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Original Communication

Treating a Methicillin-resistant *Staphylococcus aureus*-infected hallux of an insulin-dependent fifty-nine year old female using near-infrared potentiation of oral doxycycline following the failure of oral ciprofloxacin: A case report

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ABSTRACT

Diabetes mellitus is a widespread condition affecting up to 30% of the population of developing nations worldwide. Diabetic foot infections transpire when local tissue damage occurs, and colonizing surface bacteria overwhelm the diabetic immune system. This immune failure leads to critical colonization, followed by infection and deeper tissue penetration in a compromised host. With the rise of these infections, there is a commensurate rise in antibiotic resistance, most often in a group of gram positive and gram negative bacteria known as the ESKAPE group of pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumanii*, *Pseudomonas aeruginosa* and *Enterobacter* species). Herein, a case of poly-microbial Methicillin-resistant *Staphylococcus aureus* (MRSA) cellulitis, progressing from the infected paronychia of the hallux, in a 59-year old diabetic Caucasian female on daily insulin injections is reported. This infection occurred secondary to onychocryptosis (ingrown nail) surgery. After the failure of two self-administered courses of ciprofloxacin, the patient was successfully treated with an 870 nm/930 nm laser system that is customarily utilized to treat onychomycosis, and an oral regimen of doxycycline. This photo-biologic technology was chosen for a combined therapy with the oral doxycycline, as it has been previously shown to, (a) potentiate tetracycline, erythromycin and ciprofloxacin *in vitro* against MRSA and levofloxacin-resistant *Escherichia coli*, and (b) potentiate topical erythromycin in human clinical studies, clearing erythromycin-resistant MRSA from the human nares.

KEYWORDS: laser, diabetic foot, potentiation, antibiotic resistance

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Introduction

Erythromycin, tetracycline and ciprofloxacin are generally recognized as ineffective against resistant *Staphylococcus aureus* and *Escherichia coli* strains that are genetically capable of producing ATP-driven efflux pumps [1]. In 2010, Bornstein *et al.* reported on a dual wavelength near-infrared laser system that can potentiate these antimicrobials via irradiation of bacteria with multiplexed 870 nm and 930 nm energy at physiologic temperatures. The published mechanism of action is an optically mediated reduction of plasma membrane potentials ($\Delta\Psi p$) in Gm+ and Gm- bacteria, and mitochondrial membrane potentials ($\Delta\Psi m$) in fungi [2-4]. This optical reduction of $\Delta\Psi$ in bacteria and fungi has been shown to inhibit efflux pumps in organisms that are resistant to first generation macrolide, ketolide, fluoroquinolone, allylamine and azole antimicrobials *in vitro*, and in Investigation Review Board (IRB)-approved human studies; (a) eradicating methicillin-resistant *Staphylococcus aureus* in the

nares, and (b) the treatment of onychomycosis with concomitant topical antifungal therapy [5, 6]. Targeting and weakening the membrane potentials of gram positive *Staphylococcus aureus*, gram negative *Escherichia coli* and fungi have been described in the literature as a mechanism by which antimicrobial efflux can be inhibited in these organisms [7-9].

Onychocryptosis is a very common disease of the nail. This painful onychopathy occurs when the nail grows abnormally, and presses into the sides of the paronychium or nail bed. Pain and infection then occur in the paryonychium as a result of microbial infiltration and inflammation that can result in an infected granuloma, as the nail actually penetrates the surrounding nail areas [10]. In a 2010 review of the management of antibiotic prophylaxis in onychocryptosis surgery, Cordoba-Fernandez *et al*. suggested that the fluoroquinolone levofloxacin be used in patients with increased risk of surgical-site infection for this surgery [11]. The following is a case report concerning a MRSA cellulitis of the hallux in an insulin-dependent diabetic middle aged female. This patient was successfully treated with an 870 nm/930 nm photo-biologic laser system in combination with oral doxycycline, after the failure of two oral courses of the fluoroquinolone ciprofloxacin.

Case presentation

A 59-year old Caucasian woman with a previous history of MRSA, presented with a MRSA infection in the left hallux. This occurred as a result of partial nail avulsion surgery, secondary to trauma to the left hallux and onychocryptosis. The infection was cultured (Quest Diagnostics) and returned 'MRSA Positive' and 'Candida Positive'. This is a common presentation in diabetic foot ulcers, as it has been revealed through polymerase chain reaction genetic testing of wound sites that many non-healing diabetic wounds contain significant numbers of both gram positive and gram negative bacteria, along with fungus [12, 13].

This patient had previous MRSA infections in proximity to insulin injection sites in the buttocks region, where swab cultures were previously positive for MRSA. These prior infections had been successfully treated in the past with 14 day regimens of oral levofloxacin. For this MRSA cellulitis of the hallux, the patient had 'self-prescribed' oral ciprofloxacin, which failed despite taking two courses of the antibiotic, prompting the decision for a combinatorial therapy.

Medical history

The patient has been taking injectable insulin for type II diabetes for 10 years.

Medications

Glucotrol	-	Oral glucose control
Januvia	-	Glucose control
Lipitor	-	Cholesterol control
Enalapril	-	Hypertension
Lantis	-	Injectable insulin

Examination findings (Figure 1)

- A significant MRSA cellulitis of the left hallux.
- Peeling skin, non-purulent with superficial candida infection.

Pharmacologic treatment

The patient was treated with 200 mg oral doxycyxline 1 hour prior to the laser procedure, as a loading dose, and then continued with 100 mg doxycycline twice a day (BID) for 10 days. The hallux was also treated with topical Nystatin cream daily to suppress and prevent candida overgrowth on the nail and hallux.

Photo-biologic treatment

The patient was treated twice (day 1 and day 3) with the 870 nm/930 nm onychomycosis laser system with a 1.7 cm diameter flat-top projection spot size, at a power density of 1.4 W/cm^2 and a pre-determined optical dose (Figure 2), utilized for onychomycosis therapy. Monte Carlo tissue simulations have forecast that large spot size 'broad-beam' energy projections, with a top-hat geometry, will achieve a higher fluence distribution (deeper) within the tissue than could be achieved with Gaussian projections and a smaller spot size, at the same energy dose. This is because the fluence rate Φ within the tissue of the hallux being irradiated is greater than the irradiance or power density E_o at the air-tissue boundary [14].

In this patient, by utilizing the large diameter top-hat beam of the onychomycosis system, a greater

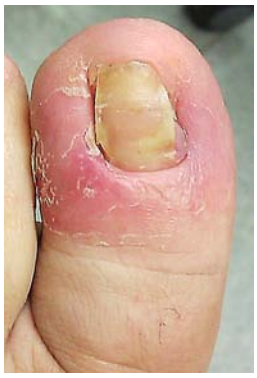

Figure 1. Day 1 – Pre-operative superior view, MRSA cellulitis of the left hallux.

Figure 2. Day 1 – Treatment with 870 nm/930 nm with (large) 1.7 cm diameter flat-top laser system.

area of tissue in the hallux could be irradiated, producing more scattered light, and a higher fluence in the tissue. The higher fluence is a function of greater internal scatter of the laser energy creating 'more light' inside the tissue, as more photons are present for a longer period of time, before they are absorbed by the tissue and bacteria [14]. For this 870 nm/930 nm laser system, the area of tissue volume to be treated is generally defined as ($\pi r^2 \times$ depth) with a higher fluence rate Φ beneath the air-tissue boundary [15].

Discussion

Prior publications and data have described *in vitro* and *in vivo* bacterial and fungal photo-damage

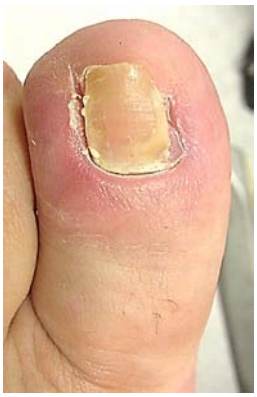

Figure 3. 48 hours after the first treatment showing significant improvement.

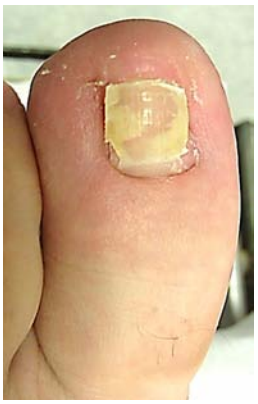

Figure 4. 21 days after the first laser treatment and 11 days after the last antibiotic dose; infection is cleared.

with the 870 nm/930 nm laser system occurring via the perturbation of $\Delta\Psi$, with concomitant generation of endogenous reactive oxygen species, and the inhibition of $\Delta\Psi$ or ATP driven efflux pumps. This efflux pump inhibition has been shown to potentiate generic antibiotics and antifungals in human clinical trials;

(a) MRSA in the human nares and
(b) Fungi in onychomycosis [2-6].

With this historical *in vitro* and *in vivo* data, and the unique poly-microbial infection in this patient (cultured as containing MRSA and Candida), it was decided with informed consent to treat this patient with the 870 nm/930 nm onychomycosis laser system, oral doxycycline, and topical Nystatin, an antifungal agent with efficacy against candida [16]. In this

patient, there appears to have occurred a successful synergy between the 870 nm/930 nm laser system and the doxycycline, as the infection was significantly improved 48 hours after the first laser treatment and the first dose of doxycycline (Figure 3). The choice of doxycycline was made (as the concomitant antibiotic), for the following reasons:

(a) The correlation between tetracycline and prior laser potentiation seen *in vitro* against MRSA with the 870 nm/930 nm laser system [3];
(b) The fact that doxycycline is recommended for gram positive and gram negative organisms found in diabetic foot infections [17];
(c) Doxycycline achieves its maximum blood level in human subjects within 90 minutes of administration [18].

As diabetic foot infections are considered a significant cause of morbidity in susceptible patients, and frequently a cause for hospitalization, any prospective therapy improvement to the standard of care should be considered. This is especially important, as infected diabetic foot ulcers can lead to limb amputation and death in susceptible patients [19]. Two recent reviews have discussed innovations in medical devices as important additions to traditional pharmacology in health care in general, and wound bioburden management in particular [20, 21].

This case report documents a third anatomical area of human infection, successfully treated with the 870 nm/930 nm photo-biologic laser system and a potentiated antimicrobial; (a) onychomycosis [5], (b) MRSA in the nares [3], and (c) MRSA cellulitis of the hallux (Figures 1 and 4). The failure of this patient, with MRSA cellulitis of the hallux, to respond to ciprofloxacin, is consistent with her prior multiple regimens of levofloxacin to treat prior MRSA infections [22]. The 870 nm/930 nm laser system is currently undergoing further IRB-controlled human clinical trials for the decolonization of MRSA in the human nares with the topical antibiotic mupirocin, and is expected to begin human trials for the treatment of diabetic foot infections within the next 18 months [6]. The photo-biologic mechanism of action is believed to be an optically mediated reduction of plasma membrane potentials ($\Delta\Psi p$) in Gm+ and Gm- bacteria, and mitochondrial membrane potentials ($\Delta\Psi m$) in fungi, at physiologic temperatures [2-4].

CONFLICT OF INTEREST STATEMENT

Dr. Eric Bornstein is the Chief Science Officer and Chief Medical Officer of Nomir Medical Technologies, the inventor of the 870 nm/930 nm phototherapy device. Dr. Bornstein is employed by Nomir and retains stock in the company.

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