The Efficacy of Topical Manuka Honey and Combination Antibiotic Therapy in the Treatment of MRSA Skin Infections

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Pacific Adventist University

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The Efficacy of Topical Manuka Honey and Combination Antibiotic Therapy in the Treatment of MRSA Skin Infections

Abstract

Background: Infectious diseases continue to impact human health and life expectancy. Currently, there are numerous methicillin-resistant Staphylococcus aureus (MRSA) strains with multiple antibiotic resistance which presents a major concern to human health. Thus, treatment is becoming increasingly difficult as so many bacterial organisms present resistance to current antibiotics. Combination therapy has been used to limit the emergence of antibiotic resistant strains. Manuka honey is a unique honey produced in New Zealand. It has demonstrated inhibition of growth in vitro including S. aureus and Pseudomonas aeruginosa, two bacteria common in skin wound infections. The combined use of manuka honey and antibiotics ought to limit further emergence of antibiotic resistance. What is the efficacy of the combination of manuka honey and antibiotic therapy in treatment of MRSA skin infections?

Methods: A comprehensive search of available medical literature was conducted using Medline-OVID, PubMed, and Web of Science using the keywords: manuka honey and MRSA. The search was then narrowed to include only English language articles. The bibliographies of the articles were further searched for relevant sources. Articles with primary data evaluating the efficacy of manuka honey's impact in topical treatment of MRSA skin infections along with combination antibiotic therapy were included.

Results: The initial result of the search yielded 29 articles for review. After screening articles for relevance, a total of three articles met inclusion criteria. These articles include three in vitro studies analyzing the synergy of manuka honey and specific antibiotics in treatment of bacterial skin infections. All studies demonstrated a synergistic effect between manuka honey and various antibiotics against MRSA skin infections.

Conclusion: The use of antibiotics and manuka honey has demonstrated in vitro to eradicate varieties of MRSA strains. Combination therapy has been proven to limit the emergence of antibiotic resistance during therapy, increase synergism and efficacy of treatment, and reduce the amount of each antibiotic used. Manuka honey is a viable adjunct to modern medicinal treatment of wound pathogens which will reduce treatment costs and limit side effects. Controlled clinical studies are needed to investigate the synergism between manuka honey and antibiotics in vivo before potential introduction as a standard of care.

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The Efficacy of Topical Manuka Honey and Combination Antibiotic Therapy in the Treatment of MRSA Skin Infections

Kyle Liban

A Clinical Graduate Project Submitted to the Faculty of the School of Physician Assistant Studies

Pacific University

Hillsboro, OR

For the Masters of Science Degree, August 2014

Faculty Advisor: Eric Foote

Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS
Biography

Kyle Liban is a native of Southern California where he majored in Biopsychology and minored in Exercise and Health Sciences at UCSB. After completion of his undergraduate degree, he moved back home to San Diego where he worked for 2 years as an EMT-basic for a local ambulance service and a patient care technician in the ICU at a nearby hospital. He is interested in pursuing a career in critical care or emergency medicine.
Abstract

Background: Infectious diseases continue to impact human health and life expectancy. Currently, there are numerous methicillin-resistant Staphylococcus aureus (MRSA) strains with multiple antibiotic resistance which presents a major concern to human health. Thus, treatment is becoming increasingly difficult as so many bacterial organisms present resistance to current antibiotics. Combination therapy has been used to limit the emergence of antibiotic resistant strains. Manuka honey is a unique honey produced in New Zealand. It has demonstrated inhibition of growth in vitro including S. aureus and Pseudomonas aeruginosa, two bacteria common in skin wound infections. The combined use of manuka honey and antibiotics ought to limit further emergence of antibiotic resistance. What is the efficacy of the combination of manuka honey and antibiotic therapy in treatment of MRSA skin infections?

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Keywords: Manuka honey, MRSA
Acknowledgements

To my parents: Thank you for helping me to succeed and for supporting me when began to question why I was putting myself through this much work. The end is worth it.
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Figure I: Antibiotic sensitivity testing of EMRSA-15 by disc diffusion.

List of Abbreviations

FIC………………………………………….Fractional Inhibition Concentration Index
MGO..................................................................................................Methylglyoxal
MRSA………………………………………Methicillin Resistant \textit{Staphylococcus Aureus}
MIC………………………………………….Minimum-Inhibitory Concentrations
W/V..................................................................................................Weight/Volume
The Efficacy of Topical Manuka Honey and Combination Antibiotic Therapy in Treatment of MRSA Skin Infections

BACKGROUND

Infectious diseases continue to impact human health and life expectancy. In 1961, methicillin resistance was discovered in *Staphylococcus aureus*. Currently, there are numerous Methicillin-resistant *Staphylococcus aureus* (MRSA) strains with multiple antibiotic resistance which presents a major concern to human health.¹ Thus, treatment is becoming increasingly difficult as so many bacterial organisms present resistance to current antibiotics.¹ *S. aureus* is one of the main causative agents of critical acute and chronic skin infections.² In the United States alone, chronic wound infections affect 6.5 million patients and cost the United States $25 billion annually with an increase in estimated future costs.³

Combination therapy has been used to limit the emergence of antibiotic resistant strains as the use of at least two antibiotics with differing methods of action promotes an increase of bacterial death secondary to each organism possessing fewer traits necessary to survive. This reduces the risk of achieving antibiotic resistance during therapy as each mode of action affects the bacteria differently.⁴ Combination therapy can promote increased synergism and thus improve the efficacy of treatment as well as reduce the amount of each antibiotic used. This will reduce treatment costs and limit side effects associated with antibiotic use.⁵ These improvements are exceptionally important for chronic wounds as they require long-term antibiotic therapy.
Honey is a possible treatment option for synergistic activity with antibiotics. It is a broad-spectrum antibacterial agent used among multiple wound pathogens. Medical-grade honey has been first licensed for wound care treatment in Australia in 1999 and has extended to Canada, Hong Kong, Europe, New Zealand and the United States. Currently, honey is available as a licensed medical device and is used in conjunction with sterile dressings or sterilized in tubes.

Manuka honey is a unique honey produced in New Zealand which is derived from the nectar collected by honey bees rummaging in the manuka shrub native to New Zealand. It has demonstrated inhibition of growth in vitro including S. aureus and Pseudomonas aeruginosa, two bacteria common in skin wound infections. Two components, methylglyoxal and leptosin, have been recently identified to contribute to manuka honey’s antibacterial properties, yet further bioactive factors have not yet been discovered. Manuka honey has already demonstrated lack of resistance to honey-resistant strains. The combined use of manuka honey and antibiotics should limit further emergence of antibiotic resistance. What is the efficacy of the combination of manuka honey and antibiotic therapy in treatment of MRSA skin infections?

METHODS

A comprehensive search of available medical literature was conducted using Medline-OVID, PubMed, and Web of Science using the keywords: manuka honey and MRSA. The search was then narrowed to include only English language articles. The bibliographies of the articles were further searched for relevant sources. Articles with primary data evaluating the efficacy of manuka honey’s impact in topical treatment of MRSA skin infections along with combination antibiotic therapy were included.
Studies included the general population infected with MRSA or *in vitro* MRSA bacterial strands treated with manuka honey, use of antibiotics in combination with manuka honey, and resolution of infection. Excluded were studies that were in a non-English language, systemic MRSA infections, and use of strictly oral antibiotics.

**RESULTS**

The initial result of the search yielded 29 articles for review. After screening articles for relevance, a total of three articles met inclusion criteria. These articles include three *in vitro* studies\(^5,8,9\) analyzing the synergy of manuka honey and specific antibiotics in treatment of bacterial skin infections.

**Synergy Between Oxacillin and Manuka Honey Sensitizes MRSA to Oxacillin**

This *in vitro* study\(^8\) investigated an array of different laboratory techniques to assess the inhibitory effects of both manuka honey and oxacillin on bacterial MRSA strands when used in combination or separately. EMRSA-15 strands were tested against manuka honey, oxacillin, and a combination of both manuka honey and oxacillin. Etest strips, disk diffusion, chequerboards, growth curves, and serial broth dilutions were used to assess the inhibition of MRSA. This study intended to explore the possibility of a synergistic effect of oxacillin and manuka honey on MRSA growth.\(^8\)

Sub-inhibitory concentrations of sterile, antibiotic-free manuka honey (2.5% and 5%) were determined by serial doubling dilutions; whereas the minimum-inhibitory concentrations (MIC) of oxacillin was determined by serial doubling dilutions and with oxacillin Etest strips. Chequerboards were used to assess synergism of MRSA inhibition between manuka honey and oxacillin. A fractional inhibition concentration index (FIC) was used to determine which interactions had a synergistic interaction. A FIC \(\leq 0.5\)
indicates synergy; >0.5 to ≤4, additivity; and >4, antagonism. Time-kill curves were performed using varied concentrations of manuka honey and oxacillin.8

The MIC of manuka honey was 6% determined by broth dilution. AST, Etest strips, and broth dilution resulted in resistance of MRSA to oxacillin; however, there was a reversal of oxacillin susceptibility in MRSA with the addition of manuka honey. The best combination of MIC of manuka honey (5% weight/volume (w/v)) and oxacillin (0.25mg/L) prevented growth of MRSA. These FIC values were ≤ 0.5 which indicated a synergistic effect between manuka honey and oxacillin to inhibit MRSA growth.8

Synergism Between Medihoney and Rifampicin Against MRSA

This in vitro study9 investigated the effects of a combination treatment of rifampicin, honey (sugar solution), and manuka honey when used to inhibit MRSA strains. An MIC for each of agent used was defined as the least amount of agent to inhibit MRSA. Checkerboard microdilution assays, agar diffusion tests, and time-kill curves were used to determine each MIC and thus the antibacterial effects of each agent on MRSA.9

Checkerboard microdilution assays performed indicated a decrease in resistance against rifampicin when used in combination with manuka honey against MRSA.9 The corresponding FIC was ≤ 0.5 demonstrating synergism. The MIC for manuka honey was determined to be 8% (w/v). When rifampicin was used in combination with a sugar solution replicating honey, the data indicated no synergistic effect. Further analysis with time-curve assays confirmed a synergistic effect between rifampicin and manuka honey with a decreased MIC of 7% (w/v). Agar diffusion tests, which measured a mean diameter of inhibitory zone of each agent, confirmed the above results of synergism
between rifampicin and manuka honey; however, it also indicated that manuka honey, when used alone, had no significant effect on the growth of MRSA on the agar plates.\textsuperscript{9}

A checkerboard microdilution assay was performed to determine if methylglyoxal (MGO) is the sole antimicrobial component of manuka honey. The results indicated that an amount of 150-160 µg/mL of MGO, comparable to the amount of 16-17% (w/v) of MGO in manuka honey, displayed an inhibitory component against MRSA strains; however, the combination of rifampicin and MGO did not demonstrate a synergistic effect against MRSA strains. Rifampicin and MGO used in the presence of sugar, a main component of manuka honey, demonstrated a decreased FIC >1, thus indicating weaker synergism when in presence of sugar.\textsuperscript{9}

An agar disk diffusion assay was performed to investigate if manuka honey was able to restore resistance to rifampicin, as it had been proven with oxacillin.\textsuperscript{8} No inhibition zones could be demonstrated around rifampicin disk in contrast to the 25mm diameter zones that appeared around oxacillin disks.\textsuperscript{9}

Time-kill experiments demonstrated antimicrobial activity of rifampicin against MRSA; however, at 24 hours the bacterial level of MRSA strains displayed growth to a level consistent with normal growth of MRSA. When used in combination with manuka honey, the MRSA bacteria resulted in a complete inhibition of growth.\textsuperscript{9}

**Improving Antibiotic Activity Against Wound Pathogens With Manuka Honey in Vitro**

This *in vitro* study\textsuperscript{5} investigated the potential synergistic interaction of 15 different antibiotics when used in combination with manuka honey against both MRSA and *Pseudomonas aeruginosa*. See Figure I. This interaction was tested using disc
diffusion, broth dilution, Etest strips, chequerboard titration, and growth curves. A MIC was discovered to be 6% (w/v) for manuka honey against MRSA and 1% below the MIC were used for testing in combination with antibiotics.\(^5\)

Disc diffusion was used to assess antibiotic susceptibility when used in combination with manuka honey. The greatest zones of inhibition present against MRSA were rifampicin, piperacillin/tazobactam, imipenem, mupirocin, and tetracycline. However, this study did not pursue further testing with rifampicin and piperacillin/tazobactam as broth dilution demonstrated an additive yet not synergistic effect. This study preferred to focus on single antibiotics in combination with manuka honey. Therefore, the evidence suggests that manuka honey used in combination with tetracycline, imipenem, and mupirocin demonstrate the greatest synergistic effects.\(^5\)

Imipenem and manuka honey displayed a synergistic effect against MRSA but had no effect against \(P.\ aeruginosa\). Tetracycline and manuka honey demonstrated the greatest synergistic effects towards both bacteria.\(^5\)

**DISCUSSION**

The potential use of manuka honey in combination with antibiotics creates a promising avenue of treatment against MRSA infections. Although the literature in this systematic review included only \textit{in vitro} studies, the overall results demonstrate overwhelming evidence of eradication of MRSA bacteria. In just the small amount of time between publications assessed in this review, a mere 23 months, the evolving impact of manuka honey has greatly expanded.

In the study discussing the synergism between oxacillin and manuka honey,\(^8\) it was shown that MRSA displays resistance against oxacillin; furthermore, when used in
combination with manuka honey, it enhances the susceptibility of MRSA to oxacillin. In the laboratory experiments, a MIC of 6% (w/v) was discovered as a sub-lethal concentration of manuka honey. Since honey can be used undiluted in dressings to wrap chronic venous ulcerations or MRSA skin infections, 6% concentration of manuka honey is easily attainable. In addition to the synergism displayed by both agents against MRSA, manuka honey has been shown to restore susceptibility of MRSA to oxacillin. Laboratory results have shown that honey down-regulates the  \textit{mecR1}  gene, a gene known to promote methicillin resistance in MRSA. This study hypothesizes that the down-regulation of this gene directly decreases the resistance of MRSA to oxacillin.\textsuperscript{8}

In the study discussing synergism between manuka honey and rifampicin,\textsuperscript{9} it demonstrated a combined effect of complete inhibition of MRSA growth. The MIC for manuka honey was 8% (w/v) indicating that an undiluted topical application of the honey would be feasible. While MGO may present as a powerful ingredient in manuka honey, this study demonstrates that it is not the sole component of its broad-spectrum antibacterial effects. Since MGO and rifampicin had an additive, yet not synergistic effect against MRSA and an even weaker effect in presence of sugar, it has been surmised that manuka honey contains other ingredients that give its antimicrobial activity. The chemical breakdown of manuka honey most likely has components that act together synergistically; however, when isolated, each component may behave differently when affecting bacterial growth.\textsuperscript{9} It has been postulated that hydrogen peroxide and other active substances that have yet to be defined contribute to its broad-spectrum activity.\textsuperscript{6}

MRSA can develop resistance to rifampicin just after one dosage. This study\textsuperscript{9} provides evidence that when rifampicin is used in the presence of manuka honey, MRSA
strains do not develop resistance to rifampicin. Unlike manuka honey’s unique resistance restoration properties evident when used in combination with oxacillin, it is not able to improve susceptibility to rifampicin.\textsuperscript{8,9} However, if used with the initial dose of rifampicin and subsequent dosing, MRSA will not develop rifampicin resistance. In long term therapy, this combination may reduce the incidence of rifampicin resistance in clinic and the environment.\textsuperscript{9}

The final study\textsuperscript{5} assessed antibiotic activity against both MRSA and \textit{P. aerginosa} with manuka honey. Fifteen antibiotics were used in combination with manuka honey against both wound pathogens. Results initially demonstrated synergistic effects against MRSA with use the combined use of tetracycline, mupirocin, and imipenem, rifampicin, and piperacillin/tazobactam. Rifampicin showed an additive, but not synergistic effect, and initial results showed piperacillin/tazobactam to be synergistic as well.\textsuperscript{5} These findings of rifampicin’s activity contradict results found in a later study conducted by Muller et al.\textsuperscript{9} However, more comprehensive laboratory studies were conducted in the latter publication which proved rifampicin to be synergistic with manuka honey.\textsuperscript{9} This study chose to focus on single antibiotics and thus, did not conduct further testing with piperacillin/tazobactam.\textsuperscript{5}

Imipenem and manuka honey had the greatest synergistic activity against MRSA. However, it did not affect \textit{P. aerginosa}. Tetracycline and manuka honey demonstrated the most powerful synergistic effect on both pathogens. As both bacterial organisms are nosocomial infections prevalent in the hospital setting, it may be difficult to isolate one organism when treating a skin bacterial infection until after culture results are known. Since wounds, such as chronic venous ulcerations, tend to maintain a variety of
polymicrobial communities, a broad-spectrum antibiotic like tetracycline may be the best choice of antibiotic to investigate in the future as it affects both organisms tested.\(^5\)

The primary weakness of the literature reviewed is its shared methodology of being *in vitro* studies. What is the clinical application of *in vitro* studies? Its application to practice is not clear. There have been concerns about the artificial non-physiologic conditions the cells are maintained in, potential impairment of intracellular signaling, compromise in homeostatic culture conditions, and too rapid of cellular growth. Since *in vitro* testing may not be the most accurate replication of human tissue, the most beneficial representation of testing should be studied *in vitro* and *in vivo*, respectively, to demonstrate a more detailed and widespread picture.\(^10\)

**CONCLUSION**

The use of antibiotics and manuka honey has demonstrated *in vitro* to eradicate varieties of MRSA strains and have bactericidal effects against *Pseudomonas aeruginosa*. Combination therapy has been proven to limit the emergence of antibiotic resistance during therapy, increase synergism and efficacy of treatment, and reduce the amount of each antibiotic used. Manuka honey is a viable adjunct to modern medicinal treatment of wound pathogens which will reduce treatment costs and limit side effects.

Currently, all literature has demonstrated overwhelming support for trials of combination therapy *in vitro*. Further investigation is needed to define the underlying mechanism of action of manuka honey and synergistic interaction with various antibiotics. Controlled clinical studies are needed to investigate the synergism between manuka honey and antibiotics *in vivo* before potential introduction as a standard of care.
References


Figures

Figure I: Antibiotic sensitivity testing of EMRSA-15 by disc diffusion.

EMRSA-15 susceptibility to antibiotic discs ± honey

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<tr>
<td>Piperacillin/Tazobactam</td>
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<tr>
<td>Erythromycin</td>
<td>60 µg</td>
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<tr>
<td>Penicillin G 10 IU</td>
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<tr>
<td>Kanamycin 1000 µg</td>
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<td>Rifampicin 15 µg</td>
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<td>Tetracycline 10 µg</td>
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<tr>
<td>Imipenem 10 µg</td>
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<td>Ceftizoxime 30 µg</td>
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<td>Vancomycin 30 µg</td>
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<td>Gentamicin 10 µg</td>
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<tr>
<td>Ciprofloxacin 1 µg</td>
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<td>Mupirocin 20 µg</td>
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