resistance and on the prevalence of different fungal species. This effect is linked to the “ecological cost” of antifungal prophylaxis. Ecological costs represent the costs paid by future patients given inappropriate treatment due to the higher resistance to frequently used antifungal agents and by individual patient costs, ie, the costs of development of resistance in the individual patient, assuming that antifungal use will change the flora in the individual.

Above all, azole use has been linked to an increased incidence of fluconazole-resistant *Candida* isolates and to a shift towards isolation of *Candida* species other than *C. albicans*. Exposure to fluconazole is an already known risk factor associated with fluconazole resistance,²⁶ and several investigators have reported an increased frequency of isolation of *C. glabrata* subsequent to azole use.^{27–29} These phenomena would have a strong impact on mortality from *Candida* infections. It has been shown that *Candida* species other than *C. albicans* have a worse prognosis.^{30–32} Similarly, in critically ill patients, infection with *Candida* strains resistant to fluconazole doubles the risk of death.³³ As a consequence, a higher mortality rate would be responsible

for an increase in costs. Moreover, in a setting with a higher prevalence of fluconazole-resistant *Candida* and of isolates other than *C. albicans*, the antifungal options would include the newer azoles and echinocandins, with a further significant increase in costs.

Resistance to echinocandins and the newer azoles would also increase as a consequence of greater use, so the cost–benefit of antifungal prophylaxis would be even more unfavorable. The role of antifungal prophylaxis in the emergence of resistant *Candida* and strains other than *C. albicans* is still controversial. An observational study in a surgical ICU where fluconazole prophylaxis had been utilized for three years, revealed that, when invasive candidiasis occurs, the causative agent is likely to have reduced susceptibility to fluconazole, whether or not it was ICU-acquired.³⁴ However, three meta-analyses of azole prophylaxis reported neither development of resistance among the fungal isolates nor a shift from *C. albicans* toward other *Candida* species.^{19,20,23}

The economic impact of the use of antifungal prophylaxis in surgical patients has not been systematically evaluated, but some authors have tried to extrapolate economic data from their investigations on antifungal prophylaxis.

In a double-blind, placebo-controlled trial evaluating the prophylactic use of enteral fluconazole to prevent *Candida* infections in 260 critically ill surgical patients, it was calculated that the number needed to treat to prevent one fungal infection was 9.5.³⁵ The authors chose the enteral rather than the intravenous route for fluconazole because it costs less and has good bioavailability. The cost for a 400 mg dose was \$90, whereas the calculated cost of *Candida* infections was \$230 per ICU patient-day.¹⁵ It was concluded that, given the low cost of enteral fluconazole and the low number of patients needed to treat to prevent fungal infections, the use of antifungal prophylaxis in this population is likely to be cost-effective.

Similarly Ho et al, with a baseline risk of candidemia that in the placebo arm of their meta-analysis was 4.5%, calculated that 25 patients would need to be treated to prevent one episode of candidemia. Assuming a cost of \$490 for a 2-week prophylactic course of fluconazole per patient, the cost to prevent one episode of candidemia would be \$12,250, which is markedly less expensive than the calculated cost of each episode of candidemia.²³

A study that investigated a risk-based fluconazole prophylaxis program included 36 patients admitted to a medical ICU.³⁶ It was reported that the total cost of fluconazole prophylaxis was \$6000, which is much less expensive than the \$567,000 of excess health care costs associated with

nine episodes of *Candida* bloodstream infection that occurred in the same unit before the start of the prophylaxis program.³⁶ However, these data do not refer to surgical patients, and the study was conducted in a small ICU and consequently analyzed very few episodes of candidiasis.

Some authors have suggested that a more efficacious and economically feasible strategy could be to utilize colonization screening to guide the choice of patients who would benefit from antifungal prophylaxis. *Candida* colonization has been recognized as an important risk factor for subsequent infection, and it has been reported that, in the absence of fungal colonization, infection is unlikely.¹⁶ However, its positive predictive value of infection ranges between 12% and 18%. Moreover, the variability in design of the published studies and in the reporting of the extent and duration of colonization does not allow us to give an exact indication on how to use colonization data for this purpose. Interestingly, the corrected colonization index, ie, ratio of highly positive samples to the total number of samples cultured, developed by Pittet et al,¹⁷ was utilized in a before-after study to guide the decision about which patients should receive pre-emptive treatment with fluconazole.²⁶ The incidence of proven surgical ICU-acquired candidiasis significantly decreased while the incidence of imported candidiasis did not change.²⁶ A corrected colonization index cutoff of 0.4 was defined as a probable indication of unnecessary prophylaxis. This strategy would probably be less expensive than if prophylaxis was administered to all patients, but the cost of mycological screening performed on all admitted patients is not negligible. No specific economic data are available for this strategy.

Discussion

The costs of fungal infections are very high, and surgical patients seem to be at greater risk for developing serious and invasive *Candida* infections, with a high mortality rate. The azoles are affordable, but the incidence of fluconazole resistance with isolates other than *C. albicans* needs to be investigated further because the available evidence does not exclude a strong impact on these phenomena. Similarly, further studies with adequate sample sizes are needed to define better the adverse effect profile of azole prophylaxis, particularly for hepatotoxicity.

Obviously, the economic balance of a prophylaxis strategy does not result from a simple opposition of the cost associated with *Candida* infections against the cost for antifungal agents and the related side effects.

The economic advantage of antifungal prophylaxis is linked to the incidence of infection and to the impact of

prophylaxis on mortality. The fungal infection rates reported by the published studies are variable and consequently the data on efficacy and cost are not generalizable. Also, the incidence of invasive infections in surgical ICUs varies widely between hospitals, and all the trials have the limitations of being heterogeneous and including small patient populations.

If we can identify patients at very high risk for infection and administer a prophylactic regimen only to a selected population, the economic balance would probably be favorable. Unfortunately, there is not a defined group of patients at greatest risk as yet, and the strategy of colonization screening has many gaps and needs further investigation.

Some experts have suggested that prophylaxis would be advantageous when the rate of candidemia is at least 10%.³⁷ However, Ho et al reported a likely cost-benefit of antifungal prophylaxis pooling studies with a baseline candidemia risk of 4.5%.

Recently published guidelines for the management of candidiasis recommend the use of antifungal prophylaxis in patients at high risk (>10%) of invasive candidiasis hospitalized in ICUs with very high rates compared with the “normal rates” of 1%–2%.²⁵

Another essential determinant of the economic balance is the actual impact of antifungal prophylaxis on the mortality rate. Not all published trials found lower mortality in the treated groups, and the pooled analyses performed by different investigators yielded conflicting results. The meta-analysis by Cruciani et al reported a reduction in mortality attributable to *Candida* infection and in overall mortality in the azole-treated group.²⁰ In the meta-analysis by Playford et al, the subgroup analysis of postsurgical patients demonstrated a significant mortality reduction in the fluconazole/ketoconazole prophylaxis groups.²¹ The other meta-analyses failed to show a benefit on mortality rate.^{19,22,23} The inability to detect a survival advantage with antifungal prophylaxis might be due to small sample sizes and to the selection of populations at insufficiently high risk to show a benefit. Future studies are needed with adequate sample sizes to define better the highest risk surgical population, and to assess the impact of prophylaxis on the incidence of infection and mortality.

A likely economic benefit of this strategy does emerge from the published studies on antifungal prophylaxis in surgical patients, but a specific cost-benefit analysis is lacking and is urgently needed.

The usefulness and the cost-benefit of antifungal prophylaxis in surgical patients should be evaluated in each surgical

unit in light of local data concerning the incidence of invasive *Candida* infections and the clinical and epidemiological characteristics of the patient population treated, because the available evidence does not permit a universal recommendation.

It is important to underscore that, beyond prophylaxis with antifungal agents, standard measures to prevent nosocomial infections should always be applied both for their efficacy and for their low cost. Because transmission of *Candida* could occur via the hands of health care workers, especially during the care of catheters, all hospitals need to improve their adherence to hand hygiene. Also, extremely important is adherence to current recommendations for placement and care of central venous catheters. Finally, the correct use of antibiotics is another important component of candidemia prevention that would lead to a decrease in economic and ecological costs.

Disclosure

The authors report no conflicts of interest in this work.

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