Clinical Update on Resistance and Treatment of *Pediculosis capitis*

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Abstract

The anatomy and physiology of head lice make them extremely adaptable to their human hosts but also difficult to eradicate. Their coloring and small size make them difficult to see, and the larvae, or nymphs, have multiple exoskeletons for protection. When exposed to pediculicides, a nymph can shed its outer exoskeleton and receive only a sublethal dose. Through natural selection, head lice have developed resistance to commonly used pediculicides, making it increasingly difficult to eliminate infestations.

Other contributors to resistance include changes in formulations of pediculicides and improper use. Over the last 20 years, the efficacy of pyrethrins has declined because of necessary safety changes in formulations and unintentional effects of new packaging on chemical components of these products. Pediculicides designed to be applied to wet hair may become too diluted to produce the desired effect. Patients also may use too little product to conserve costs. The combination of decreased product efficacy and exposure of head lice to diluted or insufficient amounts of pediculicides has reduced their effectiveness substantially. Studies comparing the current efficacy of several over-the-counter and prescription pediculicides with effectiveness in the 1980s has shown that OVIDE® (malathion) Lotion, 0.5% is the only product that has retained its efficacy over time. The efficacy of over-the-counter pyrethrin products had declined significantly, and lindane, another prescription product, was least effective of all products tested both in the 1980s and in more recent studies. In addition to retaining its efficacy, malathion 0.5% also is effective when applied for only 20 minutes. The shorter application time is safer for children and also decreases the likelihood that residual product remains in the hair, further contributing to resistance.

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Lice Anatomy and Physiology

Pediculus humanus capitis, or head lice, have lived among humans for thousands of years. Their anatomy and physiology have evolved to make these ectoparasites well adapted to their human hosts. **Figure 1** shows a family of lice. The female (left) is distinguished from the male (center) by her larger size and by the posterior protrusions that create an invaginated "V" structure, which she uses to clasp around the hair shaft to lay eggs. The male has dark brown bands across his back. Unlike the larvae of some other insects, the louse larva, called a nymph or instar (right), looks like a miniature adult louse. The nymph has multiple exoskeletons, which it progressively sheds as it goes through 3 molting cycles before becoming an adult. There are 3 or 4 days between each molt.[1] Third stage instar nymphs are the most difficult to kill with pediculicides because they are protected by their layered exoskeletons. A nymph that has been exposed to a pediculicide can shed its exoskeleton and receive only a sublethal dose, which contributes to resistance. Nymphs that have just molted are most vulnerable to pediculicides. The development of pediculicide resistance might vary during different stages of louse development and molting. At any given time, lice will exist on the host's head at various stages of molting, so they will not all die at once after exposure to a pediculicide.

Lice that have just hatched and have not fed on the host's blood are nearly transparent. The blood of a nymph, called hemolymph, is clear. The red color of a recently fed nymph is due to the host's blood meal. Nymphs are extremely small, at about the size of a 12-point font period at the end of a sentence. Their transparency and size make newly hatched nymphs extremely difficult to see during examination. Nits, the eggs laid by lice, are attached to the hair shaft with an adhesive substance. Since they are stationary, nits are actually easier to find and remove than nymphs.

The feeding structures of lice are complex, including the haustellum, a proboscis-like tube with teeth, which is used to pierce the host's skin, and a cibarial pump that draws blood through the haustellum. The teeth of the haustellum anchor it to the host's skin while the louse feeds. There are 3 stylets within the haustellum, as shown in **Figure 2**. Two of the stylets inject a substance to make feeding easier, including an anticoagulant and a vasodilator, while the third is used to draw back the blood to feed. The mouthparts retract when the louse is not feeding.[1] The ability of lice to anchor themselves while feeding, as well as their color and small size, make it nearly impossible to identify and remove them manually through nit combing.

There is no information to date suggesting that head lice spread disease, but research is ongoing. Body lice are known to spread diseases such as typhus, relapsing fever, and trench fever, a reemerging disease in the United States caused by *Bartonella quintana.* Information about disease transmission was derived from colonies of body lice that have been maintained and studied on rabbits, but no similar colony of head lice exists. Although attempts have been made, head lice will feed only on human blood.

Figure 1. Female and Male Adult Lice and Nymph

Contributors to Resistance

Over the last 2 decades, pediculicide packaging and formulations have changed, contributing to resistance. The synergized pyrethrin RID® was originally packaged in brown glass bottles. When permethrin 1% (Nix®) was introduced to the market in a plastic bottle and received favorable consumer attention, the manufacturers of RID repackaged their product in plastic. They did not realize that plastic affected the formulation, decreasing its efficacy. Another pyrethrin, A-200®, caused irreversible corneal damage in some patients, so the formulation was modified. Neither product is as efficacious as it was during studies conducted in the 1980s.[2]

Another contributor to resistance is the dilution of pediculicides that are designed to be applied to wet, towel-dried hair. The amount of water left in towel-dried hair is very subjective, and some hair types naturally retain more water than others. Patients also may apply too little product, often because more than 1 family member is infested. Conserving product also conserves costs. When pediculicides are diluted or are used too sparingly, lice are exposed to sublethal doses and eventually develop resistance. Conversely, patients may use too much product or may use it as preventive treatment when there is no lice infestation. Resistance may develop from overexposure to pediculicides.

Clinical Efficacy of Pediculicides

An in vitro study was conducted in April 2000 to assess the extent to which the efficacy of pediculicides had changed since the early 1980s because of alterations in their

Figure 2. The 3 Stylets Within the Haustellum

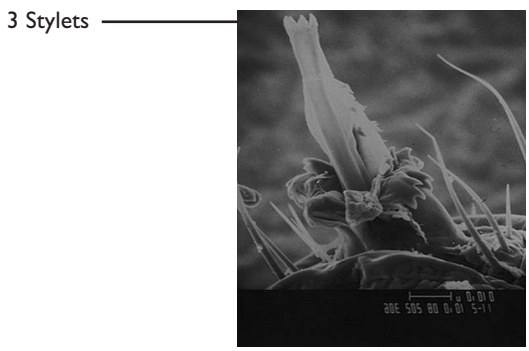


Table 1. Comparative Pediculicidal Activity: 1984 to 2000

Comparative Ranking of Activity (1 = Most Effective)	
1984 Ranking	**2000 Ranking**
1. Malathion 0.5% (OVIDE®)	1. Malathion 0.5% (OVIDE)
2. Pyrethrin (RID®)	2. Undiluted permethrin 1% (Nix)
3. Pyrethrin (A-200®)	3. Diluted permethrin 1%
4. Lindane	4. Pyrethrin (A-200)
Undiluted permethrin 1% (Nix®) – N/A	5. Pyrethrin (RID)
Diluted permethrin 1% (Nix®) – N/A	6. Lindane

N/A indicates not applicable; product was not marketed in 1984.
Sources: References 2 and 3.

formulations.[2] The pediculicidal and ovicidal activities of 5 head lice products were evaluated using head lice and eggs harvested from healthy children in Panama, where lice are still sensitive to most therapies. Results from this study were compared with an earlier 1984 study evaluating pediculicide efficacy in Panama.[3] The comparative ranking of the products is presented in **Table 1**. There was no change from 1984 to 2000 in the ranking of malathion 0.5% as the most effective product. Permethrin 1% was not marketed in 1984 for the first study. In the second study, permethrin 1% was evaluated in diluted and undiluted form because the product is applied to damp hair and, as stated, dilution may affect efficacy. A follow-up study was conducted from July through November 2000 to assess the efficacy of the same 5 products in killing lice harvested from people in a south Florida clinic. The Florida study was a replication of the Panama protocol, using the same products and methods. However, people attending the south Florida clinic had treated themselves before seeking care, so the lice collected were thought to include both sensitive and treatment-resistant specimens. The main outcome measure was the percentage of lice dead at regular observation intervals between 5 minutes and 3 hours of continuous exposure to the pediculicides. Results are presented in **Table 2**.

Of the 5 products tested, malathion 0.5% produced the fastest and most effective result, killing 88% of lice at 10 minutes and 100% at 20 minutes. The second most effective product, the pyrethrin A-200, killed 60% of lice at 20 minutes, 82% at 1 hour, and 100% at 3 hours. Although synergized pyrethrin has the same active ingredients as A-200, it killed only 8% of lice in 20 minutes and only 34% after 3 hours of continuous exposure. It is likely that the disparity in efficacy between these 2 products is because of differences in formulations and methods of delivery. The slowest and least effective product was 1% lindane shampoo, which killed only 2% of lice at 20 minutes, 8% at 1 hour, and only 17% after 3 hours of continuous exposure.[3]

Efficacy of Adjunctive Nit Combing

Another study evaluated the efficacy of combing as an adjunct to treatment with

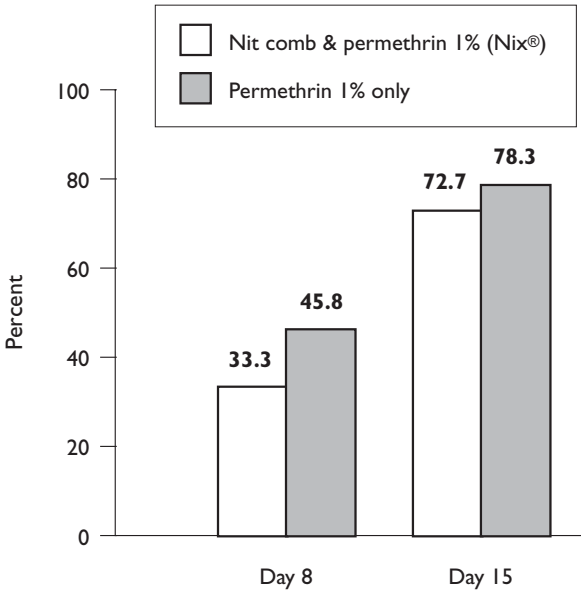
Table 2. Comparative Efficacy of Pediculicides in Resistant Head Lice in the United States

	% Dead at 20 Min*		% Dead at 1 Hour*		% Dead at 3 Hours*	
Pediculicide	**Panama**	**Florida**	**Panama**	**Florida**	**Panama**	**Florida**
Malathion 0.5%	100†	100†	100†	100†	100†	100†
Pyrethrin (A-200®)	97	60‡	99	82‡	100	100†
Undiluted permethrin 1%	90	10‡	100	49‡	100	74‡
Diluted permethrin 1%	73	8‡	94	18‡	100	46‡
Pyrethrin (RID®)	73	8‡	50§	21‡	53	34‡
Lindane	17	2‡	15	8	61	17‡

*Data are percentage of lice.
†All lice were dead at this time interval at both sites; χ^2 statistic cannot be calculated.
‡$P < .001$.
§Resurrection effect (knocked down and appeared dead but revived).
Source: Reference 3.

permethrin.[4] The study was performed because it is commonly believed that repeated combing with a fine-toothed comb is an effective way to eradicate lice. The National Pediculosis Association, a consumer organization, promotes wet combing alone as adequate therapy and markets a nit-removal comb (LiceMeister). The patient population for this study was located in south Florida. All 95 patients in the study were treated with permethrin 1%, and one third were given a nit-removal comb and instructed in its proper daily use. Each person in a household was given an individual, numbered comb and instructed not to share it to prevent the transmission of lice from the comb. The group that did not receive combs was asked to not manually remove nits (using fingers or other types of combs). Patients were evaluated at 8 and 15 days. If lice were observed at day 8, patients received a second treatment with permethrin. Results are presented in **Figure 3**. At day 8, nearly 46% of patients who received permethrin treatment alone were free of lice, compared with 33% of those using adjunctive combing. At day 15, a higher percentage of patients in the permethrin-only treatment group were lice-free, although the difference between the groups was not statistically significant. Overall, the combing group had a higher treatment failure rate compared to patients who did not comb. Nit removal combing performed by caregivers and advocated in the United States by many schools and consumer organizations was not effective as an adjunct to treatment with pediculicides and therefore is not an appropriate method of lice eradication when used alone.[4]

Figure 3. Lice Eradication With and Without Nit Combing



Residual Pediculicide Effects: A Contributor to Resistance

Pediculicides often have residual effects even after being rinsed from the hair. These effects were previously viewed as beneficial, providing continued protection from infestation. Over time, lice exposed to sublethal residual pediculicides adapted and became resistant to some agents. Residual effects are now considered undesirable because of their long-term contribution to pediculicide resistance.

One approach to reducing residual effects is limiting the amount of time the pediculicide is left on the hair and scalp, thereby potentially reducing residue. Decreasing exposure time raises the question of whether pediculicide efficacy declines, however. A study was recently conducted to evaluate the efficacy of malathion 0.5% applied for 20 minutes and permethrin 1% applied as labeled for 10 minutes. The original labeling for malathion 0.5% dates to the product's introduction to the market and recommends an application time of 8 to 12 hours specifically to promote residual effects. A second objective of the study was to determine whether the 10-minute application for permethrin 1% retained the same efficacy it had when it was introduced in 1986. Patients were treated with either malathion 0.5% or permethrin 1% and were evaluated at 8 and 15 days for the presence of live lice and viable nits. Among the 66 patients enrolled in the study, 44 were treated with malathion 0.5% and 22 were treated with permethrin 1%. At day 15, 98% of patients treated with malathion 0.5% and 55% of patients treated with permethrin 1% were free of lice and viable nits ($P < .0001$). Malathion 0.5% applied for 20 minutes was

effective without producing residual effects. Permethrin 1% demonstrated decreased efficacy compared to its documented pediculicidal effects in 1986.[5,6] Malathion 0.5% is effective in killing lice and nits during all stages of parasitic development and molting.

Conclusions

Head lice are extremely host-specific, feeding only on humans, and have demonstrated increased resistance to pediculicides. Current clinical data demonstrate that most pediculicides do not meet advertising claims of "killing lice on contact." Slow pediculicidal action, ineffective formulations, and sublethal residue on the hair and scalp have contributed to resistance over time. Malathion 0.5% is the only pediculicide that has retained its efficacy, killing both lice and nits.[2,3] Other commonly used products have demonstrated resistance in the United States. Although malathion resistance has been documented in the United Kingdom, the formulations there are very different from OVIDE that is sold in the United States. The US formulation includes synergistic components to deter the development of resistance. When US-manufactured OVIDE was tested on malathion-resistant lice from the United Kingdom, it maintained its efficacy.[7] Recent data suggest that a decreased application time for OVIDE is effective without producing residual effects.[5] The reduced application time is beneficial for the pediatric population, particularly in terms of limiting the risk for potential adverse events, such as itching or burning of the scalp.

Of particular interest is the failure of nit combing to produce better outcomes, even when used as an adjunct to pediculicide therapy.[4] Schools and organizations often advocate nit combing as a safe and effective way to eradicate lice and nits. Study results suggest that nit combing is not effective.

The clinical history of pediculicides and the increase in resistance over time strongly suggest the need for better management of therapies that remain efficacious, such as malathion 0.5%. Currently, it is the only pediculicide to demonstrate no resistance and no change in efficacy; however, overuse of malathion 0.5% may lead to resistance in the United States as it has in other countries. Since malathion 0.5% is a prescription product, physicians are urged to regulate its use and to educate patients and others, such as school administrators and public health policy developers, about the proper use of pediculicides.

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