



Complete clinical response to combined antifungal therapy in two cats with invasive fungal rhinosinusitis caused by cryptic *Aspergillus* species in section *Fumigati*

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ABSTRACT

Cryptic species in *Aspergillus* section *Fumigati* are increasingly reported to cause invasive aspergillosis in humans and animals. These infections are often refractory to treatment because of intrinsic antifungal resistance. We report two cases of invasive fungal rhinosinusitis in domestic cats caused by *A. udagawae* and *A. felis*. Clinical signs resolved after combined therapy including posaconazole, caspofungin and terbinafine. Both cases remained asymptomatic more than 2 years from initial presentation.

1. Introduction

Cryptic species in *Aspergillus* section *Fumigati* cause invasive fungal rhinosinusitis (FRS), also known as sino-orbital aspergillosis (SOA), in apparently immunocompetent cats. However, cats of Persian and related breeds, such as Himalayans or Exotic Shorthairs, are over-represented for FRS and for other invasive mycoses, including dermatophytic pseudomycetoma [1,2]. These breeds are suspected to harbor an as yet uncharacterized genetic defect in fungal immunity [3,4].

The course of invasive FRS in cats is characterized by local spread of infection from the sino-nasal cavity to involve contiguous structures including the orbit, nasopharynx, other tissues of the head (skin, subcutis and/or muscle) and the central nervous system (CNS). Once CNS involvement occurs, disease is usually fatal. Most cats with SOA are presented for unilateral exophthalmos and/or exposure keratitis associated with an expanding orbital fungal granuloma [1].

The prognosis for cure of SOA is poor with <20% of cats cured [1,5]. There is no evidence to support a benefit from surgical resection (orbital exenteration) over systemic antifungal therapy alone. Here we present two cases of SOA in domestic cats that responded to combination

antifungal therapy and remained clinically well more than two years from initial presentation.

2. Case 1

A 4-year-old desexed male domestic shorthair (DSH) cat was presented with an acute onset of left-sided facial swelling (Day 0). The cat had a previous history of cat-bite abscesses. Intermittent sneezing and serous ocular discharge from the left eye (OS) during the past 2 months were reported. On physical examination, a firm subcutaneous swelling over the left maxilla, a reduced interpalpebral aperture and serous ocular discharge (OS) were noted. A sinus that was discharging purulent material was identified in the alveolar mucosa proximal to the left maxillary second premolar tooth (207). Results of a complete blood count were within reference intervals (RIs). On serum biochemistry there was mild hyperglobulinaemia (globulin 52 g/L; RI 28–48 g/L). A presumptive diagnosis of cat-bite abscess was made and cefovecin 8 mg/kg SC (Convenia®, Zoetis) was administered.

On Day 14 signs had progressed, with mild prolapse of the left nictitating membrane. A second oral mucosal sinus was identified in the

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caudal hard palate adjacent to the left carnassial tooth (208) (Fig. 1a). Serum tested negative for feline immunodeficiency virus (FIV) antibody (Witness FIV, Zoetis, Australia). Intra-oral radiographs revealed increased lucency of the alveolar bone around the left maxillary carnassial tooth (208) and left maxillary molar tooth (209). The latter was loose and was extracted. Clindamycin 11 mg/kg PO q12 h was prescribed for treatment of a suspected tooth root abscess. On Day 29 facial swelling had further progressed to involve the left lower eyelid and there was a firm diffuse submucosal/maxillary swelling dorsal to the left upper canine tooth. An inflamed friable mass discharging purulent exudate was present in the left pterygopalatine fossa. Clindamycin was discontinued due to planned biopsy and culture. On Day 33 the maxillary swelling and pterygopalatine fossa lesion were biopsied under general anaesthesia. Purulent fluid aspirated from the maxillary swelling was submitted for cytology and culture. Buprenorphine 0.013 mg/kg sublingual q12 h and clindamycin 11.36 mg/kg PO q 12h were commenced. The next day the cat developed marked exophthalmos with persistent prolapse of the nictitating membrane (OS) (Fig. 1b).

Gram and Ziehl-Neelsen stains of the fluid revealed occasional epithelial cells, moderate leucocytes and no bacteria. Bacterial culture was negative. On Day 36 histopathology revealed severe pyogranulomatous inflammation with necrotic foci containing numerous

branching, septate fungal hyphae. A provisional diagnosis of SOA was made. Treatment was instigated with terbinafine 14.5 mg/kg PO q24 h. On Day 40 caspofungin (Cancidas, Merck Sharp & Dohme (Australia) Pty Limited) was given at a loading dose of 1 mg/kg IV, then at 0.75 mg/kg IV q 24 h for 7 days. Caspofungin was administered as a 0.2 mg/mL solution in 0.9% saline over 2 h, as previously described [6]. Posaconazole was also commenced on Day 40, (loading dose 15 mg/kg PO then 7.5 mg/kg PO q24 h with food [7]). The terbinafine dosage was increased to 30 mg/kg PO SID. The left eye was lubricated with topical carboxymethylcellulose drops q12 h (0.5%, Refresh, Allergan) to reduce the risk of corneal ulceration. By Day 44 the facial swelling had mildly improved. The cat was discharged from hospital on Day 48 and treatment with oral antifungals was continued. At re-examination on Day 53 the subcutaneous swelling had reduced and was localised to ventral to the left eye (Fig. 1c). The caudal oral mucosal sinus was still discharging purulent exudate.

Approximately 3 weeks after commencing anti-fungal therapy (Day 59) the patient presented with a 7-day history of inappetence, facial pruritus, acute worsening of the unilateral facial swelling and moist dermatitis of the left cheek. A moderate amount of purulent exudate was expressed from the left cheek. On repeat serum biochemistry there were moderate elevations in liver enzymes AST 198 IU/L (RI 5–80 IU/L) and

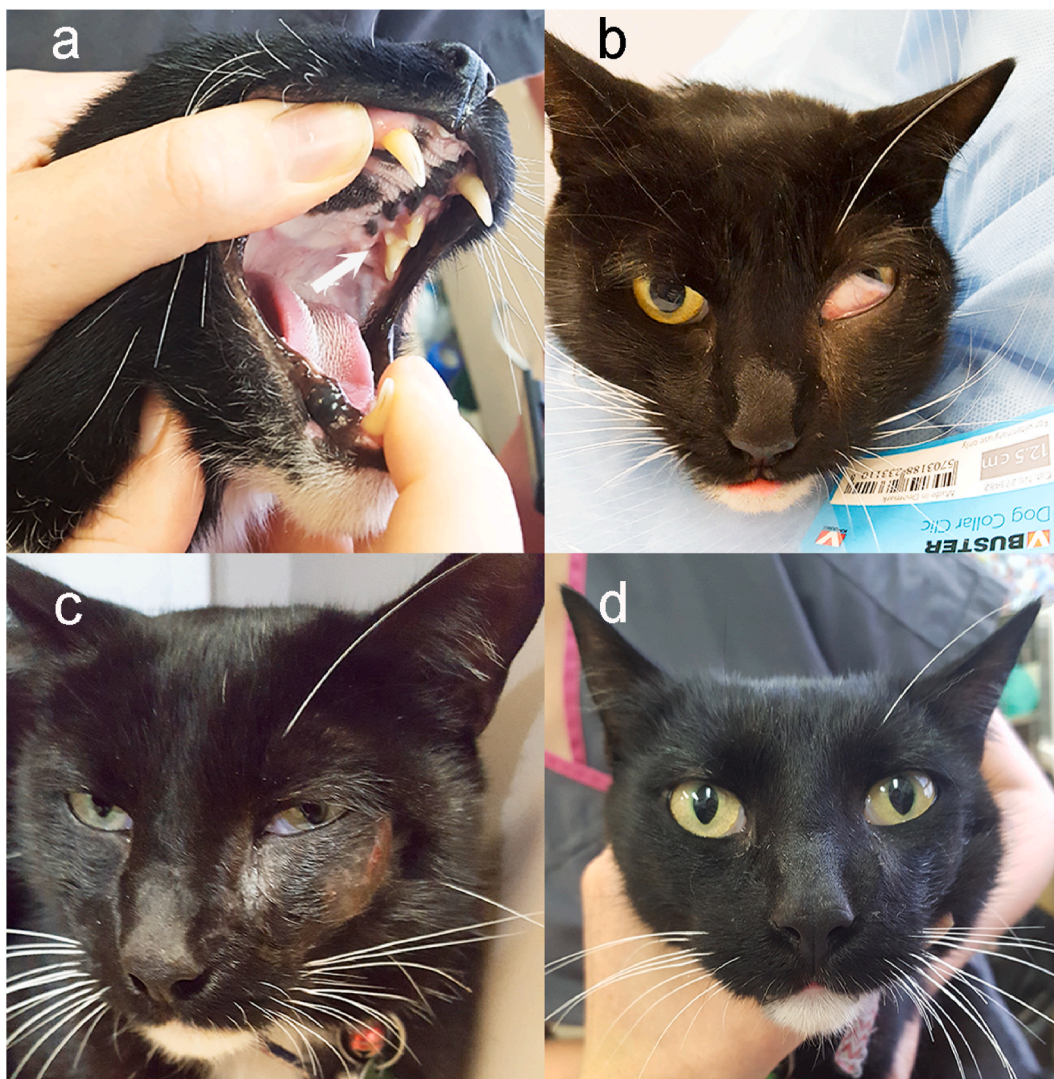


Fig. 1. Pre-treatment images of discharging sinus in oral cavity (white arrow, a) secondary to an orbital fungal granuloma (OS) which also caused severe exophthalmos and facial swelling with prolapse of the nictitating membrane (b). Thirteen days after starting treatment, on Day 53, the subcutaneous swelling had reduced (c), and by Day 123 all clinical signs had resolved (d).

ALP 196 IU/L (10–60 IU/L). Due to suspected hepatotoxicity, posaconazole therapy was ceased but terbinafine was continued.

On Day 60 the fungal culture results were reported as an *Aspergillus* section *Fumigati* species. The results of antifungal susceptibility testing using broth microdilution (Sensititre YeastOne YO10, Trek Diagnostic System Ltd) are shown in Table 1. Comparative sequence analysis of partial betatubulin gene and ITS1-5.8S-ITS2 rDNA sequenced from PCR amplification of DNA extracted from fungal colony material [8], yielded sequences matching Type material of *A. udagawae*, which were deposited on Genbank (MZ513460, MZ496635).

Posaconazole was restarted on Day 62 (7.5 mg/kg PO divided q12 h), when appetite and demeanour had returned to normal. Facial pruritus had resolved and the abscess was healing. On Day 82 recurrent inappetence was reported and weight loss of 200 g was detected. On repeat serum biochemistry ALT (136 IU/L) and AST (108 IU/L) were elevated, and ALP was within the RI. Posaconazole treatment was stopped for a second time. Terbinafine was also stopped 4 days later (Day 86), after which the cat's appetite markedly improved within 48 h. Posaconazole was restarted on day 88 (7.5 mg/kg PO divided q12 h) and terbinafine was permanently discontinued.

On Day 123 the cat was re-examined and all clinical signs had resolved (Fig. 1 d). Facial features were symmetrical with no swelling and all oral mucosal lesions had healed. A serum biochemistry panel on Day 135 was unremarkable. Posaconazole was continued until Day 255. Three and a half years after the initial presentation the cat remains disease free with chronic mild epiphora of the left eye as the only apparent sequela to SOA.

3. Case 2

A 3.5-year-old male neutered DSH cat was referred to the University Veterinary Teaching Hospital, Sydney (Day 0) with a 12-week history of sneezing which had progressed to bilateral mucopurulent nasal discharge, stertor, left-sided exophthalmos (OS), lethargy, inappetence and weight loss (700 g). The cat had outdoor access and routine healthcare was up to date. Pertinent physical examination findings included a body weight of 4.85 kg, body condition score of 5/9, 6–8% dehydration, bilateral mucopurulent nasal discharge, moderate stertor, mild to moderate nasal bridge swelling, mild left nictitating membrane prolapse and left-sided exophthalmos (Fig. 2).

Diagnostic tests performed by the referring veterinarian after a lack of response to doxycycline (5 mg/kg PO q12 h) for 10 d, then azithromycin (8 mg/kg PO q48 h) for 21 d, included haematology and biochemistry, which were unremarkable except for mild eosinophilia ($1.2 \times 10^9/L$; RI 0.0–1.0) and hyperglobulinaemia (55 g/L; RI 31–52). Serology for FIV antibody and Feline leukaemia virus antigen (Anigen Rapid, BioNote) was negative. Thoracic radiographs were normal. Bacterial culture of a nasal swab sample was negative, while fungal culture identified a light growth of an *Aspergillus* spp. Histopathology of a nasal mucosal biopsy showed fungal hyphae and moderate to marked eosinophilic to ulcerative rhinitis, supporting a diagnosis of aspergillosis. Treatment with itraconazole (50 mg PO q24 h, Sporanox, Jansen) was commenced 6 weeks before referral, with prednisolone (5 mg PO

q24 h) added after 1 month due to lack of response.

Pre- and post-contrast enhanced CT of the skull performed on Day 2 revealed a marked amount of non-contrast enhancing, and mildly contrast-enhancing, soft-tissue attenuating material within the nasal cavity, frontal sinuses and nasopharynx. This soft-tissue material extended through the left sphenopalatine foramen into the left retrobulbar space with mass effect (Fig. 3 a, b). There was a mild region of left lacrimal bone lysis. The medial retropharyngeal lymph nodes, left submandibular and deep cervical lymph node were enlarged and rounded.

On antegrade and retrograde rhinoscopy, material within the nasopharynx was occluding both choanae. Large amounts of mucopurulent discharge, including orange, granular, particulate matter, were removed during nasal saline irrigation. Bilateral antegrade nasal biopsies were collected for histopathology and fungal culture. A left sided oesophageal feeding tube was placed and thoracic radiographs post-placement were unremarkable. Urinalysis was unremarkable. Nasal biopsy histopathology revealed marked eosinophilic fungal rhinitis with numerous PAS positive septate fungal hyphae with 5–7 μm wide parallel walls, acute angle branching and terminal bulbous structures. A filamentous fungus grew on Sabouraud dextrose agar after 3 days of incubation at 37 °C, with morphology consistent with an *Aspergillus* section *Fumigati* species. PCR and sequencing of the ITS1-5.8S-ITS2 region yielded a sequence with 99.8% nucleotide homology to the reference strain of *A. felis* (CBS 130245) (Genbank MZ496636). Anti-fungal susceptibility testing was performed as for Case 1 (Table 1).

Supportive care included intravenous fluid therapy for 3 days, buprenorphine 0.015mg/kg IV q8 h for 5 days, mirtazapine 3.75 mg PO q72 h and oesophageal tube feeding for 14 days. Antifungal treatment included terbinafine (Lamisil, Novartis) 62.5 mg PO q24 h, posaconazole (Noxafil, MSD) 4 mg/kg PO q12 h and caspofungin acetate (Cancidas) (1 mg/kg loading dose IV on Day 4 followed by 0.75 mg/kg q24 h thereafter for an additional 13 days). In addition, three doses of liposomal AMB (Ambisome, Gilead Sciences) were administered on days 13, 15 and 19 (1 mg/kg diluted in 20mL of 5% glucose IV over 2 hours). The AMB dose interval was increased between days 15 and 19 then discontinued because of increasing serum creatinine (121–164 $\mu\text{mol/L}$; RI 71–212) despite intravenous fluid therapy. Creatinine had normalized (127 $\mu\text{mol/L}$) on Day 21.

Two weeks after commencing antifungal treatment, stertor and nasal discharge resolved and exophthalmos was markedly reduced. The cat was discharged on Day 20 on oral terbinafine (increased to 125 mg PO q 24h after one month) and posaconazole. One month after discharge (Day 57) the cat weighed 5 kg and complete resolution of clinical signs, apart from occasional sneezing, had been achieved. Four months after discharge (Day 140) the cat weighed 5.8 kg and had no recurrence of clinical signs.

Eight months after discharge (Day 263), the cat remained well. A repeat skull CT showed resolution of most changes (Fig. 3 c) except for a small amount of equivocally contrast-enhancing soft tissue attenuating material in the left sphenoid sinus and caudal nasal cavity. There was also a mild increased bone density on the lateral aspect of the right frontal sinus. Oral antifungal therapy was continued. Twelve months after presentation (Day 367), the cat remained well and weighed 6.19 kg. Haematology and biochemistry were within reference ranges. Urinalysis was unremarkable with a urine specific gravity of 1.050. On Day 457, the cat was clinically well and terbinafine and posaconazole were discontinued. Repeat CT scan findings on Day 525 were similar to those on Day 263.

More than 2 years after initial presentation (Day 802), the cat was clinically well and weighed 6.3 kg. A repeat CT scan showed changes suggestive of mild progression of rhinitis with left frontal sinusitis. There were small amounts of non-contrast enhancing material in the sphenoid sinus (Fig. 3 d). Treatment with posaconazole was recommenced for another 3 months and then discontinued on Day 899. Further CT scans were declined by the owners, who reported very occasional sneezing (twice a month) as the only clinical sign noted since initial presentation

Table 1

Results of antifungal susceptibility testing by broth microdilution for *Aspergillus udagawae* (Case 1) and *A. felis* (Case 2). Minimum inhibitory concentrations (MICs)/Minimum Effective Concentrations (MECs) expressed in $\mu\text{g/mL}$.

Drug	Case 1	Case 2
Amphotericin B (AMB)	4	1
Itraconazole	0.5	1
Posaconazole	0.5	1
Voriconazole	1	4
Anidulafungin	0.03	0.03
Caspofungin	0.06	0.03
Micafungin	0.03	0.015

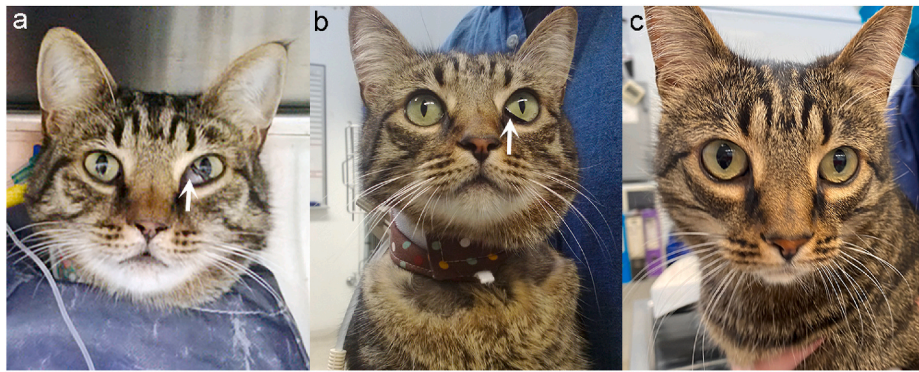


Fig. 2. Case 2 at presentation, Day 0, (a) with exophthalmos and prolapse of the nictitating membrane (OS). By Day 14, (b), exophthalmos was markedly reduced with only mild residual nictitating membrane prolapse (arrow). Post-treatment, (c) the cat was clinically well almost 3 years from initial presentation (Day 1071).

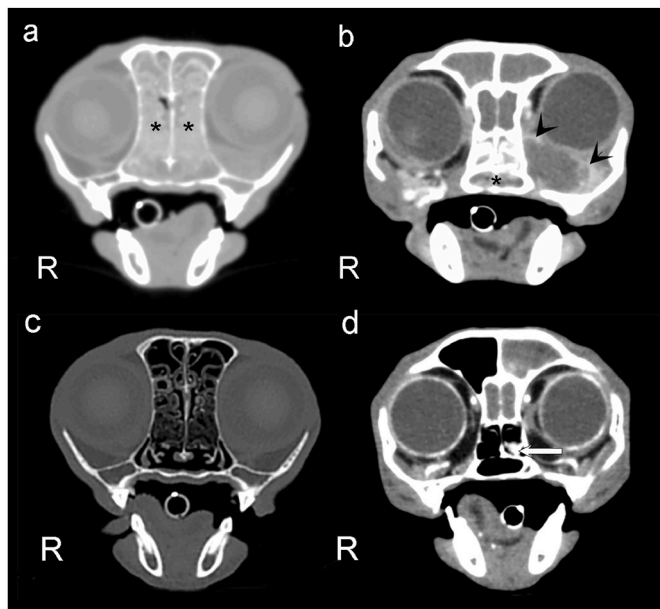


Fig. 3. Transverse CT skull images of Case 2, soft-tissue (a, b, d) and bone algorithms (c). Pre-treatment, post-contrast (a) the nasal cavities were obstructed by soft-tissue attenuating material (asterisks) and there was a lobulated ventromedial left orbital mass displacing the globe dorsolaterally, which after the administration of contrast (b) showed peripheral rim enhancement (arrowheads). Both frontal sinuses were occupied by soft-tissue attenuating, non-contrast enhancing material. The choanae was filled by soft-tissue attenuating material with heterogeneous enhancement (asterisk). In (c) on Day 263 the rostral nasal cavity and orbital changes had resolved. On Repeat CT on Day 802 (d) there was soft-tissue attenuating material in the left frontal sinus and a mineralized structure in the left sphenoid sinus (white arrow).

and discharge from hospital. On Day 1071, almost 3 years after initial presentation the cat remained clinically well.

4. Discussion

Aspergillus felis and *A. udagawae*, detected in the two cases reported here, are the most common causes of invasive FRS in cats, and are increasingly reported to cause invasive aspergillosis in humans [9–12]. *A. felis* and *A. udagawae* are members of the *A. viridinutans* species complex in section *Fumigati* [13]. Their definitive identification is clinically relevant because intrinsic resistance to antifungal drugs is common for these species [14,15]. PCR amplification and sequencing of both internal transcriber spacer regions and the intervening 5.8S rDNA gene (ITS1-5.8S-ITS2) from DNA extracts of fungal culture or fresh/frozen

biopsy tissue is usually sufficient to identify *A. viridinutans* species complex members to species level [8]. Useful secondary gene targets include betatubulin, calmodulin and RPB2 [13].

The high MIC of AMB for the *A. udagawae* isolate from Case 1 is typical for this species, which has the highest MICs of AMB amongst all 10 *A. viridinutans* species complex members [14]. By contrast, MICs of AMB for *A. felis* are more variable [14,15]. Both isolates in this report had high voriconazole MICs and low MECs of echinocandins, which is typical of all *A. viridinutans* species complex members. Voriconazole is often used for first-line therapy in invasive aspergillosis in humans, highlighting the importance of performing both definitive species identification and antifungal susceptibility testing of clinical isolates of *Aspergillus*.

The *A. felis* isolate from Case 2 was unusual in that it had a relatively low MIC of itraconazole (1 µg/mL) and a relatively high MIC of posaconazole (1 µg/mL) compared to the mean MICs of itraconazole (13.3 µg/mL) and posaconazole (0.2–0.39 µg/mL) reported for 23 and 27 clinical isolates of *A. felis*, respectively, in two other studies [14,15]. Itraconazole is the most common antifungal azole drug used in veterinary companion animal practice, but is generally unsuitable for treatment of feline SOA because of intrinsic resistance in causative section *Fumigati* cryptic species including *A. felis*, *A. udagawae*, *A. wyomingensis*, *A. thermomutatus* and *A. fischeri* [14,16,17]. In contrast, the reliably low MICs of the echinocandins make them an attractive choice for treatment of infections involving cryptic species. We chose caspofungin since pharmacokinetic modelling data support its use in treatment of feline SOA [6]. The combination of caspofungin and posaconazole was curative in one previously reported case of SOA caused by *A. felis* in a 5-year old Cornish Rex cat [5]. The cat initially responded to posaconazole and terbinafine but relapsed with refractory disease 19 months after stopping treatment. After treatment with caspofungin and posaconazole the cat remained disease-free until its death from unrelated causes at 19 years of age ([5], Barrs, pers comm). The combination of caspofungin and posaconazole has also been used to treat aspergillosis in humans including a case of severe vertebral osteomyelitis with spinal cord impingement caused by *A. udagawae* in a patient with X-linked chronic granulomatous disease (CGD) [12].

In addition, combination antifungal therapy has been used to treat human *A. felis* infections, including a patient with CGD and invasive pulmonary aspergillosis treated with caspofungin and liposomal AMB [10]. We elected to use terbinafine in addition to caspofungin and posaconazole in both cases here since it is fungicidal and was shown to be synergistic with voriconazole in an invertebrate model of aspergillosis using azole-resistant *A. calidoustus* strains [18].

In conclusion, combination systemic antifungal therapy without surgery, can be effective for management of invasive FRS caused by *A. viridinutans* complex species in cats. Prospective multi-centre treatment trials would be useful to inform treatment guidelines for this

increasingly reported, frequently fatal feline disease.

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