A generally established principle for systemic therapies that treat infectious disease is that the therapy must have an efficacious dose that is nontoxic to the patient. In the past, these therapies have generally affected bacterial or fungal cellular processes that are not common to the mammalian cells of the patient. These factors are what provide for the safety and value of systemic antimicrobial therapies. With medical devices however, the topical application of light to areas of disease can also have effects on the mammalian tissues that are being irradiated, and hence must satisfy different safety criteria in the local environment. These criteria include those espoused by the Individual Maximum Safe Radiant Exposure (IMSRE) guidelines for human phototherapy.

A practitioner should also have a general understanding of possible adverse events associated with the improper use of different light therapies. Data have recently been published on the use of three possible phototherapy devices, testing each device’s antimicrobial effects, each with a different mechanism of action. These three devices have emerged as the leading potential candidates to aid the podiatric physician in topical antimicrobial therapy for onychomycosis. Table 1 summarizes the available data, technology, and potential concerns. Onychomycosis is usually caused by the fungal pathogen *Trichophyton rubrum*, which invades the nail bed and the underside of the nail plate, beginning at the hyponychium, and then migrating proximally through the underlying nail matrix in extensive disease.

The first device is the Noveon (Nomir Medical Technologies, Inc, Waltham, Massachusetts). It is a novel, dual-wavelength, near-infrared diode laser that has been employed in vitro and in vivo in institutional review board (IRB)-approved antibacterial and antifungal studies. For antifungal treatment, the Noveon employs a photoinactivation mechanism to kill *T rubrum*, *Candida albicans*, *Phaeoannellomyces*, and *Rhodotorula* in human onychomycosis therapy. Results from human antibacterial studies have also been published, which present data on a unique photo-damage mechanism to reverse resistance in methicillin-resistant *Staphylococcus aureus* (MRSA) in nasal decolonization therapy.

The second device (a free-running pulsed Nd:YAG laser) has been used in vitro in laser antisepsis experiments, with a mechanism of selective ablation of the pigmented dental bacteria *Porphyromonas gingivalis*. Laser ablation is defined as the removal of local material by a rapid temperature increase within the target tissue to a state of disintegration and vaporization. As of this writing, there are no published data from an IRB-approved onychomycosis therapy using an Nd:YAG laser.

The third technology is ultraviolet (UV) light generated from either a low-pressure mercury lamp (UVC...
only) or a xenon pulsed-light device (UVA, UVB, and UVC). The mercury lamp has been used as an 85% nonpulsed UVC light source in in vitro studies, to decontaminate porcine hoof and human nail clippings against *T. rubrum*, *Trichophyton mentagrophytes*, *Epidermophyton floccosum* and *Microsporum canis*.16, 17 This lamp has also been used to generate in vivo data from an IRB-approved study on onychomycosis. In the same human study, as a comparison ultraviolet light source, the xenon-pulsed light was also employed to kill the fungi causing onychomycosis. Both devices produce their effects with a mutagenic interaction on fungal genetic material as the mechanism of action.16-20 This mutagenic effect is the creation of germicidal DNA photoproducts from the UV light.16

Near-Infrared Photo-Inactivation with Dual Wavelength Diode Laser

The Noveon (first prototype device fabricated in 2005) is a near-infrared diode laser system that is specifically designed to use only 870 nm and 930 nm wavelengths. This choice was made on the basis of the published work of Neuman et al,21 who observed that these specific wavelengths had the propensity to kill both eukaryotic and prokaryotic cells being studied with confocal microscopy. The killing of these cells was postulated by Neuman to occur as a result of the generation and interaction of toxic singlet oxygen species that are created by the absorption of these energies in intracellular endogenous chromophores. This device, which combines the 870 nm and 930 nm energies in a multiplexed beam, has shown a unique antimicrobial action spectrum in vitro.22 Additionally, the Noveon has produced safe and efficacious therapeutic results in multiple IRB-approved studies of onychomycosis treated with a 1.5 cm diameter beam spot at physiologic temperatures (Fig. 1).9, 23, 24 Similar results were produced when treating MRSA in the human nose with a diffuser probe, also at physiologic temperatures.10, 23 There are reports in the literature of excessive exposure to near-infrared light causing an oxidative stress response in human skin that leads to premature photo-aging effects.25 This stress response originates from the mitochondrial electron transport chain, which causes a significant decrease in the antioxidant content of human skin. Further, repeated exposure to infrared light can reduce the expression of type I procollagen. There are no other significant negative effects, and no references to DNA photo products reported in the literature with correctly administered near-infrared phototherapy.25-29

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Human studies with the Noveon have also met the published criteria for calculating the Individual Maximum Safe Radiant Exposure (IMSRE)5 for human pho-
totherapy, as no negative interactions were reported in either the onychomycosis or MRSA IRB-approved studies, and continuing studies are ongoing.

**Free-Running Pulsed Nd:YAG Laser**

Use of the Nd:YAG laser was first demonstrated 45 years ago by Geusic et al at Bell Laboratories in 1964. Four years later, in 1968, the first medical use of the Nd:YAG laser was reported in the treatment of cutaneous vascular lesions.

Today, clinicians using the free-running pulsed (FRP) Nd:YAG laser have the capability to use pulse durations in the millionths of a second (10^{-6} sec), allowing for high-peak powers (1–2 thousand watts/pulse) for the safe and rapid ablation of soft tissues. Exploiting this laser-tissue interaction, a clinician using an FRP Nd:YAG laser has the ability to apply an intense burst of laser energy, for a very short time interval to the tissues being irradiated. This ability will cause quick, safe, and precise ablation of the tissues involved, as long as the physician performing the procedure is particularly careful not to employ pulse stacking. Pulse stacking is an overlapping localization of laser pulses (going over the same spot more than once) that occurs from the inconsistent manual aiming of small to medium laser spot sizes over large areas of tissue. This will lead to excessive heating of areas of treatment and potentially ablate healthy tissues.

The Nd:YAG ablation interaction has since been modified to act as a laser antiseptic treatment in vitro, with a reported method designed to eliminate only the microorganisms that cause disease. In three different publications describing in vitro studies, the Nd:YAG laser was used for an antisepsis procedure with a threshold energy density (fluence) proving to be lethal to the pigmented dental pathogen *P. gingivalis*. These data described the antisepsis fluence as the “ablation threshold” necessary for destruction of *P. gingivalis*. The ablation threshold was defined as the radiant exposure that is toxic to this pigmented pathogen in vitro without damaging the bacterial-growth media. In these in vitro studies, each laser pulse was delivered through a 320-micron fiber in noncontact mode, diverging in a Gaussian pattern to a fresh 1-mm diameter spot, to avoid the cumulative thermal effects of pulse stacking. The Nd:YAG laser has also recently been successfully used in new human ablative therapies in dentistry.

If one were to employ Nd:YAG technology for the antisepsis of *T. rubrum*, it is possible that the frequency doubled Nd:YAG (532 nm, visible green) laser would be the superior choice for laser antisepsis, because there is an endogenous red pigment in *T. rubrum* (xanthomegnin) that would be an apparent candidate, as an absorbing pigment for green light. This alternative Nd:YAG antisepsis interaction has also been previously described in vitro.

Finally, Demetriou and Hsia filed US and PCT patent applications entitled “Method and apparatus for treating a diseased nail.” These patent applications include published data on the use of a yellow dye laser (595 nm) on humans and also describe the use of Nd:YAG lasers for the treatment of diseased nails.

**Ultraviolet Light**

Xenon flash lamps were invented in the early 1930s by Dr. Harold Edgerton for the purpose of stop-motion photography. A xenon flash lamp is a gas-discharge lamp designed to produce extremely intense, incoherent, full-spectrum white light (including UVA, UVB, and UVC) for very short durations. Xenon lamp technology has continued to advance in the past 80 years and is now used in many industries. Its first reported use in the medical literature is for the in vitro sterilization of dialysis connections.

In the past 10 years, ultraviolet light has been tested in various IRB-approved trials. Within the arena of wound decolonization, Thai et al showed a considerable reduction of MRSA in chronic wounds by using 2.8 J/cm² (1.54mW/cm² × 180 sec) generated by a 254-nm cold quartz generator. In the past 2 years,
multiband ultraviolet light from a xenon-pulsed light device has been used in an IRB-approved trial,\textsuperscript{17-20} with data showing 73\% improvement in treatment of human onychomycosis. This human study encompassed four treatments, each 7 days apart. It is assumed that appropriate precautions were taken in those human studies, as the authors of the in vitro study specifically noted in proposing to use, “UVC irradiation to treat onychomycosis, it is clearly of crucial importance to minimize or avoid UVC exposure to skin either surrounding the nails (perionychium, hyponychium, and cuticle) or to the tissue underneath the nail (nail bed).”\textsuperscript{16(p1245)} This safety precaution is given because of the mutagenic effects seen with ultraviolet light in human skin.\textsuperscript{51-54}

**Conclusions**

The preceding review has categorized three different medical devices currently being studied for the topical and phototherapeutic treatment of onychomycosis. This information from available published data and references, should give podiatric physicians up-to-date information on these systems, and their experimental protocols, so that they may make informed decisions for their patients and practices if the systems achieve FDA approval for treatment of the diseases.

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**Conflict of Interest:** Dr. Bornstein is the chief scientist officer of Nomir Medical Technologies, the creator of the Noveon phototherapy device. Dr. Bornstein is also employed by Nomir and retains stock in the company.

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