Dilated cardiomyopathy and severe heart failure. An update for pediatricians

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ABSTRACT
Dilated cardiomyopathy is the main cause of heart failure leading to heart transplant. Its prognosis is variable and depends on the etiology, the patient’s age at onset, and the severity. The management of dilated cardiomyopathy is aimed at minimizing symptoms and preventing disease progression; it requires a comprehensive screening for comorbidities and the prevention of complications to improve the overall status of these children and mitigate their prognosis. Here we present a review oriented at the multidisciplinary management that pediatricians should consider when seeing these patients.

Key words: dilated cardiomyopathy, heart failure, treatment, prognosis, pediatrics.

http://dx.doi.org/10.5546/aap.2018.eng.e421

INTRODUCTION
DCM is a progressive and almost always irreversible disease of the heart muscle, characterized by left ventricle dilation and a reduced systolic function, leading to HF and, later, to multiple organ failure, with a 20% mortality rate at 1 year and a 56% mortality rate at 4 years, so it is the main indication for heart transplant in children and adults. The symptoms of DCM are non-specific (fatigue, dyspnea on exertion, and edema), thus hindering the possibility of making an early diagnosis; the actual incidence of DCM has been estimated at 0.57 cases per 100,000 persons/year. DCM has different stages (latent, established, advanced) and it may be approached with various treatments. This review will focus on the multidisciplinary management of advanced DCM.

ETIOLOGY
The etiology of DCM is varied; in children the main causes are myocarditis and neuromuscular disorders. However, a cause may not be found in up to 70% of cases, so idiopathic DCM is the most common presentation and the diagnosis is one of exclusion. Among the identifiable causes, myocarditis and arrhythmias may show functional improvement with a timely treatment (Table 1).

DCM is more common among younger infants, males (x-linked and mitochondrial inheritance), and black people.

Pathogenesis and compensation mechanisms
In DCM, the heart shows an adaptive response with a diffuse lesion characterized by cardiomyocyte stiffness and fibrosis, hypertrophic generalizations...
and atrophic cell interposition, glycogen storage, abnormal mitochondria, and myosin, actin, troponin, and troponin T reduction or absence.\textsuperscript{15-17} In specific etiologies, such as post-infection DCM, there is also an increase in inflammatory infiltrate where TH1 and TH2 cells may be responsible for the perpetuation of inflammation.\textsuperscript{18-20} Some viruses that introduce RNA into the myocardial cell may

<table>
<thead>
<tr>
<th>Etiological groups</th>
<th>Subgroups</th>
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<tbody>
<tr>
<td>Infections</td>
<td>Viral</td>
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<td>Group A and B coxsackievirus</td>
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<td>Echovirus</td>
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<td>Adenovirus</td>
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<td>Mumps</td>
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<td>Rubella</td>
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<td>Staphylococcus and Staphylococcus</td>
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<td>Salmonella</td>
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<td>Neisseria</td>
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<td>Bacterial</td>
<td>Mycobacterial, mycoplasma, and Chlamydia</td>
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<td>Fungal</td>
<td>Candida</td>
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<tr>
<td>Fungal</td>
<td>Aspergillosis</td>
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<tr>
<td>Protozoan</td>
<td>Trypanosoma cruzi</td>
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<td>Spirochete</td>
<td>Lyme disease</td>
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Table 1. Etiology of dilated cardiomyopathy during childhood

<table>
<thead>
<tr>
<th>Etiological groups</th>
<th>Subgroups</th>
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<tbody>
<tr>
<td>Metabolic</td>
<td>Endocrine</td>
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<td>Storage diseases</td>
<td>Glycogen storage</td>
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<td></td>
<td>Macropolysaccharidosis</td>
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<td>Sphingolipidosis</td>
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<td>Hemochromatosis</td>
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<td>Nutritional deficiency</td>
<td>Kwashiorkor</td>
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<td></td>
<td>Carnitine</td>
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<tr>
<td>Systemic</td>
<td>Connective tissue system</td>
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<td></td>
<td>Lupus erythematosus</td>
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<tr>
<td></td>
<td>Juvenile rheumatoid arthritis</td>
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<td></td>
<td>Polyarteritis nodosa</td>
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<td></td>
<td>Kawasaki disease</td>
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<td></td>
<td>Pseudoxanthoma</td>
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<tr>
<td>Infiltrations and granulomas</td>
<td>Leukemia</td>
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<td></td>
<td>Sarcoïdosis</td>
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<tr>
<td></td>
<td>Amyloidosis</td>
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<tr>
<td>Others</td>
<td>Hemolytic uremic syndrome</td>
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<td></td>
<td>Reye syndrome</td>
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<td></td>
<td>Mitochondrial disease</td>
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<tr>
<td>Genetic</td>
<td>Muscular dystrophies and myopathies</td>
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<tr>
<td>Neuromuscular disorders</td>
<td>Duchenne muscular dystrophy</td>
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<tr>
<td></td>
<td>Steinert muscular dystrophy and Barth syndrome</td>
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<tr>
<td>Gene mutations of cardiac structural proteins</td>
<td>X-linked cardiomyopathy</td>
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<tr>
<td></td>
<td>Progressive juvenile spinal muscular atrophy</td>
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<td></td>
<td>Myotubular myopathy</td>
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<td></td>
<td>Friedreich’s ataxia</td>
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<tr>
<td></td>
<td>Sarcomere, cytoskeleton, desmosome</td>
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<td></td>
<td>Sarcoplasmic reticulum, nucleus, mitochondrion, extracellular matrix, and ion channels</td>
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<tr>
<td>Toxic</td>
<td>Drugs</td>
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<td></td>
<td>Sulfadiazine</td>
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<td></td>
<td>Penicillins</td>
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<td>Anthracyclines</td>
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References: \textsuperscript{5-13}. 
be capable of causing an autoimmune response induced by myocardial epitope recognition and inducing cardiomyocyte apoptosis. At the same time, an increase has been observed in plasma proinflammatory cytokines (IL-6 and TNF-α), directly associated with cardiomyocyte remodeling, a reduced myocardial contractility, and ventricular dilation.21-23

In the early stages of DCM, LV remodeling is an adaptive response that compensates for reduced contractility. However, over time, the LV becomes dilated and turns dysfunctional, which leads to an antegrade failure with peripheral hypoperfusion and to retrograde failure with lung edema and venous congestion, which are responsible for symptoms, and ends in HF, the main cause of death.

The main compensation and underlying mechanisms, together with early and late symptoms, are detailed in Table 2. The activation of the sympathetic nervous system helps to maintain an adequate CO in the case of a mild to moderate reduction in ejection volume; therefore, the recommendation is that any drug capable of suppressing such response should be used cautiously, e.g., systemic anesthetic agents, which in the long term induce a 60-70% decrease in β1-receptor expression and a reduced response to β2-receptors24,25 (see below). In addition, prostaglandin levels rise and maintain renal blood flow and locally antagonize the effects of ADH; therefore, it is advisable to use non-steroidal anti-inflammatory drugs with caution. Other mechanisms that have also been described include an increased atrial natriuretic peptide level, which stimulates diuresis, an increased BNP level, which is responsible for myocardial hypertrophy, and kinin-kallikrein system activation, which induces renal vasodilatation.26

### Diagnostic suspicion

Symptoms may be non-specific because they may simulate a respiratory disease. The diagnostic suspicion is higher when tachycardia and HF symptoms and signs are detected. A chest X-ray screens for an enlarged cardiac silhouette, and subsequent X-rays may show the transition from oligemia to pulmonary congestion. An electrocardiogram and a cardiac enzyme test may be requested, and an echocardiogram is confirmatory. The cardiologist may complement this procedure with magnetic resonance imaging, coronary catheterization or other tests.27

### Clinical and echocardiographic prognostic factors

Some clinical factors are associated with a higher mortality, such as diagnosis in children younger than 14.3 years, established HF,27,28

### Table 2. Compensation mechanisms of heart failure

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Mediators</th>
<th>Short-term effects</th>
<th>Long-term effects</th>
</tr>
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<tbody>
<tr>
<td>Ventricular hypertrophy</td>
<td>RAA axis</td>
<td>Water and sodium retention</td>
<td>Increased blood volume</td>
</tr>
<tr>
<td></td>
<td>ADH</td>
<td></td>
<td>Increased BP</td>
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<tr>
<td></td>
<td>Endothelin</td>
<td>Increased contractility</td>
<td>Increased HR</td>
</tr>
<tr>
<td></td>
<td>ADH</td>
<td></td>
<td>Enlarged myocardial mass</td>
</tr>
<tr>
<td></td>
<td>ADH</td>
<td></td>
<td>Increased O₂ consumption</td>
</tr>
<tr>
<td>Ventricular dilation</td>
<td>RAA axis</td>
<td>Water and sodium retention</td>
<td>Increased blood volume</td>
</tr>
<tr>
<td></td>
<td>ADH</td>
<td></td>
<td>Increased BP</td>
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<tr>
<td>Adrenergic stimulation</td>
<td>Noradrenaline</td>
<td>Peripheral venoconstriction</td>
<td>Blood volume</td>
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<tr>
<td></td>
<td>Dopamine</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adrenaline</td>
<td>Increased contractility</td>
<td>Reduced β1-receptors</td>
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<td></td>
<td>Reduced β2-receptor response</td>
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<tr>
<td></td>
<td>SVR</td>
<td></td>
<td>Increased BP</td>
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<td>Arrhythmias</td>
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</tbody>
</table>

RAA: renin-angiotensin-aldosterone; ADH: antidiuretic hormone; BP: blood pressure; HR: heart rate; 
SVR: systemic vascular resistance; O₂: oxygen.

nutritional status, and carnitine deficiency. Other factors are associated with a higher morbidity, such as vitamin D deficiency and anemia, which are detailed below.

The echocardiography is used to confirm diagnosis and assess disease severity and progression. EF, LVFS, end-systolic and end-diastolic LV dimensions, and their corresponding Z-scores are used as prognostic factors. A study showed that children with an EF < 35% had a 50% survival rate at 4 years versus 90% in children with a higher EF. When comparing patients with DCM and severe HF, the mean LVFS of deceased patients was 12% versus 21% among survivors.28 Another study determined that an end-diastolic LV dimension with a Z-score > 7.7 and a LV flow propagation velocity with a Z-score > -0.28 were predictors of disease progression.27-30

Elevated biomarkers, such as atrial natriuretic peptide and BNP, are considered as poor prognostic factors, even in asymptomatic patients, and a direct correlation has been observed with the echocardiographic dimension used during the cardiological follow-up of these patients: end-diastolic LV measurement, isovolumic contraction time of the LV, Tei index, and M-mode assessment of the interventricular septum diameter in systole and diastole.27

It has also been observed that, although less specific than DCM, an increase in uric acid and procalcitonin levels may correlate with a poor prognosis, especially among patients with pulmonary hypertension.27

Comprehensive management of patients with dilated cardiomyopathy

Most of the times, there is no etiological treatment for DCM, so its management is aimed at relieving symptoms, delaying heart failure, and prolonging survival. However, it has a 40% failure rate at 2 years and may lead to refractory HF requiring heart transplant.

Pharmacological support is based on ACE inhibitors, diuretics, beta-blockers, digitalis, and anticoagulants. These should be accompanied by a complete multidisciplinary assessment, as detailed below.

a) Nutritional care

Malnutrition is an independent marker of mortality and morbidity in children and adolescents with DCM and HF, and has been associated with frequent hospitalizations, growth retardation, and poor post-transplant outcomes.31 There is a risk for energy imbalance and malnutrition given the high energy output and low food intake.

Structural and functional gastrointestinal alterations may be observed as causes of malnutrition. Structural alterations include changes in the gastric mucosa, intestinal wall edema, and increased collagen levels in the small intestine. Functional changes are caused by intestinal hypoperfusion, which leads to an alteration in protein transport, a high rate of bacterial colonization, and endotoxin absorption. In the long term, a reduced intestinal absorption and nutrient loss occur.32

In addition, malnutrition contributes to myocardial dysfunction, endothelial dysfunction, musculoskeletal atrophy, insulin resistance, and lipolysis. Therefore, it is critical for pediatricians to understand metabolism and the ways in which children may achieve a comprehensive development.

Volume restriction is an important barrier with few nutritional alternatives. An optimal nutritional support means not only meeting energy output but also macro- and micronutrient requirements. To this end, concentrated infant formula or high-calorie additives are used, but they provide a smaller protein intake which may result in muscle breakdown. To avoid this, the recommendation is to provide a protein intake of 1.5-2.5 g/kg for infants and 0.8-1.5 g/kg for older children. An early strategy aimed at reducing energy output is the placement of an enteral feeding tube. Continuous enteral feeding is usually done during the night so as to avoid interference with the patient’s routine.33

Nutritional assessment is not easy. Weight estimation is limited by fluid changes, even during the day, and the use or not of diuretics. The measurement of skinfolds, including the triceps, and arm circumference may not be useful to estimate lean body mass because they are altered in the presence of edema. For this reason, it is necessary to perform a complementary assessment of biochemical markers, such as albumin, prealbumin, transferrin, transferritin, retinal-binding protein, and C-reactive protein. It has been observed that patients with an albumin level below 3 g/dL have a longer length of stay, regardless of the cause of hospitalization. In addition, patients with a higher blood albumin level showed lower BNP values and lower inotrope use during their hospital stay.34-36

Children with chronic diseases and an
increased inflammatory cytokine level have
growth hormone resistance, so nutritional status
and cytokine levels are the main determinants of
such resistance. Proinflammatory cytokines, such
as TNF-α, act on the CNS by altering appetite
and energy metabolism and provide a signal that
causes the loss of muscle mass (nuclear factor
κB and ATP-dependent ubiquitin proteolytic
pathways). A poor calorie and protein intake
may interfere during a critical growth period
and is irreversible, especially if it started during
puberty. Cytokines seem to alter gonadotropin-
releasing hormone secretion and its ability to
have an endogenous response to testosterone,
thus worsening the effects of malnutrition and
delaying pubertal development.37

When DCM is caused by metabolic
errors, such as beta-oxidation defects and
mitochondrial diseases, intermediate organic
acids accumulate and, once they conjugate
with L-carnitine, may be excreted in urine.
Therefore, L-carnitine supplementation is the
cornerstone of treatment.38,39 In addition, its use
in children with HF improves their nutritional
status, with an increased lean body mass, EF,
and LV surface area, probably secondary to an
enhanced performance of non-hypertrophic
cardiomyocytes, which compensate for this by
exerting a higher contractile force.40-42

Vitamin D is not only responsible for
calcium absorption but also for an adequate
immune performance and cell proliferation.
Cardiomyocytes have vitamin D receptors that
are directly involved in contractility, without
calcium interaction. Children with heart disease
are at a higher risk for vitamin D deficiency.
Although some studies had contradictory results,
vitamin D deficiency has been related to higher
inotrope requirements, a longer length of stay,
a higher risk for infections, and an unstable
fluid management.43-46 Supplementation for
12 months with 1000 U/day of cholecalciferol in
children with HF and DCM or other systolic LV
dysfunction reduces inflammation markers and
improves LV dimensions and the index of systolic
function.47

b) Physical activity

The combination of a poor nutritional status
and immunological activation may induce skeletal
muscle abnormalities, a reduced physical ability,
and a worsened quality of life. Lack of physical
activity induces a loss of muscle mass and
worsens malnutrition, so the recommendation
is to encourage physical activity and maintain a
range of motion in accordance with the patient’s
cardiovascular condition.48

c) Blood products

Iron deficiency anemia is frequent due to
poor iron intake, malabsorption, intestinal loss,
abnormal red blood cells, renal involvement,
chronic inflammation, hemodilution, and
chronic drug use. Based on such varied causes,
it is critical to provide oral or intravenous iron
supplementation.

In the case of potential transplant receptors, it
is suggested to limit the exposure to transfusions
because they are considered a risk factor for the
development of anti-HLA antibodies in relation
to allograft rejection.49

d) Anesthetic considerations

These patients are more prone to have severe
hypotension following the administration of
sedative and anesthetic agents, either because
of their underlying disease or the use of
vasodilators (ACE inhibitors, beta-blockers).
The use of anesthetic agents causes venodilation
and a resulting decrease in preload, which may
accentuate hypovolemia. Therefore, even if vital
signs are recorded to be in the normal range, using
inotropes before a procedure that requires sedation
may notably reduce the drop in CO. In general,
hospitalized patients have a higher risk for severe
hypotension than outpatients.50

The most commonly used agents for
sedation/anesthesia in patients with DCM are
propofol, ketamine, thiopental, and etomidate.
Propofol and thiopental have a dose-dependent
hypotensive effect and cause a sudden decrease
of preload and postload, and even myocardial
contractility. Besides, ketamine increases heart
rate and BP in the normal heart, but it may also
induce myocardial depression in these patients,
secondary to catecholamine depletion. Patients
with cardiomyopathy and end-stage HF have
shown a decrease in postload that results in
hypotension, together with a higher risk for
ischemia, arrhythmias, and cardiac arrest. It has
not been demonstrated that etomidate reduces
contractility, but it does reduce cortisol levels and
suppresses the adrenal response to stress. Still, it
is recommended for patients with end-stage HF
because the relative risk for severe hypotension
is lower than that of other anesthetic agents.51-53
High-dose opioids alter heart function and
have a smaller response to stress, especially
during surgical procedures; morphine is the most widely known drug used to decrease preload and/or SVR. The combined use of opioids and benzodiazepines doubles the risk for circulatory depression.53,54

Anesthetic gases suppress contractility and reduce SVR, which makes CO dependent only on preload and vasoactive drug use. Nitrous oxide seems to have little effect on SVR. Based on the risk for complications, it has been suggested that patients with HF and a LVSF < 25% should be hospitalized before undergoing an anesthetic procedure because there is a 38% risk for vasoactive support requirement.54-57

e) New therapies

In patients with histological evidence of active chronic inflammation, the use of immunoglobulins and interferon-beta improve EF and functional capacity.58,59

Doing genetic tests in family members of patients with DCM or muscular dystrophy may help to make an early diagnosis and eventually administer treatment to prevent myocardial fibrosis and remodeling.5

The high cost of a transplant makes it necessary to look for other alternatives. In this regard, the use of stem cells has been proposed as a potential and innovative approach that promotes cardiac regeneration by replacing injured tissue. The largest clinical trial included 9 children with DCM, where 5 showed an improvement in functional capacity, reduced BNP levels, and a better contractility. Among these 5 patients, 3 did not make it to the transplant.60,61 Further studies are necessary to establish their role.

f) Immunizations

Patients with HF have a higher risk for hospitalization because they tend to have decompensations triggered by a lack of treatment adherence, myocardial ischemia, and respiratory infections. Considering that pulmonary congestion is a predisposing factor for respiratory infections, the heart associations of North America, South America, and Europe have recommended to administer the palivizumab vaccine to infants younger than 1 year old and the influenza and Streptococcus pneumoniae vaccines to all children with DCM so as to maximize immunization coverage.62

g) Psychosocial considerations

Another aspect to be taken into account is the management and acknowledgement of emotional alterations. These patients usually have anxiety and fears typical of a terminal illness. They and their families require psychological counseling to address symptom progression, diagnosis, treatment, and prognosis. The objective is to identify irrational thoughts about their disease and normalize emotions as they are expressed. In addition, psychosocial disorders should be suspected and identified so that patients are referred for treatment in a timely manner. The subsequent stages and the emergence of new complications typical of immunosuppression after a transplant should be addressed so that patients and their families have the necessary tools to deal with them.

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