Clinical and Cost Effectiveness of Hexaminolevulinate-guided Blue-light Cystoscopy: Evidence Review and Updated Expert Recommendations

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Abstract

Context: Non-muscle-invasive bladder cancer (NMIBC) is associated with a high recurrence risk, partly because of the persistence of lesions following transurethral resection of bladder tumour (TURBT) due to the presence of multiple lesions and the difficulty in identifying the exact extent and location of tumours using standard white-light cystoscopy (WLC). Hexaminolevulinate (HAL) is an optical-imaging agent used with blue-light cystoscopy (BLC) in NMIBC diagnosis. Increasing evidence from long-term follow-up confirms the benefits of BLC over WLC in terms of increased detection and reduced recurrence rates.

Objective: To provide updated expert guidance on the optimal use of HAL-guided cystoscopy in clinical practice to improve management of patients with NMIBC, based on a review of the most recent data on clinical and cost effectiveness and expert input.

Evidence acquisition: PubMed and conference searches, supplemented by personal experience.

Evidence synthesis: Based on published data, it is recommended that BLC be used for all patients at initial TURBT to increase lesion detection and improve resection quality, thereby reducing recurrence and improving outcomes for patients. BLC is particularly useful in patients with abnormal urine cytology but no evidence of lesions on WLC, as it can detect carcinoma in situ that is difficult to visualise on WLC. In addition, personal experience of the authors indicates that HAL-guided BLC can be used as part of routine inpatient cystoscopic assessment following initial TURBT to confirm the efficacy of treatment and to identify any previously missed or recurrent tumours. Health economic modelling indicates that the use of HAL to assist primary TURBT is no more expensive than WLC alone and will result in improved quality-adjusted life-years and reduced costs over time.

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Conclusions: HAL-guided BLC is a clinically effective and cost-effective tool for improving NMIBC detection and management, thereby reducing the burden of disease for patients and the health care system.

Patient summary: Blue-light cystoscopy (BLC) helps the urologist identify bladder tumours that may be difficult to see using standard white-light cystoscopy (WLC). As a result, the amount of tumour that is surgically removed is increased, and the risk of tumour recurrence is reduced. Although use of BLC means that the initial operation costs more than it would if only WLC were used, over time the total costs of managing bladder cancer are reduced because patients do not need as many additional operations for recurrent tumours.

1. Introduction

Bladder cancer (BCa) is one of the most frequently diagnosed tumour types, with an estimated 166 583 newly diagnosed cases and 58 742 deaths due to the disease in Europe in 2012. Because of this relatively low mortality rate in relation to incidence, the 5-yr prevalence rate amounts to almost half a million people in Europe [1].

Most patients are diagnosed with non–muscle-invasive BCa (NMIBC), which, although it is unlikely to prove fatal, has a high risk of recurrence (up to 61% within 1 yr and 78% within 5 yr of initial resection) and a not negligible risk of progression to muscle-invasive disease (up to 17% risk at 1 yr and up to 45% risk at 5 yr) [2]. This risk of recurrence and progression places a substantial burden on patients and health care resources, as patients require frequent and regular follow-up [3], making the lifetime costs of managing BCa among the highest for all cancers (see [4] for a review of economic data).

One reason for the elevated recurrence risk of NMIBC is likely to be the persistence of lesions following initial transurethral resection of bladder tumour (TURBT). Incomplete resection may be a result of various factors, including the presence of multiple lesions and difficulty identifying the exact extent and location of tumours (especially carcinoma in situ [CIS]) using the current standard of white-light cystoscopy (WLC) [5,6]. Tools to improve visualisation of tumours at first TURBT can help urologists to achieve a more complete resection and thereby reduce the risk of recurrence and burden of disease.

Hexaminolevulinate (HAL) (Hexvix, Photocure ASA, Oslo, Norway; Ipsen SA, Boulogne-Billancourt, France) is an optical-imaging agent used with blue-light cystoscopy (BLC) as an adjunct to WLC in the diagnosis of NMIBC. HAL has been commercially available in Europe since 2006 and has become an established tool in the detection of NMIBC. However, the settings in which HAL is used vary from hospital to hospital and from country to country, depending in part on the availability of equipment and local reimbursement arrangements. We believe that the case for the use of HAL has been clinically proven, but we acknowledge the cost and resource constraints placed on health care providers. We have therefore reviewed the most recent data on both clinical and cost effectiveness of HAL to provide updated expert guidance on the use of this tool, including optimal patient selection, to improve management of patients with NMIBC.

2. Evidence acquisition

A group of European urologists with expertise in the management of patients with BCa met in Munich, Germany, in November 2013 to consider existing guidelines, personal experience, and the most up-to-date evidence on the use of HAL-guided BLC in NMIBC. Financial support for the meeting, and for the preparation of this manuscript, came from Ipsen SA, which provided factual information and verification but did not influence the meeting or the conclusions of the authors. Three of the authors (P.G., J.P.R., and A.S.) were not able to attend the meeting but provided input into the manuscript.

As a basis for the discussion, a literature search of PubMed and key congresses was undertaken to identify abstracts on HAL. No language restrictions were applied. For the PubMed search, no time restrictions were applied, whereas conference searches were restricted to meetings from January 2009 to September 2013, on the assumption that key data presented before 2009 would have been published since then. The search terms, conferences searched, and results are presented in Supplement 1.

3. Evidence synthesis

The literature search identified 209 potentially relevant abstracts (see the Supplemental Appendix for full details), of which 85 reported results from clinical trials or retrospective cohort analyses. There have been eight abstracts reporting six meta-analyses of the key clinical data [7–14], including five abstracts reporting data for both HAL and its precursor 5-aminolevulinic acid (5-ALA), which is not commercially available [7–9,11,12]. Most meta-analyses were based on reported results for groups of patients, whereas Burger et al. [14] analysed patient-level data (requested from the study sponsor or principal investigator), using the DerSimonian-Laird model to account for heterogeneity of studies [15] and weighting the results relative to the number of patients in each study.

Almost all the meta-analyses confirm a significant benefit for BLC compared with WLC in terms of increase in detection of lesions (papillary or CIS) and reduction in recurrence rates [7,8,10,12–14,16]. Only one meta-analysis, by Shen et al. [11], found no benefit; however, our analysis of their report has identified a few inconsistencies in the data that they cite compared with the original studies, which may explain their findings. By contrast, a more recent
meta-analysis from the same department (by Yuan et al. [12]), which reports the original data more accurately, came to conclusions that are consistent with the general literature. The results of the meta-analyses by Yuan et al. [12] and by Burger et al. [14], as well as a systematic review by Rink et al. [16], all published in 2013, take into account the latest follow-up data on HAL (Table 1).

On the basis of the positive findings for BLC to aid NMIBC detection, this technique has been recommended in many national and international guidelines on BCa management [3,17–22]. Many of the national guidelines are consistent with the European Association of Urology 2013 guidelines, which make a grade B recommendation for the use of BLC “when bladder CIS or high-grade tumour is suspected” [3]. In addition to these guidelines, which cover the management of NMIBC, several statements have been published by expert groups looking in detail at HAL-guided BLC [23–26]. Recommendations on BLC from the most recent European guidelines and expert-group statements are summarised in Table 2.

In some cases, apparent variation in recommendations may be due to definition or interpretation of terminology (eg, whether or not assessment of recurrence is included in follow-up of patients at risk of recurrence rather than as a specific separate activity). Taking into account our own experience with HAL and the latest data, especially the

| Table 1 – Pooled evidence for the use of hexaminolevulinate-guided blue-light cystoscopy in non–muscle-invasive bladder cancer [12,14,16] |
|-----------------|-----------------|-----------------|
| **Report type** | **Yuan et al. [12]** | **Burger et al. [14]** | **Rink et al. [16]** |
| Articles included, no. | Meta-analysis | Meta-analysis | Systematic review |
| Patients included, no. | 12 (11 studies) | 10 (9 studies) | 44 |
| Receiving BLC | 2258 | 2212 | NR |
| Photosensitiser | 5-ALA or HAL | HAL | 5-ALA or HAL |
| **Detection analysis** | | | |
| Ta/T1 detection rate | | | |
| By BLC, % | 95 | 92–100 |
| By WLC, % | 86 | 50–100 |
| 95% confidence interval | 4.9 | NC |
| p value | <0.001 | |
| T1 OR (BLC vs WLC) | 2.3 | NC |
| 95% confidence interval | 1.0–5.1 |
| p value | 0.050 |
| CIS detection rate | | | |
| By BLC, % | 95 | 49–100 |
| By WLC, % | 59 | 5–68 |
| OR (BLC vs WLC) | 12.4 | NC |
| 95% confidence interval | 6.3–24.1 |
| p value | <0.001 |
| **Recurrence analysis** | | | |
| Overall recurrence | | | |
| BLC, % | 32.7 | 34.5 | NR |
| WLC, % | 47.8 | 45.4 |
| OR/RR (BLC vs WLC) | OR: 0.5 | RR: 0.8 |
| 95% confidence interval | 0.4–0.6 | 0.6–0.9 |
| p value | <0.00001 | 0.006 |
| Time to first recurrence, mo | | | |
| BLC | 8–14 | 12–17 |
| WLC | 7–16 | 5–9 |
| Mean difference (BLC – WLC) | 1.7 | NC | NC |
| 95% confidence interval | 0.9–2.5 |
| p value | <0.001 |
| Recurrence-free survival at 1 yr | | | |
| BLC, % | | 55–94 |
| WLC, % | | 39–78 |
| Hazard ratio (BLC vs WLC) | 0.7 | NC |
| 95% confidence interval | 0.6–0.8 |
| p value | <0.00001 |
| Progression analysis | | | |
| Progression-free survival at 1 yr | | | |
| BLC, % | | 89–98 |
| WLC, % | | 89–96 |
| Progression OR (BLC vs WLC) | 0.9 | NC |
| 95% confidence interval | 0.6–1.2 |
| p value | 0.39 |

BLC = blue-light cystoscopy; CIS = carcinoma in situ; 5-ALA = 5-aminolevulinic acid; HAL = hexaminolevulinate; NC = not calculated; NR = not reported; OR = odds ratio; RR = relative risk; WLC = white-light cystoscopy.

* See Supplement 1 for a list of articles included in each meta-analysis or the systematic review.
patient-level meta-analysis by Burger et al. [14], we hope to clarify some of these potential areas of confusion or debate by offering the following expert opinion and recommendations on the optimal use of HAL-guided BLC in the management of patients with NMIBC.

### 3.1. Clinical settings

#### 3.1.1. At initial transurethral resection of bladder tumour in patients with suspected non–muscle-invasive bladder cancer: recommended

Given the clear evidence of benefit that can be achieved with HAL-guided BLC across all NMIBC tumour types (Ta, T1, and CIS) and regardless of risk of recurrence [14], we recommend that HAL-guided BLC be used for all patients during their first TURBT (unless it is anticipated that they will require complete bladder resection, for example, because of suspected muscle-invasive disease). The purpose of BLC is to aid cystoscopic assessment and resection of the tumour and to assess the completeness of TURBT. Use of BLC can improve the quality of resection (and consequently also aid in training junior surgeons), reduce the risk of recurrence, and delay time to recurrence, thereby improving outcomes for patients and reducing the need for repeated hospitalisation and resection for recurrent tumours.

The use of HAL may be limited by reimbursement considerations in some countries (eg, excluding patients with small, solitary, low-grade papillary lesions), in which case the decision whether to use HAL may need to be made after initial outpatient WLC. However, based on the clinical evidence, we believe that BLC should be advocated as best practice for all patients suspected of having NMIBC, as it has been proven that WLC can miss additional lesions (both papillary and CIS). In the meta-analysis by Burger et al., 22.6% of patients with Ta or T1 tumours had additional lesions found by BLC that were missed by WLC ($p < 0.001$), while 25.4% (68 of 268) of the patients with CIS were identified by BLC but not by WLC ($p < 0.001$) [14]. It is important to bear in mind that these missed lesions can convert a patient with only one apparent tumour on WLC at initial diagnosis (who may therefore be classified as low risk) to a higher risk level, requiring a change in management.

Even in patients with low risk of recurrence, evidence indicates that HAL can reduce this risk further compared with WLC (from 34.7% with WLC to 17.9% with BLC at 12 mo, $p = 0.029$, in the meta-analysis by Burger et al. [14]). These data translate into “a number needed to treat” with BLC of one in six patients to prevent one recurrence in 12 mo in the whole group of patients treated for NMIBC. These patients did not receive a single post-TURBT dose of intravesical chemotherapy, which could change these results.

#### 3.1.2. For assessment at time of tumour recurrence: recommended with provisos

In many hospitals, HAL-guided BLC is used for patients suspected of having recurrent tumours only if it was not used during the initial diagnosis and resection. However, many other centres have used HAL more than once for the same patient, with no adverse effects. Although not documented in clinical studies, our experience underlines the idea that in patients with suspected recurrence, it is important to ensure optimal clearance of tumour through improved detection and resection, whether or not the patients previously had HAL at first diagnosis. So based on personal experience, not on documented literature, our recommendation is that HAL-guided BLC be used for all patients with recurrence who have not previously received HAL, and it should be considered as an option to guide TURBT even in patients who have already received HAL, especially if they initially had high-grade or multiple tumours or there is a suspicion of CIS.
3.1.3. In patients having re-resection within 6 wk after transurethral resection of bladder tumour: recommended with provisos

In damaged or repairing tissue, such as areas of recent resection, HAL induces accumulation of the photoactive protoporphyrin IX in granulation tissue involved in wound repair. The granulation tissue then fluoresces under blue light and may be difficult to distinguish from tumour tissue. Therefore, we do not recommend using HAL-guided BLC to assess the completeness of a previous TURBT < 6 wk after resection. However, particularly in patients who did not receive HAL at first assessment, if CIS is suspected or if there is reason to believe that the initial assessment did not cover the entire bladder, our personal experience in referred patients has shown that HAL can be used to inspect the rest of the bladder for lesions that may have been missed. We emphasise that the goal is to find additional tumours (especially CIS), not to evaluate the previous resection or biopsy sites.

3.1.4. In patients who have received intravesical therapy: recommended with provisos

As in tissue affected by recent resection, in bladder mucosa that has been subject to intravesical bacillus Calmette-Guérin (BCG) treatment, accumulation of protoporphyrin IX is increased following HAL instillation, leading to fluorescence under blue light. There is therefore a high risk of false-positive results, and use of HAL is not recommended during BCG therapy as a result. However, several groups have reported their experiences using HAL following induction BCG therapy, and the findings indicate that after approximately 6 wk, the risk of false-positive results begins to be outweighed by the potential benefit of identifying persistent lesions, which may indicate a change in management [27–30]. The false-positive risk also appears to decrease as surgeons become more familiar with the use of BLC and may be able to distinguish between tumour cells and areas of fluorescence due to BCG therapy (Fig. 1). For example, in our experience, the border of CIS fluorescence appears to be much sharper than that of inflammation. We therefore recommend using HAL-guided BLC in high-risk patients ≥6 wk after the last instillation of induction BCG therapy as part of any routine assessment of response to treatment (eg, in place of random biopsies).

There is no evidence that HAL uptake and use of BLC are adversely affected by intravesical mitomycin C therapy [28,31].

3.1.5. During surveillance cystoscopy: insufficient data for recommendation

Surveillance cystoscopy is typically undertaken in the outpatient or office setting, using a flexible cystoscope. Several groups have explored the use of HAL-guided flexible BLC, confirming the feasibility of this approach. The technique appears to be slightly inferior to rigid BLC and comparable to, or more effective than, standard flexible WLC in terms of NMIBC detection rates [32–35]. However, BLC may not lend itself readily to the office setting because of the time required for photosensitiser instillation and the need for rapid cleaning of the equipment, while older cystoscopes may not allow adequate biopsy material to be collected. New flexible cystoscopes are being developed that could overcome the limitations of existing equipment.

In time, therefore, there may be a role for BLC in the outpatient or office setting, and it may come to be of benefit, for example, in ruling out lesions (especially CIS) and thereby preventing the need for hospital admission and TURBT. Before such a strategy could be routinely adopted (at least in high-risk patients), the impact on cost and time if patients were assessed using flexible BLC would need to be balanced against the potential reduction in hospitalisation costs for the proportion of patients who would benefit. We await further trial results for flexible BLC with interest.

3.1.6. In patients with positive urine cytology but negative white-light cystoscopy findings: recommended

Positive urine cytology but negative white-light cystoscopy findings is considered to be one of the key indications for HAL-guided BLC, because it is likely that positive urine cytology findings in the absence of papillary tumours on WLC indicate the presence of CIS, which can be difficult to detect on WLC. Clinical trial data and our own experience show that CIS can be identified using BLC in these patients, although the evidence quantifying the benefit to be achieved from BLC in such patients is still limited [36]. Therefore, our recommendation is that HAL-guided BLC be used to assess patients with positive urine cytology but negative WLC, but we also call for well-designed prospective trials to measure the value of this approach.

In the case of positive cytology, negative WLC, but also negative BLC, evaluation of the upper urinary tract is mandatory.

3.1.7. For haematuria work-up (without biopsy of the bladder): not recommended

No more than 12% of patients with haematuria are diagnosed with urologic malignancy [37,38], and our
opinion is that a tumour large enough to cause visible haematuria could be detected using other methods. It is also important to note that gross haematuria was an exclusion criterion in most clinical trials of HAL, and evidence of the role of BLC in this setting is limited. We therefore do not recommend the use of HAL-guided BLC for the diagnostic work-up of patients with haematuria in the absence of other indications of BCa.

3.2. Cost-effectiveness analyses

Our previously described recommendations are based on the assumption that HAL will be reimbursed in each setting. However, we are aware that health care systems and providers have finite budgets and are looking to set limits on how much can be spent on different indications. In many cases, current restrictions on the use of HAL were set in place several years ago, before long-term follow-up data on recurrence rates were available and in the absence of good-quality cost effectiveness analyses. Since then, Grossman et al. have confirmed that HAL-guided BLC reduces recurrence risk and delays time to recurrence compared with WLC over a median follow-up period of approximately 4.5 yr [39]. In addition, several independent groups have reported potential cost savings with BLC as a result of reduced need for repeat TURBT and hospitalisation, even taking into account the cost of equipment acquisition (Table 3) [4,40–44]. It is important to acknowledge that some of these analyses used 5-ALA, and cost calculations are based on specific hospital centres. Thus, the economic conclusions are not readily transposable to general practice with HAL-guided BLC.

Recently, a model has been developed taking into account national health care system perspectives, with the aim of helping to identify the financial consequences of HAL-guided BLC use at a national level [45,46]. The model includes the cost of equipment and estimates the cost effectiveness of using HAL-guided BLC at initial TURBT, compared with WLC alone, over the lifetime of the patient. Assumptions concerning clinical factors were based on a 2010 health technology appraisal in the United Kingdom, epidemiological studies and national life tables, the meta-analysis by Burger al [14], national guidelines, and expert opinion. Cost and utility parameters were based on national reference costs and population data, expert opinion, and manufacturers’ information.

Using relevant national data, the model shows that in the health care systems in Italy and England (including Wales), HAL-guided BLC dominates WLC in >90% of scenarios, as it is associated with small, but significantly increased, quality-adjusted life-years (QALYs) and lower costs over the long term (the patient’s lifetime) [45,46]. The potential cost savings are consistent with those reported by earlier groups (see Table 3).

Table 3 – Potential costs and savings associated with managing patients with hexaminolevulinate-guided blue-light cystoscopy versus white-light cystoscopy

<table>
<thead>
<tr>
<th>Country, yr</th>
<th>Setting</th>
<th>Total cost per patient</th>
<th>Potential cost difference per patient (BLC vs WLC)</th>
<th>Basis of cost calculations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Germany, 2008 [41]</td>
<td>Newly diagnosed bladder cancer (including muscle-invasive disease)</td>
<td>NR</td>
<td>NR</td>
<td>€584 for TURBT only (no follow-up)</td>
</tr>
<tr>
<td>Germany, 2009 [4]</td>
<td>Not specified (initial TURBT)</td>
<td>€1527</td>
<td>€1387</td>
<td>−€140 (including follow-up cystoscopy at 3–6 mo in WLC group)</td>
</tr>
<tr>
<td>Sweden, 2009 [43]</td>
<td>Newly diagnosed bladder cancer (including muscle-invasive disease)</td>
<td>SEK35 035 (approximately €3918)</td>
<td>SEK34 385 (approximately €3845)</td>
<td>−SEK650 (approximately €73) over first year</td>
</tr>
<tr>
<td>UK, 2008 [42]</td>
<td>Newly diagnosed NMIBC</td>
<td>NR</td>
<td>NR</td>
<td>−€455 (approximately −€553) over first year</td>
</tr>
</tbody>
</table>

BLC = blue-light cystoscopy; HAL = hexaminolevulinate; NMIBC = non–muscle-invasive bladder cancer; NR = not reported; TURBT = transurethral resection of bladder tumour; WLC = white-light cystoscopy.
In conclusion, by improving lesion detection and resection, HAL-guided BLC leads to more appropriate patient management, with less need for repeat procedures and hospital visits as a result of reduced risk of recurrence and longer recurrence-free survival compared with WLC. Thus, over the lifetime management of a patient, BLC is associated with improved QALYs and reduced costs compared with WLC. Because of the need to invest in specialist equipment up front, hospitals adopting BLC for the first time may find that it takes longer to achieve cost benefits with HAL; however, once the equipment is in place, the turning point at which use of HAL becomes cost-effective is much sooner. Given the clinical benefits for patients and the need for lifelong management of these patients because of the risk of recurrence, we believe that short-term economic arguments about the initial costs of treatment should not prevail, and patients should not be denied access to HAL on the basis of the fact that the cost benefit would not be achieved immediately. Over the long term, there is a clear benefit with HAL-guided BLC versus WLC, both for the health care system and, critically, for the patient.

3.3. Potential future uses of hexaminolevulinate-guided blue-light cystoscopy

In the hospital inpatient setting, the evidence is clear that HAL-guided BLC improves the detection and resection of NMIBC and thereby reduces recurrence risk and costs while improving quality of life for patients. With increasing duration of follow-up, evidence is beginning to emerge on the potential role of BLC in reducing progression risk, although initial results (with relatively short follow-up periods) have not shown any significant difference between BLC and WLC in this regard [12,16]. However, a recent analysis of five hundred patients in France has shown a statistically significant difference in progression-free survival in favour of BLC over WLC (although the odds ratio between the two groups was not significant) [47]. We await further long-term analyses of the impact of HAL-guided BLC on progression with interest.

Future developments that could improve patients’ experience would ideally focus on reducing hospital stay by improving outpatient detection and management of NMIBC—for example, by combining BLC with flexible cystoscopy in specific settings, such as surveillance of high-risk patients and monitoring of BCG induction efficacy. BLC also holds promise in assisting new techniques to achieve en bloc resection (eg, using the water-jet HybridKnife system [48,49]), by helping to visualise tumour margins and confirming complete clearance of lesions.

4. Conclusions

We recommend that HAL-guided BLC be used for all patients at initial TURBT to increase detection and improve the quality of resection, thereby reducing the risk of recurrence and improving outcomes for patients. Another clear indication is abnormal urine cytology but no evidence of lesions on WLC, because BLC can identify CIS that may have been missed on WLC. In addition, we advise the use of HAL-guided BLC as part of routine inpatient cystoscopic assessment following initial TURBT to confirm the efficacy of treatment and to identify any previously missed or recurrent tumours. Health economic modelling indicates that the use of HAL to assist primary TURBT is no more

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**Fig. 2 – 2013 updated consensus recommendations on the use of hexaminolevulinate-guided blue-light cystoscopy.**

- **BCG** = bacillus Calmette–Guérin; **BLC** = blue-light cystoscopy; **CIS** = carcinoma in situ; **HAL** = hexaminolevulinate; **TURBT** = transurethral resection of bladder tumour.

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expensive than WLC alone and will result in improved QALYs and reduced costs over time, and the clinical benefits for patients are clear. Figure 2 summarises our recommendations about the points during the patient’s management pathway at which HAL-guided BLC may add value.

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**Drafting of the manuscript:** Witjes.

**Critical revision of the manuscript for important intellectual content:** Babjuk, Gontero, Jacqmin, Karl, Kruck, Mariappan, Palou Redorta, Stenzl, van Velthoven, Zaak.

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