Evidence-based Management of Head Lice

A group of professionals involved in health care and research, including those working in the fields of pediatrics, pediatric dermatology, family medicine, clinical pharmacy, and school nursing, convened at a roundtable to discuss ways in which they might collaborate to improve the management of head lice infestations. This newsletter focuses on information shared and issues discussed during the roundtable, in particular, the development and utilization of evidence-based treatment plans to manage head lice infestations.

In the United States (US), infestations with head lice *(Pediculus humanus capitis)* are common among children of preschool and elementary school age as well as their household members and caretakers.[1] Although reliable data on the number of infestations are not available, it is estimated that between 6 and 12 million infestations occur every year in children 3 through 11 years of age.[1] Before the development of modern head lice treatments, common remedies included inorganic poisons, botanical treatments, and petroleum products. Since then, several other pediculicides with varying efficacy and safety profiles have been introduced.[2]

CURRENT PARADIGM FOR MANAGING HEAD LICE INFESTATIONS

Most cases of head lice are diagnosed by a parent, caregiver, or school nurse rather than a physician, physician assistant, or nurse practitioner, and most are also treated without the advice of a health care professional (HCP).[3] In an independent market research study conducted in 2009, nearly three quarters of the households contacted acknowledged treating head lice on their own.[3] (**Figure 1**) Parents and caregivers may seek the advice of a trusted source, such as a school nurse or pharmacist, prior to purchasing a treatment, or they may simply call friends or research available treatment options on the Internet.[3] Therefore, head lice treatment is often based on anecdote rather than evidence.

The same survey found that among the households that do contact an HCP when they suspect head lice in a family member, about half are instructed to use an over-the-counter (OTC) product first and to contact the office or make an appointment to see the HCP if treatment fails.[3] For the remaining half who have treatment prescribed by their HCP, OTC products are recommended at about the same frequency as traditional prescription products.[3]

Current head lice treatment guidelines from the US Centers for Disease Control and Prevention (CDC) call for the use of OTC or prescription medications according to label instructions, with retreatment if indicated.[4] The American Academy of Pediatrics (AAP) also recommends initiating therapy with an OTC product, such as 1% permethrin or pyrethrins, providing that a clear diagnosis of head lice has been made and considering its effectiveness and safety, local patterns of resistance (if known), ease of use, and cost.[2]

AVAILABLE TOPICAL TREATMENT OPTIONS

A number of topical pediculicides are currently approved by the US Food and Drug Administration (FDA) as pharmaceuticals to treat head lice infestations.[5] (**Table**) Two of these, synergized pyrethrins and the closely related permethrin, are OTC products that share the same mode of action.[5] Prescription treatments for head lice approved by the FDA include 1% lindane shampoo,[6] 0.5% malathion lotion (Ovide®),[7] 5% benzyl alcohol lotion (Ulesfia®),[8] 0.9% spinosad suspension (Natroba®),[9] and 0.5% ivermectin lotion (Sklice®).[10] (**Table**)

CLINICAL CHALLENGES: WHEN CASES OF HEAD LICE PERSIST

Treatment of a head lice infestation should not be initiated unless there is a clear diagnosis.[2] The diagnosis of a head lice infestation is best made by finding a live nymph or adult louse on the head; however, lice are very small, avoid light, and can crawl quickly, making them difficult to find.[2,11] Egg cases (nits) often are seen on hair,

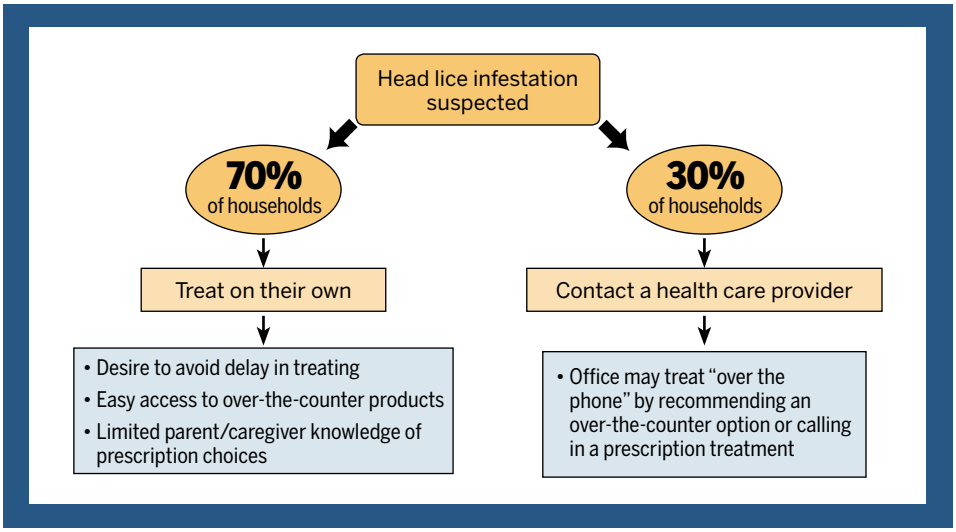

FIGURE 1. Traditional paradigm for diagnosis and treatment of head lice infestation.[3]

commonly behind the ears and near the nape of the neck, but those that are attached to the hair shaft more than one-quarter inch from the scalp are often non-viable.[2,11] Because head lice are not easily seen, it may also be difficult to ascertain whether another member of the family or a contact of the patient is free of head lice, providing an opportunity for the patient to be re-infested.[12] Re-infestation may be misinterpreted as persistence of the original infestation.[12]

Head lice infestations can persist despite treatment with an FDA-approved pediculicide.[2] Possible explanations for persistence include misdiagnosis, patients' unwillingness or inability to adhere to the treatment protocol, inadequate treatment (eg, an insufficient amount of product used to saturate the hair), re-infestation following treatment, and resistance to the pediculicide used.[2] Furthermore, not all the currently available pediculicides have the same ovicidal effectiveness or residual activity; they may necessitate reapplication to kill any eggs that hatch after the initial treatment and thus lead to self re-infestation.[2,11]

TABLE. FDA-approved head lice pharmaceuticals[5-10]

Over the Counter	• Nix®,[a] (permethrin, 1%) • RID®,[b] et al (pyrethrins with piperonyl butoxide)
Prescription	• Lindane[c] 1% shampoo • Ovide®,[d] (malathion, 0.5% lotion) • Ulesfia®,[e] (benzyl alcohol, 5% lotion) • Natroba®,[f] (spinosad, 0.9% suspension) • Sklice®,[g] (ivermectin) Lotion, 0.5%

[a] Nix® is a registered trademark of Insight Pharmaceuticals, LLC; [b] RID® is a registered trademark of Bayer HealthCare, LLC; [c] Lindane is manufactured by Morton Grove Pharmaceuticals; [d] Ovide® is a registered trademark of Taro Pharmaceuticals, USA, Inc; [e] Ulesfia® is a registered trademark of Shionogi Inc.; [f] Natroba® is a registered trademark of ParaPRO LLC; [g] Sklice® is a registered trademark of Sanofi Pasteur Inc.

IS RESISTANCE TO PERMETHRIN INCREASING?

Studies from the 1980s and 1990s demonstrated that a single treatment with permethrin, with or without nit combing, was highly effective in removing head lice infestations.[13-16] However, studies undertaken in the twenty-first century suggest that this may no longer be the case, and that even 2 applications may be ineffective in more than 50% of treatments.[17-21] Results from all of these studies are summarized in **Figure 2**.

In 1986, a study conducted in multiple states indicated that 1% permethrin crème rinse was significantly more effective for eliminating lice than 1% lindane shampoo (99% vs 85%; $P<0.001$).[13] In 1988, studies in North Carolina, South Carolina, and Arizona reported head lice elimination in 96%-100% of patients treated with 1% permethrin, and 62%-94% of those treated with 0.3% pyrethrins.[14,15] A study 10 years later in California continued to report an elimination rate close to 100% with 1% permethrin, comparable to that with 0.3% pyrethrins.[16] (**Figure 2**)

By 2001, however, clinical trial results suggested that the efficacy of permethrin was waning. A study in California found that a single application of 1% permethrin was effective in only 80% of patients, a rate comparable to a 10-day course of oral trimethoprim/sulfamethoxazole (TMP/SMX, 83%) and lower than the 95% elimination rate in patients treated with the topical permethrin-oral TMP/SMX combination.[17] (**Figure 2**)

Similar outcomes using the permethrin-TMP/SMX combination have not been repeated, but subsequent trials in Florida provided further indication of the decreasing efficacy of 1% permethrin. In a 2004 study, 41% of patients treated with permethrin were free of lice after a single treatment, compared with 81% of those treated with 0.5% malathion lotion.[18] (**Figure 2**) Three years later, the same investigators compared the efficacy of the 2 treatments following a protocol that included retreatment if necessary after 1 week.[19] Treatment was successful in only 45% of permethrin-treated patients, compared to 100% of those treated with malathion lotion ($P=0.0006$).[19]

More recent studies found even lower efficacy rates for 1% permethrin. Two identical multicenter trials compared the efficacy of 0.9% spinosad and 1% permethrin.[20,21] Following a single application, the overall efficacy rates for spinosad were 68% and 76%, compared with 25% and 26% for permethrin.[20,21]

LABORATORY INVESTIGATIONS POINTING TO RESISTANCE

A number of studies have investigated the clinical, parasitological, and genetic mechanisms of potential pediculicide resistance.[5,22] Reports in the mid-1990s from Israel, the United Kingdom, and Europe indicating that head lice were surviving longer periods of exposure to permethrin were accompanied by increasingly frequent anecdotal reports of pediculicide treatment failures in the US.[23] Recent in vitro susceptibility studies in the US suggest that diminished permethrin efficacy may be caused by resistance.[23-25] One bioassay found that head lice from US children who had been treated previously for pediculosis were less susceptible to the effects of permethrin than were head lice in children from Borneo, who had not been exposed to permethrin/pyrethrins.[23] Another small in vitro study demonstrated that permethrin or pyrethrin was effective in killing only 28% of head lice collected from 5 children, even when the lice were immersed in the products.[24]

Another study utilizing a placebo-controlled hair tuft bioassay compared the effectiveness of increasing concentrations of ivermectin (0.25%, 0.5%, and 1.0%) on the mortality response of permethrin-resistant head lice.[25] All ivermectin formulations that were tested killed 100% of lice treated, indicating that

ivermectin is pediculicidal to permethrin-resistant head lice.[25]

MECHANISMS OF PERMETHRIN RESISTANCE

The results of the above studies suggested head lice resistance had emerged to the permethrin/pyrethrins family of insecticides and prompted investigation into the mechanisms of this resistance.[23-27] In other insects, such as house flies, studies have associated genetic mutations—specifically a knock-down resistance (*kdr*) mutation associated with increased nerve insensitivity to these insecticides—with allowing the insects to survive insecticide exposures sufficient to eliminate insects without the mutation.[28] Genetics studies in head lice from California, Florida, Idaho, Massachusetts, and Texas have identified the *kdr* mutation.[26,27] A recent report on worldwide head lice resistance calculated the frequency of the *kdr* mutation as 74% in the US, 80% in South America, 76% in countries in the European Union, 88% in Israel, 48% in Egypt, and 100% in Australia.[28]

Early detection of resistance to permethrin and other pyrethroid pediculicides is critical to slowing or suppressing the spread of resistant head lice.[28] A resistance monitoring system has been developed to predict the frequency of the mutation in large louse populations.[27,28] Such a system may be valuable in developing effective clinical approaches to regional head lice infestations.[28]

DOES IN VITRO PERMETHRIN RESISTANCE CORRELATE WITH CLINICAL FAILURE?

Laboratory evidence suggests that the reports of clinical ineffectiveness and head lice treatment failures may be due to the progressive emergence of resistance as permethrin/pyrethrins continue to be used widely.[29,30] In 1986, the effectiveness of 1% permethrin had been reported as 98% to 99% in populations that had little previous pediculicide exposure.[29] But following widespread use of permethrin/pyrethrins over a number of years, significant decreases in head lice in vitro sensitivity to these pediculicides were reported worldwide, and cure rates in clinical trials in the US and Europe were as low as 23%.[29] Within the US, clinical failures of permethrin have been reported from many states.[30] These findings all point to a growing problem of head lice resistance to permethrin/pyrethrins.

A recent in vitro bioassay study in France, however, suggests that *kdr* resistance alone may not predict clinical failure.[31] Mortality of head lice exposed to permethrin was high, even though the head lice were believed to be carrying the *kdr* mutation, raising the possibility that other mechanisms of resistance might also be at work.[31] The growing number of clinical failures may be due to multiple genetic changes that confer resistance, and the *kdr* mutation may be just a marker of the resistance pattern.[31] Further studies, both laboratory and clinical, are needed to clarify all permethrin resistance mechanisms and to document the relevance of *kdr* genotyping as a predictor of permethrin treatment outcomes. Importantly, while the *kdr* mutation does not necessarily lead to clinical failure, it indicates a strong selection pressure has been applied by the uncontrolled use of permethrin/pyrethrins.[31] As a result, the authors of the French study suggest that use of pyrethroids should be abandoned in areas in which the *kdr* mutation has been identified.[31]

It should be noted that when treatment with permethrin or pyrethrins fails despite their correct use, or when local resistance to permethrin or pyrethrins has been documented, the AAP recommends that other treatment alternatives be considered.[2]

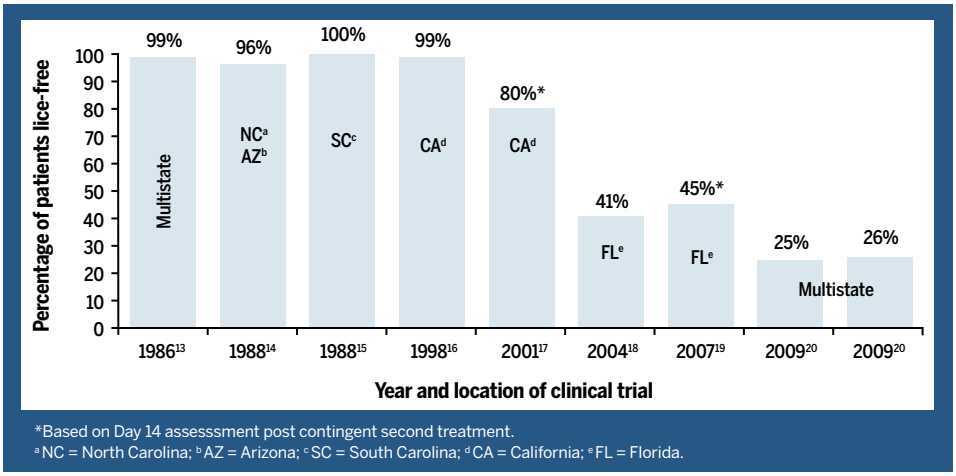

FIGURE 2. Decline in efficacy reported from clinical trials of permethrin, by year and trial location.[13-20]

FDA-APPROVED PHARMACEUTICALS FOR HEAD LICE INFESTATION

Choosing a treatment for head lice infestations must take into account not only increasing treatment failures with permethrin/pyrethrins as first-line treatments, but also factors such as lengthy and age-restricted topical applications, and infestation-related social stigma and absenteeism from school, all pointing to the need for improved therapies.[2,32]

Newer topical agents currently approved by the US FDA include 3 products—5% benzyl alcohol lotion, 0.9% spinosad suspension, and 0.5% ivermectin lotion—each with separate mechanisms of action that differ from traditional pediculicides.[21,32-34]

Benzyl alcohol lotion, approved for patients ≥6 months of age, has no ovicidal activity; therefore, 2 treatments are required 1 week apart, the second to eliminate head lice emerging from nits present when the first treatment was applied.[8,34] In 2 clinical studies in patients ≥6 months of age, a 10-minute application of 5% benzyl alcohol lotion with retreatment 1 week later led to overall treatment success rates of 76% and 75% at 14 days after the second application.[8,34] No serious adverse events were reported in the combined study safety database.[34]

Another prescription product, 0.9% spinosad suspension, is indicated for use in patients ≥4 years of age.[9] In 2 clinical studies, spinosad was more effective without nit combing than 1% permethrin crème rinse with nit combing.[20,21] Spinosad achieved efficacies of 85% and 87% following 1 or 2 treatments (a second treatment was applied if head lice were present 1 week after the first treatment)[9]; single treatments were 68% and 76% effective.[20,21] Equivalent effectiveness of 1 or 2 treatments with permethrin was <50% in the studies.[9] No severe adverse reactions were reported.[21]

A topical lotion formulation of ivermectin has been approved for patients ≥6 months of age.[33] Oral formulations of ivermectin have been used extensively to treat nematode infections and have also been used to treat scabies and stubborn lice infestations.[32] In 2 recent studies, a single application of 0.5% ivermectin lotion without nit combing was significantly more effective than the control in eliminating head lice on the day after treatment and at 1 and 2 weeks after treatment.[32] The effectiveness of 0.5% ivermectin lotion 2 weeks after treatment was 71% and 76%

(vs 16% and 19% for the control; $P<0.001$). No serious adverse events were reported in either group.[32]

HOW SAFE ARE "NATURAL" PRODUCTS?

Another approach to eliminating head lice is the use of so-called "natural" products, which have not been required to meet FDA efficacy and safety standards.[2] That is, the effectiveness of such products has not been demonstrated as it has for those with FDA registration.[2] Perhaps even more importantly, safety has not been established.[2] For example, products containing essential oils (eg, eucalyptus oil, melaleuca oil) have the potential for serious adverse effects, including allergic contact dermatitis and systemic hypersensitivity reactions,[35,36] estrogenic/anti-androgenic properties with development of prepubertal gynecomastia,[37] and ataxia and drowsiness in young children following accidental ingestion of small quantities.[38–40]

CONCLUSIONS

Prescribing/treatment decisions for head lice infestations should be data-based, with careful review of the product labels, including efficacy and safety information. New treatment guidelines based on evidence, rather than anecdote, need to be developed and utilized. The new treatment paradigm should involve better education of—and collaboration among—first-line professionals such as school nurses and pharmacists; early involvement of pediatricians, family physicians, nurse practitioners, and physician assistants; and strategic use of known-effective therapies with established safety profiles based on approved label information and published data.

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