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ARTICLE

Invasive pulmonary aspergillosis in patients with HBV-related liver failure

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Abstract Invasive pulmonary aspergillosis (IPA) has been increasingly frequent in severe liver disease. We aim to investigate the clinical presentation, predisposing factors, and treatment of IPA in patients with liver failure caused by hepatitis B virus (HBV) infection. Medical records from 798 patients with HBV-related liver failure were reviewed. A total of 43 patients with probable IPA were selected as the case group, another 43 patients with bacterial infection and 43 patients without any infections were selected, for whose age, sex, date of admission, and the disease onset were matched with the case group. We evaluated the risk factors, clinical manifestations, treatment, and subsequent outcome of IPA in patients with HBV-related liver failure. Multivariate logistic regression models were used to demonstrate risk factors associated with IPA. Compared with patients with bacterial infection and those without any infection, patients with probable IPA used more antibiotics and steroids, and had poorer conditions and the highest mortality ($P<0.0001$). Multiple antibiotics use and frequent invasive procedures were independent factors associated with the occurrence of IPA in patients with HBV-related liver failure. Patients with HBV-related liver failure are predisposed to IPA and may have a more severe condition and poorer prognosis.

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Introduction

In China liver failure is a life-threatening condition that is mainly caused by the hepatitis B virus (HBV) [1]. Due to multiple immunologic defects, patients with liver failure are at a higher risk for various infections [2]. An infection, a systemic infection in particular, may induce systemic inflammatory response syndrome and sepsis; if conditions worsen, an infection may even cause death [3]. Invasive pulmonary aspergillosis (IPA) is a rapidly progressive, frequently fatal disease; there is always a diagnostic delay due to atypical clinical features and the limitations of current diagnostic tests [4–7]. Morbidity and mortality caused by IPA are increasing because of increasing numbers of patients treated with intensive immunosuppressive therapy regimens or undergoing allogeneic hematopoietic stem cell or organ transplantation [5, 7, 8]. Recently, IPA has been described to occur in patients with liver failure because of their improved survival rate [8, 9]. However, these studies are limited in number and limited to case reports. We performed a case-control study to assess the risk factors, clinical manifestations, treatment, and subsequent outcome of IPA in patients with HBV-related liver failure to raise the awareness of clinicians and to improve the prognosis of patients with HBV-related liver failure complicated by IPA.

Patients and methods

We examined data from patients with probable IPA diagnosis who were admitted with HBV-related liver failure to the Third Affiliated Hospital of Hebei Medical University and Shijiazhuang Fifth Hospital from September 1999 to August 2009. The data of patients with bacterial infection and those

without any infection were collected from the same databases. Clinical data from all selected patients were reviewed, including demographic features, predisposing factors, clinical manifestations, results of laboratory tests, chest computed tomographic (CT) images, treatments, and prognosis.

Standardized criteria were applied for the diagnosis of HBV-related liver failure according to the guideline for diagnosis and management of liver failure made by Chinese Society of Infectious Disease and Chinese Society of Hepatology [10]. Acute liver failure was characterized by the presence of hepatic encephalopathy within weeks, of which severity was at lease grade 2. Subacute liver failure was defined as the presence of extreme fatigue, severe gastrointestinal symptoms, progressive jaundice, and coagulopathy (prothrombin activity ≤40%) between 15 days and 26 weeks. The definition of acute-on-chronic liver failure was the presence of acute liver decompensation developed on the basis of chronic liver disease. Chronic liver failure was defined as when the liver function decompensates chronically on the basis of cirrhosis. HBV-related liver failure was defined as liver failure with positive HBV surface antigen, excluding other causes that could induce severe liver injury, such as hepatoviruses other than HBV, alcohol, drugs, pregnancy, autoimmunity, and genetic and metabolic disorders.

The criteria from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group were used to diagnose IPA [11]. Definite IPA was defined as filamentous fungi confirmed by microscopic examination or by culture of a specimen obtained from sterile material, excluding bronchoalveolar lavage fluid, a cranial sinus cavity specimen, and urine. Probable IPA was defined as the presence of clinical features including low respiratory tract fungal disease (nodules, halo sign, air-crescent sign, or cavity on chest CT scan) and a positive culture for *Aspergillus* from a sputum specimen with or without a host factor as no alternative diagnosis was available. Possible IPA and probable IPA were similarly defined, except that the definition of possible IPA lacked mycological evidence.

Data from this retrospective study were analyzed using SPSS 15.0 software. Quantitative data were analyzed by the analysis of variance to assess the significance of differences in means, and qualitative data were analyzed by the χ^2 test to assess the significance of differences in proportions. The logistic model was used to predict the probability of occurrence of the risk factors. For the purpose of hypothesis testing, the probability of type I error was set at 0.05.

This study was conducted in the Departments of Infectious Diseases of the Third Affiliated Hospital of Hebei Medical University and Shijiazhuang Fifth Hospital and was approved by the Research Ethics Committee of Hebei Medical University.

Results

Selection of cases and controls from patients with HBV-related liver failure

Among all 798 patients, 66 were diagnosed with possible IPA according to their clinical features and the imaging results from their chest CT scans. However, neither lung biopsy nor sterile specimen culture was performed in all patients with possible IPA because of coagulopathy as well as the wishes of their families. Detection of galactomannan or β-d-glucan was not performed due to technical limitations. Thus, the diagnosis depended on the results of the sputum culture, which suggested that 25 patients were positive for *Aspergillus flavus* and 18 were positive for *Aspergillus fumigatus*. Therefore, these 43 patients who received the diagnosis of probable IPA were selected for the case group. Another 43 patients with bacterial infection and the 43 patients without any infection were selected from the same database as the control groups. Their age, sex, date of admission, and the disease onset were pair-matched with the case group.

Demographic characteristics

The probable IPA case group included 40 males and three females, 34 of them had chronic disease onset. Patients with probable IPA and patients with bacterial infection had longer hospital stays and more complications compared with the control group, but there were no significant differences between the former two groups. All patients with probable IPA used two or more antibiotics for more than 7 days, and 29 of the 43 patients used antibiotics for more than 14 days. In contrast, 19 of the 43 patients in the control group used antibiotics to prevent infections, just nine of them used two or more antibiotics, and six patients used antibiotics for more than 14 days ($P<0.0001$). Meanwhile, most of the patients with probable IPA used steroids to decrease persistent hyperbilirubinemia and to prevent allergic reactions to blood products, and the maximum amount of dexamethasone used was 120 mg; in comparison, 15 patients in the control group had steroid exposure ($P<0.0001$). The group of patients with bacterial infection had longer antibiotic duration than the control group ($P<0.0001$), and had less antibiotic categories and steroid exposure than the group of patients with probable IPA ($P<0.0001$). Invasive examinations or treatments were performed more frequently on patients with probable IPA and patients with bacterial infection compared with those in the control group ($P<0.0001$) (Table 1).

Table 1 Demographic features and laboratory parameters of patients with HBV-related liver failure in the three groups

Characteristics	Numbers of patients (%)			*P* value
	IPA	Bacterial infection	Control	
Age (mean ± SD)	49.79 ±14.18	48.12±13.37	48.21±14.24	0.8442
Gender				0.2111
Male	40 (93.02)	39 (90.70)	40 (93.02)	
Female	3 (6.98)	4 (9.30)	3 (6.98)	
Hospital days (mean ± SD)	45.53±13.83*	43.72±17.42*	35.93±12.83	<0.0001
Disease onset				0.9968
Acute liver failure	2 (4.65)	1 (2.33)	2 (4.65)	
Subacute liver failure	2 (4.65)	2 (4.56)	2 (4.65)	
Acute-on-chronic liver failure	5 (11.63)	6 (13.95)	6 (13.95)	
Chronic liver failure	34 (79.07)	34 (79.07)	33(76.74)	
Complication	*	*		0.0133
Hepatic encephalopathy	18 (41.86)	16 (37.21)	13 (30.23)	
Hepatorenal syndrome	9 (20.93)	7 (16.30)	4 (9.30)	
Spontaneous bacterial peritonitis	7 (16.30)	10 (23.26)	4 (9.30)	
Upper gastrointestinal bleeding	4 (9.30)	5 (11.63)	3 (6.98)	
Antibiotic category	*,**			<0.0001
One	-	16 (37.21)	10 (23.26)	
Two	8 (18.60)	13 (30.23)	5 (11.63)	
Three or more	35 (81.40)	14 (32.56)	4 (9.30)	
Antibiotic duration	*	*		< 0.0001
< 2 weeks	14 (32.56)	19 (44.19)	13 (30.23)	
≥ 2 weeks	29 (67.44)	24 (55.81)	6 (13.95)	
Steroid exposure	*,**			<0.0001
< 1 week	21 (48.84)	14 (32.56)	12 (27.91)	
≥ 1 week	15 (34.88)	6 (13.95)	3 (6.98)	
Invasive examination	*	*		0.0046
< 5 times	15 (34.88)	13 (30.23)	13 (30.23)	
≥ 5 times	19 (44.19)	17 (39.53)	6 (13.95)	
Outcome	*,**	*		<0.0001
Improvement	-	15 (34.88)	25 (58.14)	
Dead	43 (100)	28 (65.12)	18 (41.86)	
One-year survival	-*,**	7 (16.28)*	15 (34.88)	<0.0001
Laboratory parameters				
Leukocyte count ($\times 10^9$/L, mean ± SD)	14.50±3.11*,**	10.87±2.61*	8.60±2.08	<0.0001
Platelet count ($\times 10^9$/L, mean ± SD)	49.44±16.62*,**	95.43±39.50*	117.02±39.51	<0.0001
Prothrombin activity (%, mean ± SD)	22.29±7.17*,**	26.95±4.99*	31.04±9.61	<0.0001
Alanine aminotransferase (U/L, mean ± SD)	91.05±33.68*	108.07±42.45*	166.30±87.19	<0.0001
Total bilirubin (μmol/L, mean ± SD)	572.54±100.96*,**	457.64±111.18*	319.26±100.03	<0.0001
Ammonia (μmol/L, mean ± SD)	64.84±19.99	69.94±26.87	66.48±21.26	0.5745
Creatinine (μmol/L, mean ± SD)	114.63±38.90*	115.44±41.90*	73.09±19.37	<0.0001
MELD score (mean ± SD)	34.84±5.47*,**	31.91±6.50*	28.49±6.94	<0.0001

IPA invasive pulmonary aspergillosis, *SD* standard deviation, *MELD* model for end-stage liver disease

*$P<0.05$ vs. the control group; **$P<0.05$ vs. the group of patients with bacterial infection

Table 2 Laboratory parameters of 43 patients before and after being diagnosed with IPA

Parameters	Before	After	*P* value
Leukocyte counts ($\times 10^9$/L, mean ± SD)	10.00±2.29	14.50±3.11	<0.0001
Platelet count ($\times 10^9$/L, mean ± SD)	67.49±21.04	49.44±16.62	<0.0001
Prothrombin activity (%, mean ± SD)	28.63±6.06	22.29±7.17	<0.0001
Alanine aminotransferase (U/L, mean ± SD)	178.58±54.60	91.05±33.68	<0.0001
Total bilirubin (μmol/L, mean ± SD)	324.81±90.15	572.54±100.96	<0.0001
Ammonia (μmol/L, mean ± SD)	54.36±16.11	64.84±19.99	<0.0001
Creatinine (μmol/L, mean ± SD)	81.84±30.10	114.63±38.90	<0.0001
MELD score (mean ± SD)	31.81±5.30	34.84±5.47	<0.0001

IPA invasive pulmonary aspergillosis, *SD* standard deviation, *MELD* model for end-stage liver disease

Laboratory test results

Compared to the control group, both patients with probable IPA and those with bacterial infection had more white cell counts, less platelet counts, lower prothrombin activity and serum alanine aminotransferase, and higher serum bilirubin, creatinine, and scores of model for end-stage liver disease (MELD) ($P<0.0001$). Between the latter two groups, patients with probable IPA had more white cell counts, less platelet counts, lower prothrombin activity, and higher serum bilirubin and MELD score ($P<0.0001$), but serum alanine aminotransferase and creatinine were similar between the two groups (Table 1). Furthermore, these laboratory test values were compared in the case group of patients before and after *Aspergillus* infection, and the same results were obtained (Table 2).

Table 3 Clinical manifestations, imaging findings, and causes of death of 43 patients with invasive pulmonary aspergillosis (IPA)

Characteristics	Number of patients (%)
Clinical manifestations	
Fever	43 (100.00)
Cough	39 (90.70)
Hemoptysis	39 (90.70)
Chest pain	2 (4.76)
Crackles	36 (83.72)
Imaging findings	
Macronodule	36 (83.72)
Clusters of small nudules	17 (39.53)
Consolidation	14 (32.56)
Halo sign	11 (25.58)
Cavitary lesion	7 (16.28)
Air crescent sign	6 (13.95)
Causes of death	
Pneumorrhagia	16 (37.21)
Respiratory failure	15 (34.88)
Hepatic encephalopathy	5 (11.63)
Hepatorenal syndrome	3 (6.98)
Septic shock	2 (4.76)
Upper gastrointestinal bleeding	2 (4.76)

Clinical features, treatments, and outcomes of patients with probable IPA

The primary symptoms of patients with probable IPA were fever and respiratory symptoms, including cough, hemoptysis, crackles, and chest pain. The imaging results from the chest CT scan were not specific, and macronodule was the most common change rather than halo sign or air crescent sign (Table 3, Fig. 1).

Of the 43 patients with probable IPA, 12 were diagnosed within 7 days after suspicion of fungal infection, 23 were diagnosed between 7 to 14 days, six were diagnosed when disease was severe, and two were diagnosed after death. Supportive treatments (disinfecting the air and floor, washing hands frequently, decreasing visits, maintaining water-electrolyte and energy balance, modulating the intestinal flora, etc.), immunity improvements (thymosin α1 and human immunoglobulin for intravenous injection), and antivirus and antifungal therapies were used for them. Caspofungin was used as the antifungal agent at the intravenous dose of 70 mg on the first day and 35 mg later. Of the patients diagnosed with probable IPA, eight patients received empirical therapy and showed persistent fever or rebound refractory to broad-spectrum antibiotics with cough; 26 received preemptive therapy after determination of necessity from the chest CT scans; and nine (including the two patients diagnosed after death) were in severe condition and were untreated due to family wishes. All patients with probable IPA died within 14 days after diagnosis; deaths were mainly caused by pneumorrhagia and respiratory failure (Table 3). The mortality of this group (100%) was higher than that of the group of patients with bacterial infection (28, 65.12%), but the mortality in both of these groups was higher than that in the control group (18, 41.86%). The survival rate of patients with bacterial infection was 16.28% (seven patients) at one-year follow-up, which was lower than that of the control group (15, 34.88%) (Table 1, Fig. 2).

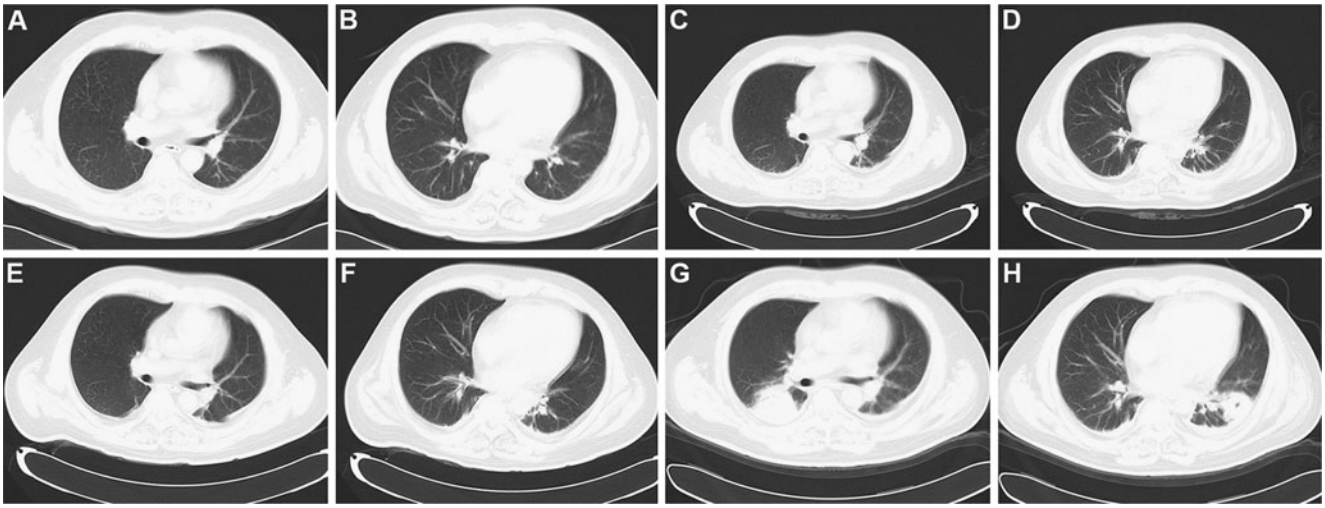

Fig. 1 Images of chest CT scan in hepatitis B virus (HBV)-related liver failure patients with invasive pulmonary aspergillosis (IPA). These images were scans of a 53-year-old male patient suffering from chronic hepatitis B for 18 years. The admitting diagnosis was acute-on-chronic liver failure. The chest CT scan was performed on the 14th day after admission, and the imaging findings were normal (**a** and **b**). However, cord-like shadows appeared in the lower right lung on the 19th day (**c** and **d**) and remained the same on the 22nd day (**e** and **f**). The patient presented with a cough, and caspofungin was used for anti-fungal therapy. The imaging findings of the chest CT scan showed a macronodule with a cavity in the left lung and clusters of small nodules in the bilateral lung fields 4 days later (**g** and **h**). The patient's condition worsened dramatically, and treatment was discontinued based on the family's wishes. The patient died two days later

Risk factors

Seven variables were considered for this logistic regression model, including age, length of hospital stay, antibiotic category, antibiotic duration, steroid exposure, invasive examination, and coinfection. On multivariate analysis, multiple antibiotics use and frequent invasive procedures were independent factors associated with the occurrence of IPA in patients with HBV-related liver failure (Table 4).

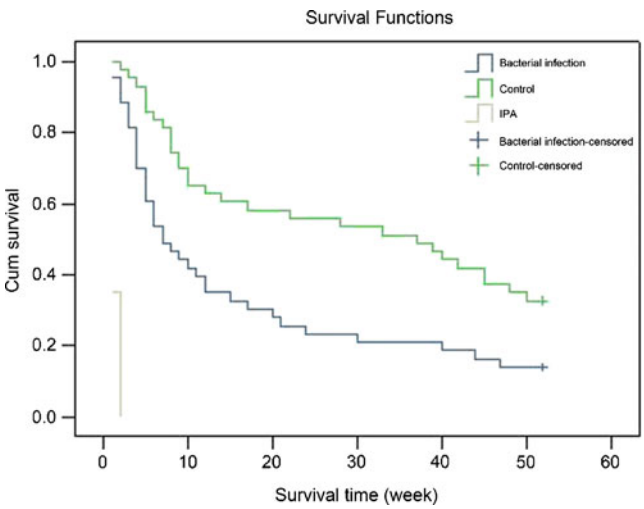

Fig. 2 Survival curve of patients with HBV-related liver failure in the three groups. The mortality of patients with invasive pulmonary aspergillosis (IPA) was higher than that of patients with bacterial infection, and the control group had the lowest mortality. The survival rate of patients with bacterial infection was lower than that of control group at one-year follow-up

Discussion

Aspergillus is a saprophytic filamentous fungus ubiquitous in the environment. Of the nearly 200 species, about 20 have been reported as causative agents of opportunistic infections in humans [5]. Among these species, *Aspergillus flavus* and *Aspergillus niger* are the most common pathogens, followed by *Aspergillus nidulans*, *Aspergillus terreus*, etc. [5, 12]. These *Aspergillus* conidia rarely cause infection in immunologically-competent hosts who were able to control the pathogens with pulmonary macrophages. However, in immunocompromised patients who may lack functional macrophages, conidia are not eliminated, and then the conidia germinate into hyphae that can invade tissues, especially the lower respiratory tract. This invasion subsequently results in vessel occlusion and ischemic necrosis of tissue areas affected by disrupted blood perfusion [5, 7]. Furthermore, dissemination may occur occasionally, mainly at the sites in the brain, skin, and heart [5, 13].

Because they have abnormal cellular and humoral immunity, patients with liver failure may fail to eliminate the *Aspergillus* conidia when inhaled and may tend to be infected with IPA [13]. However, because survival of patients with liver failure was rare, detection of the *Aspergillus* was limited, and knowledge about IPA was

Table 4 Logistic regression analysis of risk factors of HBV-related liver failure-complicated IPA

Risk factor	Standard error of B	Odds ratio	Wald value	*P* value	95% CI
Antibiotic category	0.5965	15.5897	21.2032	0.0000	4.8430~50.1838
Invasive examinations	0.5980	0.3007	4.0379	0.0445	0.0931~0.9708

HBV hepatitis B virus, *IPA* invasive pulmonary aspergillosis, *CI* confidence interval

insufficient, none of the genus *Aspergillus* were identified in patients with liver failure prior to 2006. Further development of medical science in recent years and more therapeutic methods, especially the molecular adsorbent recirculating system, have been applied successfully to improve patients' conditions and to prolong their survival, although this simultaneously results in an increased risk of *Aspergillus* infection. In addition, the increased prevalence of IPA in patients with liver failure is related to the growing utilization of broad-spectrum antibiotics, steroids, and invasive procedures. Indeed, in this study, we showed that patients with IPA used more broad-spectrum antibiotics and steroids and underwent more invasive examinations. Furthermore, environmental factors may also act as risk factors. The amount of *Aspergillus* in the air may increase when there are construction projects in progress in and around the hospital, and *Aspergillus* may spread through the air-conditioning system [7, 14].

Once patients with HBV-related liver failure are coinfected with other pathogens, especially *Aspergillus*, their health conditions worsen. Coagulation becomes poor because the platelet count and prothrombin activity decrease dramatically, and liver functions worsen because serum bilirubin increase is accompanied by a decrease in alanine aminotransferase. Renal function worsens and is accompanied by a gradual increase in serum creatinine, resulting in multiple organ failures. The MELD scores, which represent the prognosis of liver disease, are highest in patients with probable IPA but lowest in the control group, demonstrating that the patients with probable IPA have the worst prognosis. Indeed, all patients in this group died within 14 days after the diagnosis of probable IPA, and mortality was 100%, much higher compared with the other two groups. Therefore, we should diagnose IPA as early as possible in infected patients. However, it is difficult to diagnose whether patients with HBV-related liver failure have the *Aspergillus* infection; the clinical features are atypical during the early stage, and the IPA-related manifestations may be overlooked when there are worse conditions to treat and when patients are intolerant of a lung biopsy. Thus, IPA should be suspected if patients' conditions become worse and the liver functions are aggravated within a short time; some of the symptoms include persisting fevers or fevers with coughs that rebound refractory to broad-spectrum antibiotics, hemoptysis, chest pain, and chest CT scans that show the Halo sign or air crescent sign [15]. The positive sputum culture helps to diagnose probable IPA. Due to poorer prognosis and higher mortality, patients with HBV-related liver failure must receive antifungal therapy after the diagnosis of IPA or even after a diagnosis that suspects IPA. At present, voriconazole, liposomal amphotericin B, and caspofungin are the top priorities for monotherapy for IPA [16–19], but voriconazole and liposomal amphotericin B have hepatotoxicity and nephrotoxicity. Caspofungin is the best choice for patients with HBV-related liver failure who have poor liver and renal functions [17]. To reduce adverse effects, the appropriate intravenous dose of caspofungin of 70 mg should be used on the first day and reduced to 35 mg later.

In conclusion, we must increase the awareness of IPA infections in patients with HBV-related liver failure and reduce the risk of *Aspergillus* infection by improving the patients' immunity. Additionally, certain effective measures should be seriously undertaken; for example, caregivers and patients should prevent the abuse of antibiotics and steroids, decrease the frequency of invasive procedures, disinfect the air by ultraviolet light, and open the windows regularly to ventilate wards, etc. Once a patient is infected, appropriate drug treatments, especially caspofungin, must be immediately applied to improve the patient's condition and to decrease the risk of mortality.

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Competing interests The authors declare that they have no competing interests.

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