

## CONSENSUS DOCUMENT

# Consensus Document on Therapy With Bath Psoralen-UV-A

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**Abstract.** Bath PUVA is a variant of phototherapy as efficacious as oral PUVA therapy that avoids many of the adverse effects associated to this treatment. Nevertheless, the special features and the specialized equipment required for its employment have limited its application in the dermatologic clinics of our country. Following the trend initiated after the publication of the consensus document on oral PUVA therapy and narrow band (NB) UVB therapy, the Spanish Photobiology Group from the Spanish Academy of Dermatology and Venereology has developed a therapeutic guideline for bath PUVA therapy based on the literature review and the experience of its members. The document aims to be a practical reference guide for those dermatological centres that include phototherapy among their services. It reviews the concept and indications of this type of treatment and proposes recommendations concerning therapeutic procedures, drug associations of interest and prophylaxis and management of adverse effects.

**Key words:** phototherapy, PUVA, bath PUVA, ultraviolet.

## DOCUMENTO DE CONSENSO SOBRE LA MODALIDAD TERAPÉUTICA DEL BAÑO-PUVA

**Resumen.** El baño-PUVA se reconoce como una variante de fototerapia tan eficaz como la terapia PUVA oral, pero que permite evitar buena parte de los efectos adversos asociados a este tratamiento. Sin embargo, las particularidades de su empleo y la necesidad de utillaje especializado han limitado su uso en los centros dermatológicos de nuestro país. En continuidad con la línea iniciada tras la publicación del documento de consenso de la terapia PUVA oral y la terapia UVB de banda estrecha (BE), el Grupo Español de Fotobiología (GEF) de la Academia Española de Dermatología y Venereología (AEDV), ha llevado a cabo la elaboración, a través de la revisión de la literatura al respecto y la experiencia propia de sus miembros, de una guía terapéutica del baño-PUVA. El documento pretende ser una guía práctica de referencia para aquellos centros dermatológicos que incluyan la fototerapia entre sus prestaciones. En él se revisan el concepto y las indicaciones de esta forma de tratamiento y se proponen recomendaciones referidas a los procedimientos terapéuticos, las asociaciones farmacológicas de interés, la prevención y el manejo de los efectos secundarios.

**Palabras clave:** fototerapia, PUVA, baño-PUVA, ultravioleta.

## Introduction

Bath psoralen–UV-A (PUVA) is a topical phototherapy technique developed in Scandinavia as an alternative to oral psoralen therapy combined with UV-A (oral PUVA). It

involves the application of UV-A radiation after the patient has received a bath containing psoralens diluted in water<sup>1</sup> and, unlike traditional topical PUVA therapy, it allows us to treat large affected areas, leaving a uniform skin color.<sup>2,3</sup>

## Indications

As with oral PUVA, the principal indications for bath PUVA are moderate-to-severe plaque psoriasis with a score of more

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than 10 on the psoriasis area severity index (PASI)<sup>4</sup> and chronic dermatoses of the palms and soles, such as eczema or psoriasis.<sup>57</sup>

The expected response is the same as that of oral PUVA therapy and similar to or somewhat better than that expected of narrow-band UV-B phototherapy.<sup>8-12</sup>

Some studies also report a favorable response in processes such as atopic dermatitis,<sup>13</sup> lichen planus,<sup>14,15</sup> localized scleroderma and linear localized scleroderma,<sup>16,17</sup> urticaria pigmentosa,<sup>18,19</sup> mycosis fungoides,<sup>20,21</sup> or polymorphous light eruptions.<sup>22</sup> However, neither the protocols nor the indications have been clearly established in these cases. According to the clinical experience of the authors of this document, the response is particularly satisfactory in plaque psoriasis, morphea and other types of scleroderma, generalized annular granuloma, and graft-vs-host disease.

## Therapeutic Procedure in Bath-PUVA

### Pretreatment Evaluation

Before treatment, a critical evaluation should be made of whether the treatment is indicated or appropriate and whether alternatives are available. The basic aspects of pretreatment evaluation overlap with those already described for oral PUVA therapy.<sup>23</sup>

However, in bath PUVA, psoralen does not produce systemic effects, thus making it a useful alternative for patients with underlying liver disease in which oral PUVA is contraindicated.<sup>24</sup> The phototoxic effect of psoralen disappears quickly after treatment and the patient can return to normal activity without needing additional photoprotective measures.

### Psoralen

Trimethylpsoralen was the first type of psoralen to be used and it is still used in Scandinavia.<sup>25-30</sup> However, the most widely used psoralen in the rest of Europe is 8-methoxypsoralen, since it is more water-soluble and generates less prolonged phototoxicity.<sup>31,32</sup> 5-methoxypsoralen is rarely used in this format.<sup>33</sup>

### Determination of the Minimum Phototoxic Dose

It is generally agreed that the ideal therapeutic protocol should be based on the minimum phototoxic dose (MPD). To determine this dose, the patient must take a bath with 8-methoxypsoralen (see below for recommended

concentration) for 15 minutes, before immediately undergoing irradiation of 5 unexposed areas (buttocks) measuring 2 × 2-cm with UV-A lamps. The first area receives a dose of 1 J/cm<sup>2</sup>, which is then increased by 1 J/cm<sup>2</sup> in each of the 4 remaining areas. The MPD will be the minimum dose of UV-A to produce a perceivable erythema with well-defined edges.<sup>34</sup> Given that this is a delayed response test, the day the reading is taken is essential for a well-designed protocol. This should be at 72 and 96 hours.<sup>35</sup>

### Preparation of the Bath

The final concentration of 8-methoxypsoralen should be 2.5 mg/L, which is reached by diluting 36 mL of an alcohol-based solution of 8-methoxypsoralen to 1% in 140 L of water.

The bath water should be kept at a temperature of 37°C to 42°C, as there is no significant difference in MPD within this range.<sup>36</sup> With a view to minimizing severe phototoxic reactions, the temperature must remain constant, since any variations can affect the absorption of 8-methoxypsoralen.<sup>36-38</sup>

The bath lasts 15 minutes and during this time absorption is greater in areas affected by lesions.<sup>39,40</sup>

### Phototherapy Session

Once the patient receives the bath, irradiation is applied immediately or within a maximum interval of 10 minutes in a conventional phototherapy booth<sup>41</sup> that emits ultraviolet radiation at a wavelength ranging from 320 nm to 400 nm (UV-A). The patient must use ultraviolet protective goggles when in the cabin and the genital area must be protected in the same way as when PUVA therapy is administered orally.

### Procedure, Initial Dose, and Increases With Each Session

The initial dose of UV-A is 20% to 30% of the MPD, with increases of 20% to 30% of the previous dose per session, as long as the patient does not present erythema, in which case the increases will be every 2 to 3 sessions.<sup>42</sup>

If the MPD is not determined, the initial dose is administered according to the phototype<sup>4</sup> as shown in Table 1.

### Frequency of the Sessions and Maximum Number of Treatments

The patient receives 3 sessions per week (Monday, Wednesday, and Friday) with the goal of reaching a PASI

**Table 1.** Initial Dose According to Phototype

Phototype	Initial Dose (J/cm <sup>2</sup> )	Increases per Session or Alternate Session
II-III	0.25	50% of previous dose
IV-V	0.5	50% of previous dose

**Table 2.** Reduction of the Initial Psoriasis Area Severity Index at the End of Treatment

<30%	30%-60%	60%-90%	90%-100%
Poor response	Moderate response	Favorable response	Excellent response

of 0 or a 90% reduction in the initial PASI during the bleaching phase.<sup>43</sup>

Response to treatment is evaluated according to the difference in PASI at the end of therapy with respect to the baseline PASI. Thus, different categories in the response can be distinguished,<sup>4</sup> as shown in Table 2.

The number of sessions depends on whether the therapy goals are attained—in most cases these are reached within the first 20 sessions.<sup>44,45</sup> If more than 20 sessions are necessary, treatment should be suspended if a response is not obtained after an extra week of treatment.<sup>46</sup>

## Approach to Missed Sessions

The lack of a standard protocol in situations such as these, which are quite common in daily practice, means that the same regimen as that used in oral PUVA therapy should be recommended, not forgetting that erythema is more likely in this modality<sup>23</sup>:

1. If the patient misses 1 session, repeat the previous dose.
2. If the patient misses 2 or 3 sessions, the dose should be 25% to 50% of the last dose administered.
3. If 4 sessions are missed, treatment should be restarted.

## Maintenance Regimens

As with oral PUVA, the clinical response achieved during the bleaching phase will make for prolonged remission in most patients. Therefore, maintenance regimens are not recommended in psoriasis; these should be reserved—with a frequency similar to that reserved for oral PUVA therapy—for those patients who present rapid recurrences after previous regimens, or in those patients for whom alternatives were not indicated or were not effective.<sup>47</sup>

In the maintenance sessions, fixed doses corresponding to the maximum dose per session during the bleaching phase will be used.<sup>3</sup>

Similarly, maintenance regimens have been proposed for localized scleroderma (twice per week, 10 treatments; once per week, 5 treatments), mycosis fungoides (2-3 times/week, 2-4 weeks), and graft-vs-host disease (twice per week, 1 week; once per week, 4 weeks).<sup>16,21,48</sup>

## Modifications to the Protocol in Dermatoses Other Than Psoriasis

In the other conditions in which bath PUVA is indicated, the protocol is similar to that described for psoriasis.<sup>49</sup>

In dermatosis of the palms and soles, the protocol does not vary with respect to bath temperature or the time until irradiation after the bath. The dilution should be 1 mL of 8-methoxypsoralen at 1% in 1 L to 2 L of water (a final concentration of 5-10 mg/L). The initial dose of UV-A will be 0.5 J/cm<sup>2</sup>, with increases of 0.25 J/cm<sup>2</sup>, and the bath will last 30 minutes.

## Side Effects of Bath PUVA

In bath PUVA, adverse reactions are mainly localized and include Koebner (isomorphic) response or the entire range of phototoxic reactions.<sup>32,50,51</sup> Absorption of psoralen is minimal, with the result that there are no systemic effects.<sup>27,52</sup>

## Acute Side Effects

1. Phototoxic erythema: this generally presents at the fourth session when the MPD falls to 50%,<sup>53</sup> or during the last stage of PUVA therapy, when the UV-A dose is high and phototoxicity reactions arise mainly from accidental splashes on untreated areas such as the face or in skin folds.<sup>54</sup>
2. Pruritus: this is a common symptom in patients affected by extensive psoriasis.<sup>55,56</sup> During therapy, this often presents during the fourth session, coinciding with erythema. Although its significance is unknown, it may precede a phototoxic response.<sup>57</sup> In any case, it is almost always associated with treatment-induced xerosis and responds to oral antihistamine drugs and emollients.<sup>58,59</sup>
3. Skin pain: this symptom was reported in 1979 as a burning sensation that was very different from pruritus and induced by oral PUVA<sup>60</sup> and by bath PUVA.<sup>61</sup> This uncommon side effect can alter sleep cycles. It occurs in normal skin, and is not related to a prior history of cutaneous lesions. It appears at 4 to 8 weeks after the start of treatment and persists even when treatment has stopped. It can continue

**Table 3.** Patient Information Sheet

<p>You are about to undergo a treatment known as bath PUVA. This involves your skin being exposed to ultraviolet A (UV-A) radiation after a bath with a photosensitizing substance (psoralen) that aims to boost the therapeutic effects of this source of radiation.</p> <p><b>Advice for the Treatment</b></p> <p><i>Before the Session</i></p> <ul style="list-style-type: none"> <li>– Some topical products (those applied directly to the skin) may interfere with UV-A radiation or produce adverse effects. Therefore, avoid using topical products on your skin for at least 2 hours before the session. Also avoid soaps, after-shave, eau-de-cologne, perfume, and deodorants on the day of your treatment session.</li> </ul> <p><i>During the Session</i></p> <ul style="list-style-type: none"> <li>– Your eyes must be protected throughout the session. The nurse will provide you with goggles that you must wear during the session. Do not remove the goggles during the session. If you have lesions on your eyelids, consult your doctor before undergoing treatment.</li> <li>– Men must protect their genital region with black underpants. The best style is a thong, and it should be used at all the sessions.</li> <li>– You should stand in the center of the booth at an equal distance from the fluorescent tubes.</li> </ul> <p><i>After the Session and During the Rest of the Day</i></p> <ul style="list-style-type: none"> <li>– After the phototherapy session, you will be taken to a shower area. This is an important part of the treatment, as it allows you to eliminate the remains of psoralen so that you have no problems with the UV-A radiation in sunlight.</li> <li>– The treatment may make your skin appear drier than usual. Use emollients (moisturizing creams) after the sessions and at home, but not before the sessions.</li> <li>– Although with this form of treatment there is a very low possibility of experiencing problems with sunlight, you should avoid exposure for 3 to 4 hours after the treatment. You do not need to wear sunglasses. Follow the complementary topical and/or oral treatment recommended by your doctor.</li> </ul> <p><i>Throughout Treatment</i></p> <ul style="list-style-type: none"> <li>– Inform the doctor at the phototherapy unit of any new drug you are prescribed.</li> <li>– Inform the doctor at the phototherapy unit or the nurse of any doubt or side effect related to the treatment.</li> </ul>	<ul style="list-style-type: none"> <li>– Try to attend all the programmed sessions. If you are unable to go, tell your doctor or the nurse so that they can adjust the dose.</li> <li>– In order to avoid cumulative doses of UV-A, you must not expose yourself to sunlight during the treatment. Take special care with footwear such as sandals: these should not be worn during the treatment.</li> </ul> <p><i>What Side Effects Might I Suffer?</i></p> <p>Bath-PUVA is a safe treatment in the hands of experienced professionals. However, as can occur with other treatments, there may be side effects. The following are the most frequent:</p> <ul style="list-style-type: none"> <li>– Reddening of the skin and burning sensation, itching, or skin pain. This is due to the fact that, even though the treatment protocol is applied according to skin type, treatment is sometimes tailored to individual patients. If you notice this side effect, inform your doctor or nurse before the session.</li> <li>– Dry skin: use abundant moisturizing cream after the sessions. A soft gel or syndet should be used for the bath or shower.</li> <li>– Skin color. Your skin color will be similar to or darker than a summer suntan.</li> <li>– As is the case with sunlight, excess PUVA therapy can produce photoaging lesions (wrinkles, spots) and may even increase the long-term possibility (in the case of many sessions over the years) of suffering from skin cancer.</li> <li>– Consult your doctor about any other adverse event you experience during the treatment and that you consider may be related to treatment.</li> </ul> <p><i>How Long Will Treatment Last?</i></p> <p>Each complete cycle of treatment lasts 20 sessions on average. This means attending 2 or 3 days per week for at least 2 months. However, more or fewer sessions may be necessary depending on the individual case.</p> <p>Once again, remember that, in order to make suitable progress, you must adhere to the treatment. Missing a session can make treatment less effective and longer, and may increase the probability of suffering from side effects.</p> <p>Do not be discouraged if the results are not as you expected after the first few sessions; the therapeutic effects are not noticed until the first 8 to 10 sessions have been completed.</p>
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for 1 to 2 months<sup>60,61</sup> and has been treated with topical capsaicin<sup>62</sup> and gabapentin.<sup>63</sup>

4. Lentiginosities: these profuse pigmented macules appear on exposed areas.<sup>64,65</sup> Prevalence in PUVA-treated patients is high, especially when high cumulative total doses of UV-A have been administered,<sup>66</sup> and in those with a low phototype.<sup>67</sup>

5. Residual hyperpigmentation: this frequent sign appears on those areas where the patient presented lesions and is more evident when bleaching has occurred. It has been described in combined therapy with calcipotriol and oral PUVA,<sup>68</sup> and when calcipotriol is used in bath PUVA therapy.<sup>69</sup>

## Strategies for the Prevention of Side Effects

In order to prevent erythema, it is essential to ensure that the technical conditions of the procedure—water temperature, psoralen concentration, and time until irradiation—are strictly adhered to. It is also wise to ensure that the patient understands the objective of the post-treatment shower, that is, to eliminate psoralen from the skin surface.

## Modifications to the Protocol Due to Acute Side Effects

According to the report by Collins et al<sup>34</sup> on the severity of erythema, if the patient presents painful erythema with edema that persists for more than 24 hours (grade 3), treatment should be postponed until the erythema resolves. If the erythema is evident but does not cause discomfort (grade 2), treatment should be postponed until the erythema remits. In the case of almost imperceptible erythema (grade 1), the previous dose should be administered and should not be increased until 96 hours have elapsed.<sup>70,71</sup>

## Chronic Secondary Effects

Although it has been suggested that bath PUVA presents a lower risk of carcinogenesis, this has not been proven in practice. Prevention strategies are similar to those described for oral PUVA.

## Therapeutic Combinations

As is the case for oral PUVA therapy, the addition of oral retinoids can improve the results of bath PUVA.<sup>72-74</sup> Acitretin can be prescribed at 0.5 mg/kg/d before initiating photochemotherapy and can be maintained for 4 to 5 weeks.<sup>75</sup>

Combined therapy with calcipotriol and bath PUVA has proven effective, although the drug must be applied afterwards (8-hour interval) and not before the sessions.<sup>76</sup>

### Conflict of Interests

The authors declare no conflicts of interest.

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