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Submission date: 20-Jan-2022 01:12PM (UTC+0700)
Submission ID: 1744612817
File name: isk_Factors_of_Renal_Aspergillosis_in_Pigeons_Columba_livia.pdf (2.84M)
Word count: 4658
Character count: 25473

American Journal of Animal and Veterinary Sciences

Original Research Paper

Risk Factors of Renal Aspergillosis in Pigeons (*Columba livia*): Field Study

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Article history
Received: 24-03-2019
Revised: 29-05-2019
Accepted: 13-06-2019

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Abstract: Aspergillosis is the common infectious diseases in the avian species. Aspergillosis causes granulomatous lesions in the lung and upper respiratory system and rarely reported regarding its infection in the kidney. This study aims to analyse the risk factors of renal aspergillosis in the pigeon (*Columba livia*) and its association to aflatoxicosis and CD4+/CD8+ depression. Twenty-dead pigeons, feed and litter randomly collected from 10-local breeders. Each breeder was asked to fill out the questionnaire. Microbiology, immuno-histopathology and detection of aflatoxin were performed on the collected specimens. The data was analysed using SPSS 16. The results revealed that the prevalence of *Aspergillus* belonging to the "*Fumigati* section" was 85% and 80% in lungs and kidneys, respectively. Moreover, the hyphae and granulomatous inflammation with minimal expression of CD4+/CD8+ are observed from pigeons kidney. This study reflected that contamination of *Aspergillus* belonging to the "*Fumigati* section" in the litter and air significantly affect the occurrence of pigeon's renal aspergillosis.

Keywords: Aflatoxicosis, CD4+, CD8+, Pigeon, Renal Aspergillosis, Risk Factors

Introduction

For long decades, the development of the poultry industry faces a global disease problem. The poultry's diseases are caused by various infectious agents such as virus, bacteria, chlamydia, parasites and fungus. Several fungi that are highly pathogen to avian species are *Aspergillus flavus, A. niger* and *A. fumigatus* (Arne *et al*., 2011; Ghaemmaghami *et al*., 2016). The infection of *Aspergillus* species is known as aspergillosis and is firstly reported on avian by Urbain and Guillot in 1938 (Okoye and Okeke, 1986). Moreover, those *Aspergillus* species have high morbidity and mortality that impacts on the economic losses. The prevalence of aspergillosis increases synergist with a weather change especially in summer and, it occurs in both wild and domesticated birds (Alvarez-Perez *et al*., 2010).

High incidence of aspergillosis in summer is due to the dusty environment that facilitates the conidia of *Aspergillus* to transmit to the respiratory tract. In the respiratory system, the avians' body high temperature promotes the conidia to form hyphae and mycelia. Those infections cause overwhelmed inflammatory responses and generated granulomatous lesions (Tochigi *et al*., 2013). Further, the hyphae spreads to other organs such as liver, brain and kidney via the circulatory system (Beernaert *et al*., 2010). Unfortunately, kidney aspergillosis in avian species is unreported yet.

Aspergillus synthesis the aflatoxin to aggravates the infection in a suitable condition. Aflatoxin is the one of common mycotoxin that potential as the carcinogenic agent (Khoshpey *et al*., 2011). Chronic exposure can depress the systemic immune function, malnutrition, bile duct proliferation, hepatic lesion and tumorigenesis. Food contamination is the main port of entry of aflatoxin (Yu, 2012). Aflatoxin causes a disease called aflatoxicosis. As an *Aspergillus* synthesis product, aflatoxin is thought to be associated with the incidence of aspergillosis.

Even so, there are no reports regarding the synergistic effects of aflatoxicosis and aspergillosis or vice versa. Aflatoxicosis depress the immune system that is suspected supports the aspergillosis, or aspergillosis creates aflatoxicosis in several conditions. CD4+ and CD8+ are potential to destruct the conidia during the fungal infection. CD4+ is one of T cells type that regulates the tissues repair in human aspergillosis (Jolink *et al*., 2014). In the mice study, CD4+ extend the life span of infected mice with *Aspergillus* (Bozza *et al*., 2003). As T cell cytotoxic, CD8+ control the tissue from

Aspergillus invasion (Tao *et al*., 2006). The role of CD4+/CD8+ in human have been reported, however not in poultry. As the unique case, the renal aspergillosis has a piece of limited information and report. Moreover, its risk factors and the function of CD4+/ CD8+ become essential to explore. Therefore, this study aims to analyse the occurrence of renal aspergillosis in pigeons, its risk factors and association with CD4+/CD8+ depletion.

Materials and Methods

Sampling

Total 20-dead pigeons (*Columba livia*) are carried from 10-local breeders in sub-district of Krembung, East Java, Indonesia from December 2018 until January 2019.

Necropsy

The necropsy was performed following the standard guideline demonstrated by previous study (Brownlie and Munro, 2016). Several organs were obtained such as brain, lung, liver, spleen, kidney, digestive tracts. Each specimen is separated into two part. The first organ portion was stored in the 10% Neutral Buffer Formalin (NBF) for histopathological examination. The second was kept in sterile plastic for microbiological test. Further, the litter and feed of pigeons were collected using aseptic procedure and it was transported to the Laboratory of Bacteriology, Faculty of Health, University of Muhammadiyah Sidoarjo.

Microbiological Examination

The Sabouraud Dextrose Agar (SDA) is used to isolate both fungi and yeast from the pigeons' organs. Further, the isolation and identification of airborne microbial from the pigeon's cage environment were performed by sedimentation technique with exposing the open Petri-dishes that contain culture media with room air condition for 2-h (Yagoub and Agbash, 2010; Shams-Ghahfarokhi *et al*., 2014).

Questionnaire

The breeder is interviewed and the data is used as supplementary materials. Several questions were recorded on the questionnaire to facilitate the breeders to answer during the interview. The points of observation were age, sex, history of the disease, types of feed, the knowledge of breeder on the pigeon's disease and aspergillosis.

Histopathology and Immunohistochemistry

After the fixation using 10% NBF, the organs were dehydrated using graded alcohol and were cleaned using xylene. Further, it is kept in liquid paraffin and blocked. The organ block was cut using microtome in 5 µm of thickness. The tissue sections were placed on the water bath and mounted to the glass slides. This study utilised three types of staining procedures that are hematoxylin and eosin (H&E), Periodic Acid – Schiff (PAS); and Immunohistochemistry (IHC) against antibody anti-CD4+ and CD8+ (Alturkistani *et al*., 2016).

Morphometry

The morphometry is conducted by a single pathologist under a blindfold situation. The H&E and IHC slides were scored using modified scoring system as follow: absence (0); minimal (1); mild (2); moderate (3); and severe (4). The PAS slide was scored by the appearance of hyphae, unfound (1) and found (2) (Gibson-Corley *et al*., 2013).

Enzyme-linked Immunosorbent Assays (ELISA)

The ELISA was performed to analyse the residue of aflatoxin on the feeds and the organ of pigeons. It was conducted following the previous procedure (Prakoso *et al*., 2018). Based on the previous study, the detection limit of this assay is 1.25 ng g^{-1} for the poultry feeds (Rossi *et al*., 2012).

Data Analysis

All the data were reported as the semi-quantitative data and determined using the bivariate and multivariate methods. Those data are used to elucidate the risk factors that influence renal aspergillosis in pigeons. The data were analysed using SPSS 16 with a probability value at level of $P<0.05$.

Results

Microbiological Examination

The microbiological test performed from several specimens, were isolated and identified as the *Aspergillus* belonging to the "*Fumigati* section". The prevalence of *Aspergillus* belonging to the "*Fumigati* section" was 85% from lung (17/20) and 80% from kidney (16/20) of pigeons. However, there is no growth of fungus from the brain, liver, spleen and digestive tract. Surprisingly, the *Aspergillus* belonging to the "*Fumigati* section" was isolated and identified from litter, pigeon's feed and air from pigeon's cage environment as follow 80% (16/20), 90% (18/20) and 85% (17/20).

Risk Factors

The statistical result showed that the renal aspergillosis is affected by several risk factors such as the contamination of *Aspergillus* belonging to the "*Fumigati* section" in the cage litter and air in pigeon's cage environment. Those factors showed a significant value ($P<0.05$). On the other hands, the *Aspergillus* belonging to the "*Fumigati* section" contamination in pigeon's feed, the occurrence of aflatoxicosis and lungs

aspergillosis have no effects and association on the pigeon's renal aspergillosis (Table 1).

Type of feeds, owner's knowledge of the pigeon's disease and aspergillosis and the aflatoxin contamination in feeds are categorised as the other risk factors. However, those factors did not influence the occurrence of renal aspergillosis. The contamination of aflatoxin in feeds partially increases the renal aspergillosis in pigeons with the highest odds ratio 2.105 times even though it has no significant differences (Table 2). More large samples may be needed to explore these effects.

Histopathology

The histopathological change is observed from the collected specimens. It showed the diverse changing from necrosis, inflammation, the appearance of hyphae section, bile duct proliferation and lymphoid tissue depletion. The histopathological assessment was expressed as the means score from the total of 20-dead pigeons. Inflammation and necrosis were observed from lung and kidney with the highest score, followed by the bile duct proliferation of liver and white pulp depletion of the spleen (Fig. 1).

The aspergillosis pathognomonic lesions were granulomatous inflammation and giant macrophages, necrotising tissue and the appearance of hyphae section inside or surrounding a zone of demarcation. Those histopathological change were found in the lung (11/20) (Fig. 2B) and massively in the kidney (17/20) (Fig. 2D and 2E). The liver showed bile duct proliferation with inflammation that is a typical lesion for aflatoxicosis (12/20) (Fig. 2G). The different result is attested by the microscopical appearance of the brain, spleen and digestive tract that indicates the healthy tissue structure.

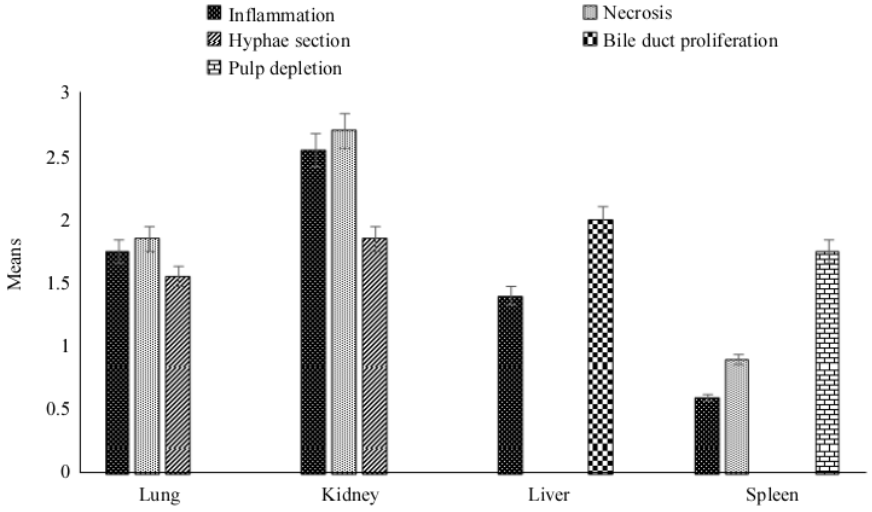
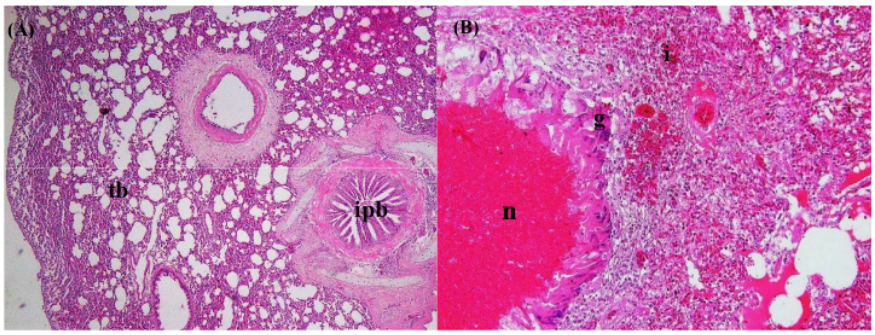


Fig. 1: Means of the histopathological score from the pigeon's organs



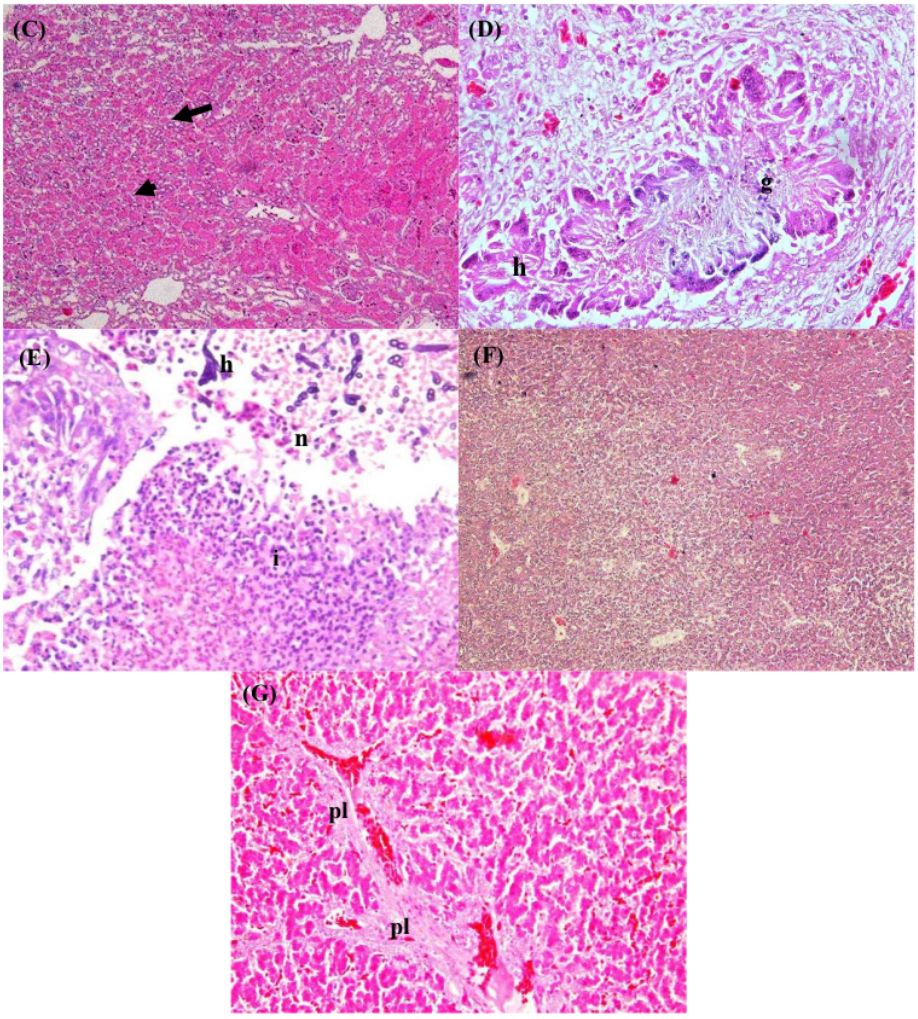


Fig. 2: Histopathological change of lung, kidney and liver from pigeons infected by *Aspergillus* belonging to the "*Fumigati* section". Normal appearance of lung in uninfected pigeon that consist of intrapulmonary primary bronchi (ipb) and intact tertiary bronchi (tb) without inflammation (A); granulomatous necrosis (n) was surrounded by giant macrophages (g) and inflammatory cells predominantly heterophil and eosinophil (i) in the lung (B); normal section of kidney with glomerulus (arrow) and tubules (arrowhead) (C); the hyphae (h) were covered by giant macrophages (g) and inflammatory cells (i) in the centre of necrosis (n) of kidney from infected pigeons (D and E); dense hepatocytes in a normal liver (F); and the bile duct proliferation (pl) of liver indicates the aflatoxicosis in an infected pigeon (G). H&E, 40×(A, B, C, F); 100× (D, G); PAS, 100×(E)

Immunohistochemistry

Renal aspergillosis has a significant impact on the immune-expression of CD4+ in kidney and spleen ($P<0.05$). Further, the minimal immune-expression of CD8+ were observed in the kidney ($P<0.05$). This result proved that minimal expression of CD4+ and CD8+ in a kidney increase risk of pigeon renal aspergillosis. Low expression of CD4+ in the spleen was maybe caused by aflatoxicosis. There is no significant difference on the others ($P>0.05$). This result showed that the decrease of CD4+, CD8+ and CD4+/CD8+ on lungs and liver were unrelated to pigeon renal aspergillosis (Table 3).

Table 1: Association between variable and renal aspergillosis in pigeons

Variable	Information	Aspergillosis (+)	Aspergillosis (-)	X^2	P-value
Aspergillus belonging to the "*Fumigati* section" contamination in litter	Positive	16	0	14.11	0.00*
	Negative	1	3		
Aspergillus belonging to the "*Fumigati* section" contamination in feed	Positive	16	2	2.13	0.14
	Negative	1	1		
Aspergillus belonging to the "*Fumigati* section" contamination in air	Positive	16	1	7.38	0.00*
	Negative	1	2		
Aflatoxicosis	Yes	8	3	2.88	0.08
	No	9	0		
Lungs aspergillosis	Yes	10	1	0.86	0.35
	No	9	0		

*P-value < 0.05 showed the significant different.

Table 2: Risk factors of renal aspergillosis in pigeons

Variable	Coef.	SE	Coef./SE	OR	P-value
Type of feeds	-2.75	2.25	-1.22	0.06	0.22
Knowledge of disease	-3.42	2.68	-1.27	0.03	0.20
Knowledge of aspergillosis	-3.97	3.35	-1.18	0.01	0.23
Residue aflatoxin in feeds	0.74	1.22	0.60	2.10	0.54

Coef. = Coefficient; SE = Standard Error; OR = Odds Ratio; *P-value <0.05 showed the significant different

Table 3: Comparison between score of CD4+, CD8+ and CD4+/CD8+ from the pigeons with and without renal aspergillosis

Organ	IHC Parameter	Renal Aspergillosis: With	Renal Aspergillosis: Without	P-value
Lungs	CD4+	1.58±0.71	2.33±0.57	0.10
	CD8+	1.70±0.46	1.66±0.57	0.89
	CD4+/ CD8+	1.05±0.63	1.50±0.50	0.27
Kidney	CD4+	1.23±0.43	3.33±1.15	0.00*
	CD8+	1.52±0.51	3.00±0.00	0.00*
	CD4+/ CD8+	0.88±0.37	1.11±0.38	0.34
Liver	CD4+	1.11±0.78	0.66±0.57	0.35
	CD8+	1.64±0.60	1.00±0.00	0.08
	CD4+/ CD8+	0.70±0.53	0.66±0.57	0.90
Spleen	CD4+	2.17±0.63	4.00±0.00	0.00*
	CD8+	2.35±0.70	3.00±0.00	0.13
	CD4+/ CD8+	1.02±0.56	1.33±0.00	0.37

*P-value <0.05 showed the significant different

Discussion

A. fumigatus is the one fungal species that causes infection in vertebrates. The prevalence of aspergillosis in human reaches a million people and it has become a global problem (Bongomin *et al*., 2017). Several cases of *A. fumigatus* infection have reported in canine (Magro *et al*., 2017), cattle, horse, cat and nonhuman primates (Seyedmousavi *et al*., 2015), bottlenose dolphin (Cassle *et al*., 2016) and among the avian species (Cafarchia *et al*., 2014). This study elucidated that contamination of *Aspergillus* belonging to the "*Fumigati* section" in the litter and air influence to the incidence of aspergillosis. The previous study demonstrates the invasive of aspergillosis can spreads through the water, air and household appliances (Paulussen *et al*., 2017). Those abilities are due to its resistance against the extreme condition. *Aspergillus* can also utilise a wide variety of substrate to resist in the environment (Cray *et al*., 2013).

Dust and wind are the most frequently reported as the mediators of the conidia spreading in the environment. *A. fumigatus* infection promotes the pneumonic aspergillosis because of its route of infection via the respiratory system, commonly. Conidia are inhaled by the host and leading to infection. In the lung, the conidia accumulate and forms the biofilm in bronchiole, alveoli (Boisvert *et al*., 2016) and air sacs (Souza and Degernes, 2005). Those conidia can be eliminated by the mucociliary epithelial and other immune defence system on the lung tissue in a healthy organism. On the other hands, the conidia survive and promote lung infection

when dysfunction of the immune system has occurred.

The dysfunction of the immune system that promotes by aspergillosis are neutropenia or heteropenia (Garth and Steele, 2017). Glucocorticoid therapy is known as another factor that impairs the immune system and increases the risk of aspergillosis (Lewis and Kontoyiannis, 2009). The dysfunction of the immune response gives a chance for the conidia to germinate and become mycelia. The mycelia invade the macrophages, lungs epithelial and vascular endothelial. Those mechanisms are defined as Invasive Aspergillosis (IA) (Barton, 2013). Extensive colonisation of *Aspergillus* in lung tissue causes severe necrosis, attracts the heterophil to forms the zone of demarcation around the necrotising area and attracts the macrophages to enfold the mycelia by forming the giant macrophages. The severe inflammation increases lung vascularisation and its compensation is generating port of entry of conidia to spreads systemically. This mechanism then leads to systemic infection.

A. fumigatus systemic infection affects several organs with high blood circulation such as liver, brain, heart and kidney. Liver aspergillosis has a similar lesion to pulmonary aspergillosis (Zhang *et al*., 2018). Another study reported that pulmonary aspergillosis in immunocompetent patient affects the abdominal organ that causes hepatomegaly, splenomegaly and giant cells granuloma in the lymph node (Urgene *et al*., 2013). In the brain, aspergillosis causes cerebral infarct with neuropathological symptoms. Commonly, cerebral aspergillosis shows a low survival rate (Li *et al*., 2015). All the systemic aspergillosis lesion is due to invasive pulmonary aspergillosis and or in other words the lung is the main port of entry for aspergillosis.

Unfortunately, none of the previous studies has reported regarding renal aspergillosis in poultry. In this study, the renal aspergillosis creates a depression of the renal tubule with the severe necrotising area and is surrounded by giant macrophages. Further, the pathognomonic lesion in the histopathology was the presence of sunflower-like fungi nodes in the kidney (Li *et al*., 2015). The hyphae are also presented. The immunocompetent is exhibited in the infected pigeons. The immunocompetent profile of the infected pigeons is determined by the immunohistochemistry of CD4+/CD8+ in several organs. The depression of CD4+/CD8+ impairs the avian immune system during infection, such as aspergillosis (Chu *et al*., 2017). Those T-lymphocytes are significant to stimulate interferon-γ in the serum that effective against several types of infections (Rohollahzadeh *et al*., 2018). This is similar to the previous study that demonstrated *Aspergillus* infection in immunocompromised pigeons which seems to be contra-indicated and, it can generate both chronic and acute infection depends on the route of transmission (Beernaert *et al*., 2008). In this study, the depletion of CD4+/CD8+ are suspected due to feed's aflatoxin contamination even though, there is no significant difference regarding this parameter.

Further, the other tested risk factors such as contamination of *Aspergillus* belonging to the *Fumigati* in feeds, aflatoxicosis, type of feeds and owner's knowledge have not showed significant difference in this study. These have been described that the main port of entry of invasive aspergillosis and especially renal aspergillosis are from the respiratory system. The minimal information and understanding of the public society regarding renal aspergillosis in the pigeons provide the opportunities of *Aspergillus* infection to be transmit to human/zoonotic, potentially. The eradication of the infected pigeons is necessary to prevent transmission to the healthy pigeons. Moreover, the disinfection of pigeon-related items must be conducted by the owner because the location of pigeon's cage is close to the settlements commonly.

Conclusion

Pigeon's renal aspergillosis is an uncommon reported case in the poultry. The mechanism of infection of this disease is unclearly demonstrated by the previous studies. Contamination of *Aspergillus* belonging to the "*Fumigati* section" in the air and litter was the main risk factors of renal aspergillosis. Histopathological change of the renal aspergillosis is similar to the other invasive lesions. However, the depletion of CD4+/CD8+ is not contributing to the severity of renal aspergillosis histopathologically. The utilisation of a larger sample is necessary to prove and analyse the potential risk factors on the pigeon's renal aspergillosis.

Acknowledgements

All laboratory staffs from Faculty of Health, University of Muhammadiyah Sidoarjo were acknowledged for their assistant.

Author's Contributions

Bagus Uda Palgunadi, Kurniasih and Yos Adi Prakoso: Contribute equally to this study. All the authors approved the final manuscript.

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