Optimal Treatment Strategies for Haemophilia: Achievements and Limitations of Current Prophylactic Regimens

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Abstract

Prophylactic application of clotting factor concentrates is the basis of modern treatment of severe haemophilia A. In children the early start of prophylaxis as primary or secondary prophylaxis has become the gold standard in most countries with adequate resources. In adults prophylaxis is reasonably continued when started as primary or secondary prophylaxis in childhood to maintain healthy joint function. Initial data support that adult patients with already existing advanced joint arthropathy benefit from tertiary prophylaxis with significantly lowered number of bleeds, almost absence of target joints and less time off work. Current prophylactic regimens, although very effective, do not completely prevent joint disease in a long-term perspective. Joint arthropathy in primary prophylaxis develops over many years, sometimes over a decade or even longer time periods. The ankle joints are the first and most severely affected joints in those patients and thus may serve in outcome assessment as an indicator of early joint arthropathy when followed by ultrasound or MRI. Optimized outcome and best utilisation of available resources is expected from individualization of therapy regimens which comprises the individual's bleeding pattern, the condition of the musculoskeletal system, level of physical activity and the pharmacokinetic profile of substituted coagulation factor, and most recently includes novel products with extended half-lives.
Prophylaxis in Haemophilia

The key to a successful long-term outcome in patients with haemophilia is an efficient prophylaxis that prevents bleeding in joints for children and adults with haemophilia. Efficient prophylaxis requires taking into account the available resources (clotting factor concentrate, trough levels), the bleeding trigger (activity levels, chronic synovitis, already existing arthropathy) and most importantly the number of acceptable bleeds, especially joint bleeds (Fig. 1). Depending on the available resources, the treatment objectives can vary between countries and treatment centers. In an almost ideal setting, the number of spontaneous bleeds should be minimized in order to prevent the manifestation of joint arthropathy. The severity of joint arthropathy mirrors as a kind of cumulative memory the number of experienced joint bleed and, thus, reflects the overall quality of the prophylactic treatment regimen. Once joint damage has occurred, it will progress over the patient's life time even if no further bleeds occurs in the affected joints. As a consequence, primary prophylaxis should aim to prevent any joint damage. Early diagnosis of joint damage currently represents a challenge with routine imaging and clinical diagnosis tools. Moreover, joint arthropathy in a patient on primary prophylaxis develops very slowly, over a decade or even longer time periods. Both, the subtle development of joint arthropathy and the limitations of its early detection hamper timely diagnosis and adequate action on treatment regimen.

Depending on the patients' age and underlying conditions, prophylaxis and its subsequent prevention of bleeds have different objectives, which are reflected by the ISTH definitions. According to these definitions, primary prophylaxis begins in early childhood in the absence of documented joint disease and before the second clinically evident joint bleed and before the age of 3 years. Patients treated in this way have the potential of a life without joint arthropathy. Secondary prophylaxis commences after 2 or more joint bleeds, but before the onset of joint disease as documented by physical examination and/or imaging studies. These patients may already have a significant risk of developing joint arthropathy. Tertiary prophylaxis is defined as treatment initiation after the onset of joint disease at any age of the patient. Objectives in those patients include slowing down progression of joint disease, reducing pain and inflammation and maintaining mobility, especially in adult haemophiliacs with already advanced joint disease.
While primary and to a lesser extent secondary prophylaxis represent the established gold standard for children in most developed countries, tertiary prophylaxis in adults is just recently becoming increasingly considered. Current approaches improving prophylaxis outcome include available resources, individualisation of treatment regimens with respect to dose, intervals and type of concentrate, considering trough levels and bleeding triggers in the respective patients.

**Initiation of prophylaxis in young children**

Prophylaxis in children is most efficient when started at an early age. Prophylaxis initiated before the age of 2 years\(^3\) resulted in a better outcome than prophylaxis commenced at age 3-5 years or 6-9 years\(^4,5\). National guidelines and recommendations in several European countries advise starting prophylaxis early\(^6,7\). In the last decade, several studies suggest beginning with a once-weekly regimen\(^8-10\). The rationale behind this is either to avoid the placement of central venous access devices and to account for the different clinical presentations, thus tailoring therapy and optimizing cost-effectiveness\(^8,9\) or to lower the risk of inhibitor formation\(^10\). The Canadian primary prophylaxis experience begins with a once-weekly regimen (50 U/kg BW), that, depending on number of bleeds, is intensified in a first step to twice-weekly treatment (2 times 30 U/kg BW) and, in a third step, to every-other-day therapy (25 IU/kg BW)\(^11\). Median ages at switching to steps 2 and 3 were 4.1 and 9.7 years, respectively. Twenty percent of the patients remained on the lowest regimen during the observation time of this study. For this regimen, switches depend on the number of bleeds. Long-term follow-up observation of this cohort is needed, in order to assess whether this regimen is still effective against late onset of arthropathy. Kurnik et al. presented data that suggest that early initiation of prophylaxis may prevent inhibitor formation\(^10\). Triggered by observations from the Canal- and Rodin-Studies\(^12,13\) where inhibitor formation was significantly less in the prophylaxis group, compared to the on-demand group, Kurnik et al. proposed beginning prophylaxis with once-weekly 25 IU/kg BW at a median age of 10 months\(^10\). The rational behind this regimen was that regularly administered, low factor VIII (FVIII) doses in the absence of bleeds, intensive treatment periods and danger signals may induce tolerance to FVIII within the first 20-50 exposure days. By the time the first major joint bleeds are expected, tolerance would already been achieved. Following
this regimen, Baxter commenced the prospective Early Propylaxis Immunologic Challenge (EPIC) study. However, the EPIC study was stopped after inclusion of only 19 patients because of unexpected high incidence of inhibitors. The reasons given for stopping the study were difficulties in adherence to the complex protocol in a multinational, multicenter study setting and an increasingly unrealistic perspective to achieve a significantly lower inhibitor frequency within this study\textsuperscript{14}.

**Dynamics of developing joint arthropathy**

*Current regimens are efficient, although they do not prevent joint arthropathy over a life-time perspective*

The onset of joint arthropathy largely depends on the number of bleeds per year, especially joint bleeds per year, which have become surrogate markers for outcome in both clinical and post-marketing studies. While on-demand treated patients experience 20-50 bleeds per year and develop joint arthropathy early in life\textsuperscript{1}, patients treated prophylactically may remain free from joint disease over 1-2 decades or even longer. Manco-Johnson and coworker performed the first controlled, randomised and prospective trial comparing the onset of joint arthropathy in on-demand treated versus prophylactically treated young children\textsuperscript{5}. Joint disease was assessed by MRI, an imaging tool allowing diagnosis of early joint damage. During an approximately 4 year observation time, 45\% of the on-demand group developed new joint arthropathy as opposed to only 7\% in the prophylactic group. This study impressively demonstrated that prophylaxis is largely protective for joint disease over a 4 year period of observation. However, joint disease still occurred during this time in about 7\% of the patients treated with an intensive prophylactic regimen (6000 IU/kg BW at the age of 6 years). Projected to a life-time treatment, this means that at the age of 30-40 years, most haemophilia patients will suffer from some joint arthropathy. Only a few studies have so far addressed long-term outcomes of prophylaxis in haemophilia patients with observation times ranging from 5 years to 2-3 decades\textsuperscript{15,16,1,5,17-19}. All studies support that, with the current treatment regimens, severe haemophilia patients will sooner or later develop joint arthropathy. Fisher et al. compared the Netherland’s intermediate dose prophylaxis (2100 IU/kg/year) to the Swedish higher dose prophylaxis regimen (4000 IU/kg/year). After a median observation time of 20 years at an age of young adulthood between 19-30 years, the
intermediate prophylaxis regimen showed a median Haemophilia Joint Heath Score (HJHS) of 7 (range 2-18) out of 144, while the Swedish group presented a median HJHS of 4 (range 2-6.8). The number of joint bleeds in the preceding five years in the groups were 2/year vs 0.5/year, respectively\(^9\). The Swedish protocol had a slightly better outcome and the difference between the two cohorts is expected to become larger with time. However, even the high dose Swedish protocol, with only 1 joint bleed every 2 years, does not entirely prevent joint arthropathy over a life-time perspective. Furthermore, it has to be taken into account that the summarized results were mainly clinical scores which are indicating joint disease later than MRI\(^6\). A 25 year follow-up of 30 Swedish patients confirmed that early initiation of primary prophylaxis continuing throughout life was successful in virtually eliminating joint bleeds and preserving an acceptable – however, not normal - joint status\(^\)\(^8\). Brackmann et al. (1992) followed 90 German patients with severe haemophilia A from 1978-1990, and found no worsening of the joint status over a 12 year period\(^16\). A 26-year follow-up of 49 patients of the same cohort, however, demonstrated that 90% of these patients treated throughout life with an intensive prophylactic regimen exhibited joint disease at 30-40 years of age\(^20\).

*The ankle joint as arthropathy indicator*

Before the era of prophylaxis, e.g. in the 1970s, knee joint bleeds were the most frequently noted joint bleeds and knees were the clinically leading joint in most patients\(^21\). With the beginning of the era of prophylaxis, the knee joint, as a muscle-controlled joint, became more stable and the ankle joints became the first joints to be affected and, thus, represent the clinically most indicative joint. Oldenburg et al. (2014) observed higher MRI scores for ankle joints and the scarcity of pathologic findings in knees for patients with unaffected ankles indicated that, in most patients, the ankle was the primary target joint of haemophilic arthropathy\(^22\). These results are consistent with previous reports showing more haemarthroses and worse joint scores for ankles, compared with knees or elbows\(^5,23-26\). Krämer et al. (2013) followed the development of joint arthropathy in the cohort on intensive life-long prophylaxis, initially described by Brackmann et al. (1992). During a 26-year follow-up Petterson scores based on plain X-rays were taken every 3-5 years and Gilbert scores were obtained once per year. Ankles were the first joints to be found affected by Petterson-score, with median pathologic findings after 10 years, followed by significant effects
for knee and elbow joints after another about 10 years\textsuperscript{20}. On average, the clinical Gilbert scores became pathologic about 1-2 decade later than the Petterson scores\textsuperscript{20}. An abstraction/simplification of the findings from Krämer (2013) is illustrated in Fig 2. Ours and other authors' studies indicate that imaging score-based diagnosis of arthropathy is possible long before being revealed by clinical scores\textsuperscript{5}. However, plain X-ray is too insensitive to diagnose early joint pathology, making it inappropriate to diagnose early joint damage. Ankles, as the first affected joints for the majority of patients, offer an interesting opportunity for diagnosing early joint disease and subsequent adapting clinical decisions.

**Outcome assessment**

Prophylaxis has greatly improved joint health and is challenging joint outcome assessment. Because of the low number of about one joint bleed every 2 years resulting from intensive prophylaxis programs\textsuperscript{5,19,20}, clinical manifestation of joint disease has become a subtle process, starting mildly, subclinically and progressing slowly over years. Thus, diagnosing early joint disease and taking timely and adequate action has become difficult.

Outcome assessment comprises several tools including annual bleed rates, physical joint examination, imaging measures such as plain X-rays, MRI and ultrasound assessment. Quality-of-life questionnaires complement the instrumentarium for outcome assessment (Blanchette et al. 2014\textsuperscript{27}). The HJHS is currently regarded as the State of the Art instrument for clinical assessment of joint status. It includes most of the elements of the previously used Gilbert score\textsuperscript{28-31}. Plain X-rays scored by the Petterson scale had been a useful tool in the past, but are not able to recognise early joint disease\textsuperscript{32,16}. Magnetic Resonance Imaging (MRI) is a very sensitive instrument for early detection of haemarthrosis, including synovial hypertrophy, hemosiderin deposition and osteochondral changes. Scoring scales for reliable assessment of haemophilia arthropathy have been established\textsuperscript{33-36}. However, MRI application to young children is limited and also expensive. More recently, ultrasound has been used for diagnosis of joint disease in haemophiliacs. Advantages are its wide availability and its low cost. Especially soft-tissue changes such as synovial hypertrophy, that preceed joint disease, can be effectively diagnosed. Standardized and simplified ultrasound scanning protocols for early arthropathy detection in ankles, knees and elbows have been published\textsuperscript{37-40}. The joint measures for long term
outcome with respect to established scores, potency of detecting early joint disease and follow up of severe arthropathy, suggested intervals for assessment and costs are summarized in Table 1.

However, the interrelationships among these scores have not been established and validated. A potential future perspective to follow joint health status might be start with annual physical and ultrasound scoring in young children and, at the age of 6-8 years, an initial MRI, preferrably of both ankle joints. Further studies are needed that compare these scores over time and comparatively assess their applicability. Quality-of-life scales support the benefits of prophylaxis with the aim of an almost normal life-long health.

The annual bleed rate (ABR) has become an important parameter in clinical studies as a surrogate for the efficiency of prophylaxis regimens. Some studies have also assessed the annual joint bleed rate. For intensive treatment protocols the mean total ABRs range from 2-5, while the joint bleed ABR is in the order of 0,5 5,20,41-43. Given the long-term dimension of developing joint arthropathy and the limitations of diagnosing early joint damage the ABR serves as an important clinical parameter to adjust treatment regimens.

**Prophylaxis in adult patients**

While primary prophylaxis represents the gold standard for preserving joint function in children with severe haemophilia, prophylaxis in adult patients is still debated. There are two groups of adult patients which have to be addressed seperately. The first group of patients includes those who started primary or secondary prophylaxis early in their life and maintained a good joint health into adulthood. A small number of published studies suggest that these patients benefit from a life long prophylaxis 16,18-20. These studies reported a follow up of 12-30 years and demonstrated that haemophilia patients with an ongoing prophylaxis regimen present with well-preserved joint function and only mild joint arthropathy at the age of 30-40 years 18-20. The patients from the Netherlands with an intermediate dosage regimen had a slightly worse outcome at the age of 30 years than Swedish patients with a high dose prophylaxis regimen 19. In the German cohort, 90% of patients showed some, mostly mild arthropathy, mainly in their ankle joints after a 26 year follow-up 20. There are several reports that a proportion of young adults switch to an on-demand and that
some of these patients stay on this regimen with only few bleeding and little joint arthropathy\textsuperscript{44,45}. However, no follow-up data are available that report joint condition of these patients at the age of 40-50 years or older. As initial joint damage always progresses, even in the absence of joint bleeds, a worsening of joint disease can be anticipated. The joint annual bleed rate might serve as a surrogate for switching those patients back to a prophylactic regimen. The joint ABR should not be higher than during an intensive prophylaxis regimen, which is about 1-2 joint bleeds within two years.

The second group of adult Haemophilia patients are those who already present with an advanced joint arthropathy and are on a tertiary prophylactic regimen. There are few studies that impressively demonstrate the reduction of total bleeds and joint bleeds in patients who are on tertiary prophylaxis compared to an on-demand regimen. The prospective randomised SPINART study found a median of about 54,5 total bleeds per year in patients treated on-demand compared to a median of 0 total bleeds in the prophylactic group\textsuperscript{41}. Interestingly, about 20\% of the prophylaxis group with 25 IU/kg BW three times per week, still had a significant number of bleeds, indicating the need for further individual adaptation of the prophylaxis treatment. A recent survey in Europe examined the use of prophylaxis in people aged 20-35 with severe haemophilia and found an inverse correlation between time on prophylaxis and occurrence of major bleeds, presence of target joints and time off work. Patients from Sweden who had spent the longest period on prophylaxis had the best preserved joints and best quality of life\textsuperscript{46}.

A cross-sectional MRI evaluation of joint status in severe haemophilia A patients treated with prophylaxis initiated at different ages versus on-demand-therapy demonstrated protective effects of prophylaxis. All prophylaxis groups had better MRI joint scores than the on-demand group. MRI scores generally increased with current patient age and later start of prophylaxis. Ankles were the most affected joints\textsuperscript{22}. These results indicate that also adults with already established severe joint arthropathy benefit from a prophylactic regimen in terms of number of bleeds, presence of target joints, mobility and time off work. However, long-term follow-up studies are needed to substantiate these effects.

**Individualising of treatment regimens**

Individualisation of therapy would not be an issue if the trough factor levels could be
raised in every patient to 15-20%, thus allowing an almost bleed-free life. However, resources are limited and individualisation is applied to get the best outcome with the given resources. On an economic basis, individualization also implicates that a certain risk of bleeding is taken. An individualised regimen comprises the individual’s bleeding pattern, the condition of the musculoskeletal system, level and timing of physical activity and actual levels as well as trough levels of coagulation factor.

**Individual bleeding risk – more than factor levels**

A subset of 10 to 15% of patients with severe hemophilia A exhibits a mitigated disease phenotype, with significantly reduced frequencies of spontaneous bleeding and lower consumption of factor concentrates. This clinical heterogeneity is also reflected by the late onset of the first joint bleed and furthermore in development of only minimal arthropathy. This mitigated clinical phenotype is chiefly determined by the underlying mutations in the F8/F9 genes. Especially missense mutations, splice site mutations outside conserved regions and small deletions within A series were associated with less bleeding. Furthermore, the inflammatory response to the presence of blood in a joint varies, which is believed to be in part dependent on genetic variations in the genes involved in the inflammatory and immune regulatory pathways. This variation may influence the subsequent development of chronic synovitis and ultimately also of joint arthropathy. Indeed, the Joint Outcome Study reported several boys with multiple episodes of hemarthrosis who remained free of joint damage. Other patients showed joint damage in the absence of clinical bleeds. In patients with greater number of bleeds or with a stronger inflammatory response to a bleed larger factor doses and more frequent application are required to prevent the onset of joint disease.

**Pharmacokinetic variation in patients and new products**

Collins et al. demonstrated a great variation of pharmacokinetics dependent on age (shorter half life in young children than in adults) but also within patient groups of the same age, where he found an almost 100% difference in time-to-trough levels of > 1% after application of a standardised FVIII dose. Several studies have shown that the level of the von Willebrand factor has a major influence on the factor VIII half-life. Higher VWF levels correlate with increasing intervals of FVIII substitutions. Therefore, assessment of the patient’s individual pharmacokinetic
profile is regarded as important for individualisation of therapy. Since, a classical pharmacokinetic profile is based on numerous blood draws over two or more days, population pharmacokinetics presents an elegant approach to assess the pharmacokinetic profile by routine factor level measurements at regular visits in the treatment center\textsuperscript{59,60}. Population pharmacokinetics will become an important measure for individualised treatment regimens\textsuperscript{60}.

A number of new factor concentrates and drugs based on other technologies with improved half-lives and alternative administration routes will soon be available\textsuperscript{61}. The advances for recombinant factor IX products have been significantly with half-life extensions to up to 100 hours, allowing substitution intervals of 1-2 weeks. For recombinant factor VIII products the advances thus far are only moderate, as the half life extension is limited to about 15-18 hours by the clearance of factor VIII through Willebrand factor\textsuperscript{61}. Using longer-acting coagulation factors with different pharmacokinetic profiles will further individualise treatment by maintaining adequate trough level with fewer infusions\textsuperscript{47}. On the horizon are novel products applying new technologies such as a bispecific antibody that mimics factor VIII\textsuperscript{61,62}. This product has the potential to almost eliminate bleeds by weekly subcutaneous injections of the bispecific antibody\textsuperscript{63}.

**Prophylaxis in Haemophilia B**

There is an ongoing discussion whether the phenotypes of haemophilia A and Haemophilia B have the same phenotype or whether haemophilia B patients have fewer bleeds and develop joint disease later and less severe\textsuperscript{64,65}. The mutation spectrum varies significantly. While in haemophilia A about 80% of the patients exhibit null-mutations with no endogenous factor VIII protein synthesis, Haemophilia B show only about 20-30% null-mutations\textsuperscript{66,67}. Especially Haemophilia B is much more commonly caused by missense mutations, which might be associated with some small amounts of endogenous plasma factor IX protein. Santagostini and coworker (2010) showed that the type of mutation was the only significant parameter influencing the phenotype\textsuperscript{49}. While this different mutation profile is explaining the different inhibitor incidence\textsuperscript{68}, it is not clear whether it may also affect the treatment regimens in Haemophophilia B patients. Most recently Clausen et al. reported a total
of 582 patients with severe haemophilia A and 76 with severe haemophilia B from the Rodin study and found that haemophilia A and Haemophilia B did not differ in age at first exposure to clotting factor, age at first bleed and age at first joint bleed. Although these data refer to a very early stage of treatment, decisions on the prophylactic treatment are made at this time and are based on criteria as the onset of bleeds, especially joint bleeds. Therefore it appears safe to follow the same principles for prophylaxis in haemophilia B patients as it has been outlined in this review for Haemophilia A patients. Anyway the longer half life of factor IX and especially the new recombinant factor IX products with extended half-lives of up to 100 hours will make a difference in the prophylactic regimens.

Conclusion

In conclusion, current therapy regimens include early start of prophylaxis as primary or secondary prophylaxis. Prophylaxis is increasingly regarded as a life-long therapy, also applied as tertiary prophylaxis in adults with already existing arthropathy. There is a trend towards a more intensive prophylaxis, achieving an almost quantitative prevention of joint bleeds. Individualized strategies intend to optimize outcome and utilization of resources. Current data are limited to a follow-up period of maximum of 25-30 years. There are no data available demonstrating outcomes in a life time perspective. Future studies are needed to provide long-term outcome data for current regimens. The parallel development of gene therapy protocols that are already in place for haemophilia B and that are at the horizon for haemophilia A may result in a cure for haemophilia patients, at least with respect to spontaneous bleeds. At the time of clinical availability of gene therapy the risks and benefits, also with respect to possible late adverse events, have to be balanced against the classical prophylaxis regimens with the new products available at that time.

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<td><strong>Haemophilia Joint Health Score</strong></td>
<td>+++</td>
<td>-</td>
<td>+++</td>
<td>Annualy (ankles, knees, elbows)</td>
<td>Low</td>
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<tr>
<td><strong>Plain x-ray (Petterson score)</strong></td>
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<td>-</td>
<td>+++</td>
<td>Every 5 years (ankles, knees, elbows)</td>
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<td><strong>MRI</strong></td>
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<td>+++</td>
<td>(+++)</td>
<td>Every 5 years starting at age of 6-8 years (ankles)</td>
<td>Very high</td>
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<tr>
<td><strong>Ultrasound</strong></td>
<td>++</td>
<td>++</td>
<td>-</td>
<td>Annualy (ankles, knees, elbows)</td>
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**Table 1:** Joint outcome measures for long term follow up with respect to established scores, potency of detecting early joint disease and follow up of severe arthropathy, suggested intervals for assessment and costs. +++ = very good, ++ = good, - = no or limited value
Legends to Figures:

**Figure 1**: Propylaxis treatment regimen has three main determinants: i) the given resources/concentrate availability to target a specific trough level and/or intervals of sustitutions, which both reflects the costs. ii) the bleeding trigger, that comprises physical activity, presence and degree of arthropathy and presence of chronic synovitis and iii) the number of bleeds, especially joint bleeds that are regarded as acceptable. This three determinants for a triangle. If you change one determinant, the other two will adjust. While with unlimited resources you may target zero bleeds and normal physical activity, with few resources you may give only 2 low dose substitutions per week, thus accepting a certain number of bleeds and limited physical activity.

**Figure 2**: Illustration and abstraction of the long-term outcome results of Krämer et al. (2013), that underline that progression of joint arthropathy during intensive prophylaxis regimens is a process with subtle progression over years. PS=Petterson Score, GS=Gilbert Score. Scores equal or greater 2 are regarded to be pathological. The ankle joints are the first joints which develop arthropathy after a median time of 10 years, followed by knee joints and elbow joints significantly later. The clinical Gilbert scores are following the Peterson scores 1-2 decades later. The grey area indicates the initial decade of prophylactic treatment when early joint disease remains undetected by the Petterson score.
The Prophylaxis Triangle

Trough level FVIII:C
Intervals of treatment (costs)

Bleeding trigger
- Physical activity
- Arthropathy
- Chronic Synovitis

Number of (joint) bleeds (accepted)
Figure 2:

Early joint damage escapes clinical diagnosis
Optimal treatment strategies for hemophilia: achievements and limitations of current prophylactic regimens

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