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Original Investigation

Cost-effectiveness of Confirmatory Testing Before Treatment of Onychomycosis

Anar Mikailov, MD; Jeffrey Cohen, MD; Cara Joyce, PhD; Arash Mostaghimi, MD, MPA

IMPORTANCE Onychomycosis is the most common disease of the nail in adults. International guidelines urge health care professionals to perform confirmatory diagnostic testing before initiating systemic therapy. This approach was determined to be cost-effective in studies from the late 1990s but has not been evaluated more recently. The effect of testing on the costs of efinaconazole, 10%, topical solution treatment is unknown.

OBJECTIVE To evaluate the cost and potential harm associated with 3 approaches to onychomycosis evaluation before treatment with oral terbinafine or efinaconazole, 10%.

DESIGN, SETTING, AND PARTICIPANTS A decision analysis that compared the costs of 3 onychomycosis management algorithms based on recently published data of test statistics, disease prevalence, and relevant costs: (1) empirical therapy without confirmatory testing, (2) pretreatment confirmatory testing with potassium hydroxide (KOH) stain followed by periodic acid–Schiff (PAS) evaluation if KOH testing is negative, and (3) pretreatment testing with PAS. There was no direct patient evaluation. Selection of included studies was based on outcome variables and the quality of study design. The study was conducted from April 1, 2014, to September 1, 2015.

MAIN OUTCOMES AND MEASURES Primary outcomes included direct cost of onychomycosis testing and therapy and cost to avoid harm when treating patients with oral terbinafine.

RESULTS At a disease prevalence of 75%, per-patient cost savings of empirical terbinafine therapy without confirmatory testing was \$47 compared with the KOH screening model and \$135 compared with PAS testing. The cost of testing necessary to prevent a single case of clinically relevant liver toxic effects related to terbinafine at a prevalence of 75% was between \$18.2 million and \$43.7 million for KOH screening and between \$37.6 million and \$90.2 million for PAS testing. At a prevalence of 75%, KOH screening and PAS testing before treatment with efinaconazole, 10%, saved \$272 and \$406 per patient per nail, respectively.

CONCLUSIONS AND RELEVANCE These results show that empirical treatment with terbinafine for patients with suspected onychomycosis is more cost-effective than confirmatory testing across all prevalence of disease, with minimal effect on patient safety. In contrast, confirmatory testing before treatment with efinaconazole, 10%, is associated with reduced costs. Blanket recommendations for confirmatory testing before systemic therapy should be reconsidered and replaced with recommendations tailored to specific therapies.

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Author Affiliations: Department of Dermatology, Brigham and Women's Hospital, Boston, Massachusetts (Mikailov, Cohen, Mostaghimi); Department of Biostatistics and Bioinformatics, School of Public Health and Tropical Medicine, Tulane University, New Orleans, Louisiana (Joyce).

Corresponding Author: Arash Mostaghimi, MD, MPA, Department of Dermatology, Brigham and Women's Hospital, 75 Francis St, PBB-B 421, Boston, MA 02115 (amostaghimi@partners.org).

Onychomycosis is the most common disease of the nail in adults, with a prevalence of 7% to 14% of individuals in North America.¹⁻⁴ Given the high prevalence of the disease and the potential for clinical misdiagnosis, several international guidelines and reviews have been developed to help health care professionals diagnose and manage potential cases of onychomycosis.^{1,5-7} Although specific guidelines vary, one common thread is the recommendation to histologically confirm the diagnosis of onychomycosis before initiating systemic therapy.

The American Academy of Dermatology's⁷ contribution to the American Board of Internal Medicine's Choosing Wisely campaign reinforces the recommendation for confirmatory testing of onychomycosis before systemic therapy in an effort to minimize wasteful or harmful care. This recommendation is based in part on a study conducted in 1999 by Mehregan and Gee⁶ that compared the cost-effectiveness of empirical therapy vs confirmatory testing in patients with suspected onychomycosis; their results favored confirmatory testing. Although the cost of onychomycosis testing and treatment has changed in the past 15 years, this paradigm has not been reevaluated. For example, a full 12-week course of terbinafine cost \$547 in 1999 compared with \$10 today.^{6,8,9} Simultaneously, the introduction of efinaconazole, 10%, topical solution presents a novel high-cost topical treatment option for patients.

The goal of this study was to perform a decision analysis to evaluate the cost-effectiveness and safety implications of empirical onychomycosis therapy with oral terbinafine or topical efinaconazole, 10%, vs confirmatory testing with periodic acid-Schiff (PAS) or sequential in-office potassium hydroxide (KOH) screening with subsequent PAS testing if KOH testing is negative.

Methods

This study was deemed exempt by the Partners Healthcare institutional review board. The study was conducted from April 1, 2014, to September 1, 2015.

Diagnostic and Treatment Approaches for Decision Tree Design

This decision analysis was based on data from previously published literature. PubMed, the Cochrane Library, and Ovid MEDLINE were searched from January 1996 (the date of terbinafine availability in the United States) to March 30, 2014, using the following search terms: *onychomycosis*, *onychomycosis treatment*, *onychomycosis testing*, *onychomycosis testing sensitivity*, *onychomycosis cost-effectiveness*, and *terbinafine safety*. References of key articles were manually searched to find additional articles. Statistics on terbinafine-induced liver injury were based on data from the National Library of Medicine liver toxicity database.¹⁰

After an initial literature review, we chose to compare 3 pragmatic approaches to diagnosing and/or treating suspected onychomycosis: (1) immediate treatment for all patients clinically suspected to have onychomycosis (ie, without testing), (2) in-clinic KOH screening followed by treatment

for all patients with KOH-positive results and PAS testing for those with KOH-negative results before treatment, and (3) PAS testing before treatment. Models 2 and 3 were chosen based on multiple studies and international guidelines that recommend the use of PAS for out-of-office testing and in-clinic KOH screening as the least costly, most broadly available in-office procedure.^{1,5,11-16}

Assigning Cost and Classification Probabilities

To determine the most accurate statistics of in-clinic KOH and PAS testing, 2 authors (A. Mikailov and A. Mostaghimi) reviewed all identified articles and eliminated those that were not prospective trials in which outcomes included the sensitivity and specificity of in-clinic KOH and PAS test results. Only 2 prospective studies^{13,14} included outcome data for the sensitivity and specificity of both diagnostic tests. The present study used test statistics from the trial by Weinberg et al¹³ given the high prevalence (99%) of onychomycosis in the trial by Haghani et al.¹⁴ The test statistics from Weinberg et al demonstrated in-clinic KOH sensitivity and specificity values of 80% and 72%, respectively, and PAS sensitivity and specificity values of 92% and 72%, respectively. Given the lack of data regarding the effect of KOH testing on sequential PAS testing, we assumed in our model that the performance of PAS was independent of KOH results.

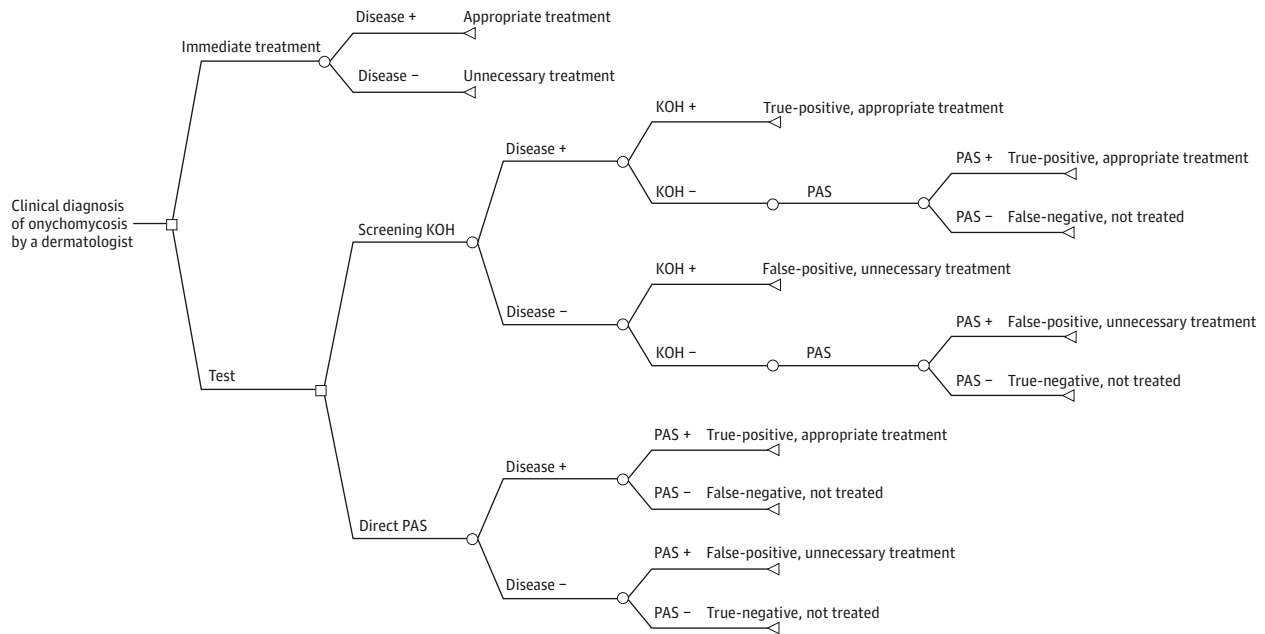
The prevalence of onychomycosis in North America is estimated to be between 7% and 14%.¹⁻⁴ In populations that seek care for nail dystrophy, the prevalence of onychomycosis is 65% to 95%.^{6,12-15} Given the potential for the wide variability in disease prevalence, we modeled cost analyses for prevalences of 30%, 60%, and 90%. In addition, we performed a cost analysis at a prevalence of 75% based on findings from a recent study¹⁷ of patients who had confirmatory testing after a clinical diagnosis of onychomycosis.

A decision tree was created for the 3 management approaches for suspected onychomycosis (Figure). The cost of a 12-week course of terbinafine, 250 mg/d, was assessed at Walmart Stores, Inc,⁸ and Target Corporation.⁹ Costs for efinaconazole, 10%, therapy were based on recommended treatment of 1 nail (1 drop/d for 48 weeks) with mean out-of-pocket cost obtained through telephone calls by one of us (A. Mikailov) to 4 national retail pharmacies: Walmart Stores, Inc (March 12, 2015); Target Corporation (March 13, 2015); CVS Pharmacy (March 12, 2015); and Rite Aid Corporation (March 13, 2015) (Table 1).

The Centers for Medicare & Medicaid Services website provided national reimbursement values for clinical laboratory testing and physician fee schedules.^{18,19} The cost for in-office KOH testing was based on the clinical laboratory fee schedule for *Current Procedural Terminology* code 87220, and the cost for PAS testing was based on a combination of professional costs for trimming the nails (G0127), pathologist examination (88302), and staining the nail (88312).^{18,19}

Alanine aminotransferase and aspartate aminotransferase laboratory codes were included in cost analyses of laboratory monitoring. The final cost calculations were based on application of testing and treatment costs to classification probabilities and disease prevalence.

Figure. Decision Tree for Onychomycosis Management



This tree describes the 3 onychomycosis management strategies evaluated (immediate treatment, screening with potassium hydroxide [KOH], and direct periodic acid-Schiff [PAS] testing). Decisions are indicated by squares; chance outcomes, by circles.

Decision Analysis

Decision tree analysis was performed using TreePlan Pro software.²⁰ *Correct treatment* was defined as a full treatment course for patients with onychomycosis (true-positives) and no treatment for those without onychomycosis (true-negatives). The percentage of individuals who received the correct treatment was calculated for disease prevalence ranging from 0% to 100% by each of the 3 management pathways (eFigure in the Supplement). The cost of testing to avoid 1 incorrect diagnosis was calculated for each treatment plan at prevalences of 30%, 60%, and 90% (Table 2). We evaluated the cost of testing required to avoid liver injury based on the estimated incidence of terbinafine-related liver injury from the National Library of Medicine liver toxic effects database (Table 3).¹⁰

of KOH testing decreased from \$123 to \$92 per patient as the prevalence increased from 30% to 90%. In contrast, per-patient cost for PAS testing increased from \$172 to \$193 as the prevalence increased. At a prevalence of 75%, the cost of the KOH screening pathway was \$100 (\$47 more than empirical therapy), and the cost of the PAS testing pathway was \$188 (\$135 more than empirical therapy).

In contrast, testing before treatment with efinaconazole, 10%, was associated with cost savings across all disease prevalence, with higher savings at a lower prevalence. The net costs of KOH testing increased from \$1548 to \$2197 as the prevalence increased from 30% to 90%. Per-patient cost for PAS testing also increased with prevalence from \$1237 to \$2123. At a prevalence of 75%, the cost according to the KOH screening algorithm was \$2035 (\$272 less than empirical therapy), and the cost of the PAS algorithm was \$1901 (\$406 less than empirical therapy).

Results

Costs of Onychomycosis Therapy

The calculated costs of treatment and monitoring (liver enzymes) associated with a 12-week course of terbinafine for 1 patient was \$53 (Table 1). A full course of efinaconazole, 10%, therapy for 1 nail was \$2307. The costs of confirmatory testing were \$6 for KOH and \$148 for PAS.

Costs for immediate treatment with either drug remained constant since no pretreatment testing was performed, whereas the net costs of KOH and PAS testing varied depending on prevalence (Table 4). The cost for immediate treatment with terbinafine was lower than the cost for either of the testing strategies across all disease prevalence. The cost

Correctly Managed Treatment

We determined the proportion of patients who received correct treatment for each decision tree pathway at various disease prevalence states (Table 4). In all 3 models, the number of patients who received correct treatment increased with prevalence. At a prevalence of approximately 95%, the 3 disease management models converged and demonstrated no marginal diagnostic benefit of performing tests (eFigure in the Supplement).

Avoiding Inappropriate Treatment

Disease prevalence also was significantly associated with rates of inappropriate therapy (ie, treatment for individuals without disease). As the prevalence increased, patients without dis-

Table 1. Costs of Onychomycosis Treatment and Testing

| Characteristic | Total Cost, \$ |
|---|-------------------|
| Efinaconazole, 10%, cost for full treatment of 1 nail | 2307 ^a |
| Terbinafine, 250-mg, full treatment course | 10 ^b |
| Aspartate aminotransferase | 21 ^c |
| Alanine aminotransferase | 22 ^c |
| KOH stain preparation in office | 6 ^d |
| PAS test | 148 ^e |

Abbreviations: KOH, potassium hydroxide; PAS, periodic acid-Schiff.

^a Efinaconazole, 10%, cost is the mean from 4 national US pharmacies sampled randomly by telephone. Full treatment is 1 drop to 1 nail daily for 48 weeks (per telephone calls by one of us [A. Mikailov] to CVS Pharmacy and Walmart Stores, Inc; March 12, 2015).

^b Cost for 90-day treatment was based on Target and Walmart generic costs lists.^{8,9}

^c Costs were based on *Current Procedural Terminology (CPT)* reference codes 84450 and 84460 and multiplied by 3 monthly evaluations (per telephone call by one of us [A. Mikailov] to CVS Pharmacy; March 12, 2015).

^d Cost was based on *CPT* reference code 87220 (to be performed by a health care professional in the clinic) (per telephone calls by one of us [A. Mikailov] to CVS Pharmacy and Walmart Stores, Inc; March 12, 2015).

^e Cost was based on *CPT* procedure code G0127 as well as 2 *CPT* professional pathology codes (88312 and 88302).

ease who received inappropriate treatment decreased, resulting in a smaller marginal benefit for testing. In comparison with the KOH testing pathway, empirical treatment was associated with an increase of patients who received inappropriate treatment (false-positives) of 36% and 5% at 30% and 90% prevalence, respectively. Compared with the PAS testing pathway, empirical treatment was associated with an increase in false-positive treatment of 50% and 7% at 30% and 90% prevalence, respectively. This group of patients will spend money on treatment unnecessarily and lose time using inappropriate therapy.

Testing to avoid false-positive results also generates cost. For terbinafine, our model demonstrated that the marginal per-patient cost to avoid false-positive results increased from \$192 to \$764 for the KOH testing pathway and from \$238 to \$1949 for the PAS testing pathway at 30% and 90% prevalence, respectively.

In contrast, both testing strategies resulted in cost savings when avoiding inappropriate treatment with efinaconazole, 10%. Our model demonstrated that the marginal per-patient cost savings by avoiding treatment for patients without onychomycosis increased from \$2092 to \$2116 for the KOH testing pathway and from \$2123 to \$2559 for the PAS testing pathway at 30% and 90% prevalence, respectively (Table 2).

Cost to Avoid Liver Failure With Terbinafine

The Clinical and Research Information on Drug-Induced Liver Injury Database¹⁰ (a subgroup of the National Library of Medicine) calculates the incidence of clinically apparent liver injury due to terbinafine to be 1 case per 50 000 to 120 000 treatments. Based on the incidence of severe liver injury and cost per patient of testing to avoid a false-positive case, the overall combined cost to avoid clinically apparent liver injury at a prevalence of 75% was between \$18.2 million and \$43.7 million using the KOH screening pathway and between \$37.6 million and \$90.2 million for the PAS testing pathway (Table 3).

Table 2. Additional per-Patient Testing Cost to Avoid 1 Inappropriate Treatment Compared With Immediate Treatment

| Prevalence, % | Cost, \$ ^a | |
|--------------------|-----------------------|--------------------|
| | Terbinafine | Efinaconazole, 10% |
| KOH screening | | |
| 30 | 192 | -2092 |
| 60 | 264 | -2095 |
| 75 | 364 | -2099 |
| 90 | 764 | -2116 |
| Direct PAS testing | | |
| 30 | 238 | -2123 |
| 60 | 452 | -2178 |
| 75 | 751 | -2254 |
| 90 | 1949 | -2559 |

Abbreviations: KOH, potassium hydroxide; PAS, periodic acid-Schiff.

^a The additional per-patient cost to avoid 1 inappropriate treatment (false-positive) was determined by dividing the total cost difference between one of the 2 testing models and immediate treatment, divided by the difference in false-positive diagnoses.

Discussion

The value of confirmatory testing before initiation of treatment for onychomycosis is largely driven by drug costs. Confirmatory diagnostic testing before initiating systemic terbinafine for clinically diagnosed onychomycosis is consistently more expensive than treating all clinically suspected cases of onychomycosis over a wide range of prevalence (30%-90%). Although adverse events from inappropriate treatment with terbinafine for patients without onychomycosis is a concern, our analysis demonstrates that current testing paradigms create a substantial cost burden and require between \$9.62 million and \$233.89 million in testing costs to avoid 1 case of clinically apparent liver injury.

Although adverse effects are less of a concern with efinaconazole, confirmatory testing before treatment yields a substantial reduction in cost, with savings of \$110 to \$1070 per nail depending on the testing strategy and disease prevalence. These savings multiply substantially with the number of nails treated.

Our findings provide a relevant and necessary update to a prevailing paradigm that urges confirmatory diagnostic testing before initiating systemic therapy for onychomycosis.^{1,5-7} The most recent US guidelines⁷ were published as part of the original Choosing Wisely-American Academy of Dermatology campaign and are based on studies published more than 10 years ago.^{5,6} Our analysis demonstrates that changes in the costs of therapy and monitoring over the past 15 years challenge the economic reasoning behind this recommendation for terbinafine.

Experience with terbinafine in the United States over the past 2 decades has defined a relatively benign adverse effect profile and very few clinically relevant toxic injuries. We now know that it is highly unlikely that any given patient will have significant harm from terbinafine exposure.¹⁰ Development of pulse treatment regimens for terbinafine (not included in this

Table 3. Costs of Testing to Avoid 1 Case of Terbinafine-Associated Clinically Apparent Liver Injury

| Model | Cost by Prevalence, \$ (in Millions) ^a | | |
|--------------------|---|-------------|--------------|
| | 30% | 60% | 90% |
| KOH screening | 9.62-23.09 | 13.19-31.66 | 38.19-91.67 |
| Direct PAS testing | 11.91-28.58 | 22.60-54.24 | 97.45-233.89 |

Abbreviations: KOH, potassium hydroxide; PAS, periodic acid-Schiff.

^a Cost was based on an incidence of 1:50 000 to 1:120 000 prescriptions.

analysis) that are not approved by the US Food and Drug Administration that use fewer pills and do not require laboratory monitoring are gaining popularity. These regimens are less costly overall and reinforce the cost savings of empirical treatment.²¹

Confirmatory testing for onychomycosis still has a place in clinical care. The emergence of efinaconazole, 10%, as a novel and expensive agent for the treatment of onychomycosis reinforces the value of confirmatory testing in an era of cost-containment.

These conclusions are most valid when the pretest probability of onychomycosis is highest. The prevalence of onychomycosis in onychodystrophy is likely significantly higher than the previously reported rate of 50%.³ Studies conducted on patients who seek medical care for onychodystrophy demonstrated a prevalence between 65% and 95%.^{6,12-15} Our institutional data demonstrate an onychomycosis prevalence of 75% based on PAS evaluation of toenail clippings for patients who received a clinical diagnosis of onychomycosis by a dermatologist.¹⁷ At this higher prevalence range, the incremental benefits of testing rapidly diminish.

These data must be interpreted in the context of the study design. First, this study includes assumptions about the cost of treatment and testing from the United States and therefore may not be generalizable internationally. Another limitation of this study is the use of testing accuracy data from prior studies. Determination of accuracy for nail plate testing depends on the health care professional performing the test as well as the predefined criterion standard. The statistics applied in our

Table 4. Full Cost for Testing and Treating 1 Patient for Each Decision Tree Model by Prevalence of Onychomycosis

| Model | Cost, \$ ^a | | |
|----------------------|-----------------------|----------------|----------------|
| | 30% Prevalence | 60% Prevalence | 90% Prevalence |
| Immediate treatment | | | |
| Terbinafine | 53 | 53 | 53 |
| Efinaconazole, 10% | 2307 | 2307 | 2307 |
| KOH screening | | | |
| Terbinafine | 123 | 108 | 92 |
| Efinaconazole, 10% | 1548 | 1873 | 2197 |
| Managed correctly, % | 66 | 80 | 94 |
| Direct PAS testing | | | |
| Terbinafine | 172 | 183 | 193 |
| Efinaconazole, 10% | 1237 | 1680 | 2123 |
| Managed correctly, % | 78 | 84 | 90 |

Abbreviations: KOH, potassium hydroxide; PAS, periodic acid-Schiff.

^a Costs are for 1 patient receiving terbinafine and 1 patient receiving efinaconazole, 10%, for 1 nail.

model are from the study by Weinberg et al,¹³ in which dermatologists performed all testing and the predefined criterion standard was the calcofluor white test. In effect, the test statistics of our model assume that health care professionals are experienced with performing in-clinic KOH testing from the nail plate/bed as well as experienced with appropriately sampling the nail plate for PAS evaluation. However, given the stability of our recommendations at lower pretest probabilities, these findings likely hold true for primary care physicians and podiatrists as well.

Conclusions

Empirical therapy of clinically diagnosed onychomycosis is more cost-effective than a standardized testing regimen for patients who receive oral terbinafine. Confirmatory testing before use of efinaconazole, 10%, is associated with substantial cost savings across a range of disease prevalence.

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Study concept and design: Mikailov, Cohen, Mostaghimi.

Acquisition, analysis, or interpretation of data: Joyce, Mostaghimi.

Drafting of the manuscript: All authors.

Critical revision of the manuscript for important intellectual content: Mikailov, Joyce, Mostaghimi.
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Conflict of Interest Disclosures: Dr Joyce is now employed by Walgreens Co, Deerfield, Illinois. No other conflicts were reported.

REFERENCES

- de Berker D. Clinical practice: fungal nail disease. *N Engl J Med.* 2009;360(20):2108-2116.
- Elewski BE, Charif MA. Prevalence of onychomycosis in patients attending a dermatology clinic in northeastern Ohio for other conditions. *Arch Dermatol.* 1997;133(9):1172-1173.
- Gupta AK, Jain HC, Lynde CW, Macdonald P, Cooper EA, Summerbell RC. Prevalence and epidemiology of onychomycosis in patients visiting physicians' offices: a multicenter Canadian survey of 15,000 patients. *J Am Acad Dermatol.* 2000;43(2, pt 1):244-248.
- Ghannoum MA, Hajjeh RA, Scher R, et al. A large-scale North American study of fungal isolates from nails: the frequency of onychomycosis, fungal distribution, and antifungal susceptibility patterns. *J Am Acad Dermatol.* 2000;43(4):641-648.
- Roberts DT, Taylor WD, Boyle J; British Association of Dermatologists. Guidelines for treatment of onychomycosis. *Br J Dermatol.* 2003;148(3):402-410.
- Mehregan DR, Gee SL. The cost effectiveness of testing for onychomycosis versus empiric treatment of onychodystrophies with oral antifungal agents. *Cutis.* 1999;64(6):407-410.
- American Academy of Dermatology. Ten things physicians and patients should question. <http://www.choosingwisely.org/societies/american-academy-of-dermatology/>. Updated August 19, 2015. Accessed February 1, 2015.
- Pharmacy, \$4 prescriptions. Walmart Stores, Inc website. <http://www.walmart.com/cp/4-Prescriptions/1078664>. Accessed April 12, 2015.
- Pharmacy, \$4 generic drugs. Target Brands Inc website. <http://www.target.com/pharmacy/generics-alphabetic>. Accessed April 12, 2015.

10. National Library of Medicine–National Institute of Diabetes and Digestive and Kidney Disease. LiverTox: clinical and research information on drug-induced liver injury: drug record: terbinafine. <http://livertox.nlm.nih.gov/Terbinafine.htm>. Updated September 30, 2015. Accessed November 12, 2015.
11. Reisberger EM, Abels C, Landthaler M, Szeimies RM. Histopathological diagnosis of onychomycosis by periodic acid–Schiff–stained nail clippings. *Br J Dermatol*. 2003;148(4):749–754.
12. Lilly KK, Koshnick RL, Grill JP, Khalil ZM, Nelson DB, Warshaw EM. Cost-effectiveness of diagnostic tests for toenail onychomycosis: a repeated-measure, single-blinded, cross-sectional evaluation of 7 diagnostic tests. *J Am Acad Dermatol*. 2006;55(4):620–626.
13. Weinberg JM, Koestenblatt EK, Tutrone WD, Tishler HR, Najarian L. Comparison of diagnostic methods in the evaluation of onychomycosis. *J Am Acad Dermatol*. 2003;49(2):193–197.
14. Haghani I, Shokohi T, Hajheidari Z, Khalilian A, Aghili SR. Comparison of diagnostic methods in the evaluation of onychomycosis. *Mycopathologia*. 2013;175(3-4):315–321.
15. Lawry MA, Haneke E, Strobeck K, Martin S, Zimmer B, Romano PS. Methods for diagnosing onychomycosis: a comparative study and review of the literature. *Arch Dermatol*. 2000;136(9):1112–1116.
16. Barak O, Asarch A, Horn T. PAS is optimal for diagnosing onychomycosis. *J Cutan Pathol*. 2010;37(10):1038–1040.
17. Williams R, Cohen J, Mikailov A, Laga A, Mostaghimi A. Clinical diagnosis of onychomycosis by physicians: is a confirmatory test necessary? Paper presented at: Medical Dermatology Society Annual Meeting; March 19, 2015; San Francisco, CA.
18. Centers for Medicare & Medicaid Services. Clinical laboratory fee schedule. <http://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/ClinicalLabFeeSched/index.html>. Accessed April 11, 2015.
19. Centers for Medicare & Medicaid Services. Physician fee schedule search. <http://www.cms.gov/apps/physician-fee-schedule/search/search-criteria.aspx>. Accessed April 11, 2015.
20. TreePlan Software (for Windows Excel and MacExcel) [computer program]. San Francisco, CA: TreePlan Software; 2015. <http://treeplan.com>. Accessed October 15, 2014.
21. Zaias N, Rebell G. The successful treatment of *Trichophyton rubrum* nail bed (distal subungual) onychomycosis with intermittent pulse-dosed terbinafine. *Arch Dermatol*. 2004;140(6):691–695.

NOTABLE NOTES

History That Will Make Your Skin Crawl—Insect Use in Dermatology

Anna Augustin, BS

When people think of bugs, it may make their skin “crawl.” It would certainly be disturbing then, to describe a treatment regimen involving insect therapy. While this seems strange in our modern world, insects have actually been widely used throughout history to treat certain medical conditions. It is no surprise that many of these insect therapies do have clinically beneficial outcomes.

For many years, maggots have been used to enhance wound healing of necrotic tissue. The larvae of maggots have been shown to eat necrotic tissue, produce antimicrobial secretions, and destroy any invading bacteria trying to colonize a healing wound. Typically used in South America and Asia, these insects are actually commonly used in remote areas where access to modern pharmaceuticals is limited or impractical.¹

Another bug implicated in defending against skin disease is the beetle. Cantharidin, a toxin that is found on the bodies of blister beetles, is widely used as treatment against warts. Alternatively, it can also be used to treat molluscum contagiosum and has been investigated as a possible anti-neoplastic agent.²

While the healing power of cantharidin is isolated from the beetle torso itself, another insect manually produces 2 compounds that also have medical implications. The bee, with its production of both honey and royal jelly, may be one of the most efficient insects involved in dermatologic healing. Honey mixtures have been shown to improve healing times in multiple skin conditions, including atopic dermatitis, dandruff, psoriasis, tinea, pityriasis versicolor, and, in infants, diaper rash. Honey has also been shown to increase skin wound healing

times and burn healing times in certain studies. In addition to treating skin disorders, honey has also been shown to improve gastroenteritis symptoms in toddlers.¹ Royal jelly, with its marked ability to promote collagen synthesis, is used in several skin conditions, namely wound healing.³

Although using bugs as effective medical treatment may seem rudimentary or outdated, the obvious benefits of insect therapy should not be overlooked. More modern methods that rely on extracts and chemicals produced by the insects, rather than on direct patient contact with an insect, are being developed. Some of these substances, such as cantharidin, are already being used in topical dermatologic agents. Perhaps in the future, removing the “ick” factor of arthropod treatment will make insect substances more normalized in the modern medical community.

Author Affiliation: Lake Erie College of Osteopathic Medicine, Bradenton Campus, OMS II, Bradenton, Florida.

Corresponding Author: Anna Augustin, BS, Lake Erie College of Osteopathic Medicine, Bradenton Campus, OMS II, 7020 45th Ave W, Apt 44, Bradenton, FL 34210 (anna.augustin@med.lecom.edu).

1. Cherniack EP. Bugs as drugs, part 1: insects: the “new” alternative medicine for the 21st century? *Altern Med Rev*. 2010;15(2):124–135.
2. Cantharidin. PubChem Open Chemistry Database. 2015. <http://pubchem.ncbi.nlm.nih.gov/compound/cantharidin> Accessed August 18, 2015.
3. American Apitherapy Society Inc. Royal jelly. Apitherapy.org. 2015. <http://www.apitherapy.org/about-apitherapy/products-of-the-hive-2/royal-jelly/>. Accessed August 18, 2015.