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Case Series

Hype or healing: unveiling the truth behind manuka honey?

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ABSTRACT

Aim of the study was to find out the effectiveness of Manuka honey (MH) in various applications to treat drug resistant ENT infections as an adjuvant therapy. The antibacterial properties and antioxidant properties of MH is attributed to the presence of high concentration of methylglyoxal (MGO) and flavonoid, phenolic compounds respectively. Unique manuka factor (UMF) rating is a scale used to determine the antibacterial potency of MH which directly correlates to the MGO and phenolic components in MH. Various cases of nasal crusting in post operative period with multidrug resistant bacterial cultures were included in the study. Each case was started on thorough nasal douching as well as manuka honey topical application. Regular and meticulous follow up was done for each case via endoscopic examination and medical record was kept of any potential side effects. Perichondritis of pinna was included in the study with potentially unique application the above-mentioned condition. MH is a natural antibiotic with low toxicity profile, allowing for prolonged use when necessary. Moreover, the development of bacterial resistance to honey has yet to be reported, making it an attractive alternative or adjunctive therapy, particularly in cases where antimicrobial resistance is a concern. While Manuka honey's antimicrobial properties have been observed in various studies, translating this knowledge into clinical practice requires rigorous investigation to ensure its effectiveness, safety, and proper integration with conventional antibiotic therapies.

Keywords: MH, UMF, MGO

INTRODUCTION

Antibiotics are used to treat infections across all disciplines of medical science, but their injudicious use has led to the emergence of drug-resistant bacteria.[1] Antibiotic resistance has become a global health threat making it more difficult and expensive to treat common infections. WHO has named antimicrobial resistance (AMR) to be among the top 10 public health concerns. By the year 2050, AMR is estimated to claim up to 10 million lives per year, costing the global economy about $100 trillion.[2] In light of emerging anti-bacterial resistance, there has been a renewed interest in finding alternative antimicrobial therapies, which includes natural antibiotics, gene therapy, bacteriophage cocktails.[3,4] The effectiveness of honey in treating topical infections, especially those that are unresponsive to conventional treatments, has been supported by an increasing body of evidence.

Since ancient times the therapeutic benefits of honey have been used to treat various ailments. Honey is produced by honey bees (Apis mellifera) and is formed by ripening nectar, honeydew, and bee secretions.[6] The medicinal properties of honey originate from the floral source used by bees; therefore, honey from different origins possesses different properties. Honey is well known for its antibacterial, wound healing and anti-inflammatory properties.[7] In particular, Manuka honey (MH) has gained attention due to its unique chemical composition and antibacterial properties. MH is a mono-floral honey obtained from the Manuka myrtle tree, which grows across New Zealand and the Eastern Australia.[5]

The antibacterial properties and antioxidant properties of MH is attributed to the presence of a high concentration of MGO and flavonoid, and phenolic compounds, respectively.[5] MGO within MH is primarily formed by the conversion of dihydroxyacetone to MGO by non-enzymatic Maillard reactions.[8] MH collected from the hive often contains relatively low levels of MGO and a high concentration of dihydroxyacetone. During storage, this relationship inverts, and MGO levels within the honey increase, due to the conversion of dihydroxyacetone. Unique manuka factor (UMF) rating is a scale used to determine the antibacterial potency of MH, which directly correlates to the MGO and phenolic components in MH.[9]

Given the ability of MH to disrupt biofilms and its synergistic action when used in conjugation with antibiotics, and its innate antimicrobial ability can be potentially used to improve treatment outcomes in chronic infections when used as a topical agent.[10,11,] In the past decade, there has been an increase in the literature supporting the use of MH for chronic rhinosinusitis, allergic fungal sinusitis, post-op FESS management, and chronic infection of the open mastoid cavity.[12,13]

This paper explores the use of MH in tackling chronic non healing persistent infections in which standard care with medical and surgical therapy has proven to be inadequate.

CASE SERIES

Case 1

A 41-year-old male patient who is a known case of chronic lymphocytic leukemia (in remission) was diagnosed with pansinusitis with possible fungal etiology on non contrast CT-paranasal sinus (NCCT-PNS). The patient underwent fess with septoplasty at a different center. Patient was empirically started on injection liposomal amphotericin B 200 mg in the post-operative period, and the biopsy report was awaited. The biopsy showed no fungal elements and was suggestive of inflammatory changes. The patient was given oral antibiotics and nasal washes but had a persistent nasal block and discharge. Two months postoperatively patient presented to us in the OPD with the same complaints. Nasal endoscopy showed thick black necrotic tissue in the bilateral nasal cavity. Tissue scrapping from the nasal cavity was sent for culture and sensitivity, KOH stain, and fungal culture. The patient underwent MRI-PNS (paranasal sinus) which showed T2 weighted mucosal thickening in bilateral maxillary, ethmoid and sphenoid sinus and blocked frontal recess and sphenoethmoidal recess. Aerobic pus culture showed (Multidrug resistant) MDR *Achromobacter xylloxidans* and patient was started on Intravenous Cefoperazone /sulbactum and oral minocycline according to sensitivity for a week. The patient was concurrently also started on nasal washes with Budecort 0.5 mg twice a day for 1 week. The nasal discharge reduced but no improvement in the state of the nasal mucosa was seen. Later the patient was started on MH nasal irrigation with ongoing medical management. After 2 weeks patient reported back, and nasal endoscopy showed pink mucosa within the nasal cavity, residual DNS with septal perforation with minimal mucoid discharge.

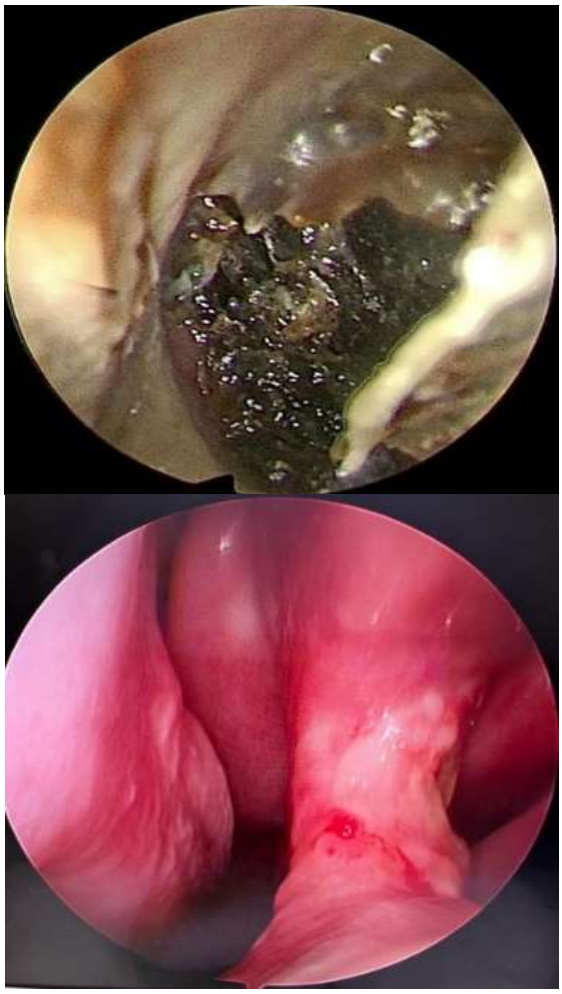

Figure 1: Pre and post MH application.

Case 2

A 49-year-old male with a diagnosis of chronic rhinosinusitis with nasal polyposis (CRSwNP) underwent FESS at a different center. Two months post operatively, patient developed right serous otitis media (SOM) with synechiae between the septum and inferior turbinate for which he was admitted and right ear myringotomy with synechiae release was done. Since then, the patient has had complaints of nasal obstruction and crusting in the nose. 1 year later the patient presented to at our center with complaints of bilateral nasal obstruction with nasal discharge. Nasal endoscopy showed mucopurulent nasal discharge with nasal synechiae in the left nasal cavity between the inferior turbinate and septum. A nasal swab showed *Staphylococcus aureus* and NCCT-PNS showed

bilateral osteo-meatal complex blocked with sinusitis and nasal septal perforation. Sample was sent for fungal stain and culture which was negative. The patient was continued on culture-directed oral antibiotics with MH nasal wash. After 10 days of treatment, the nasal discharge and crusting reduced.

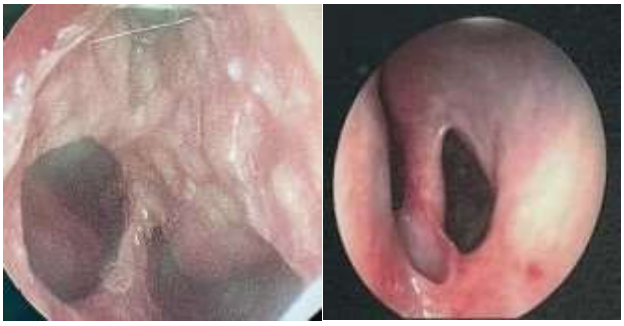

Figure 2: Pre and post MH application.

Case 3

A 47-year-old female presented to our department with complaints nasal obstruction with nasal discharge. Nasal endoscopy showed septal perforation with synechiae between the middle turbinate and septum. The patient underwent septoplasty with turbinoplasty 2 months back at a different center. Nasal swab was taken which showed Methicillin-resistant *Staphylococcus Aureus* (MRSA). Patient was started on oral antibiotics with nasal saline irrigation and MH washes. After 2 weeks of antibiotics and washes, normal healthy nasal mucosa was restored.

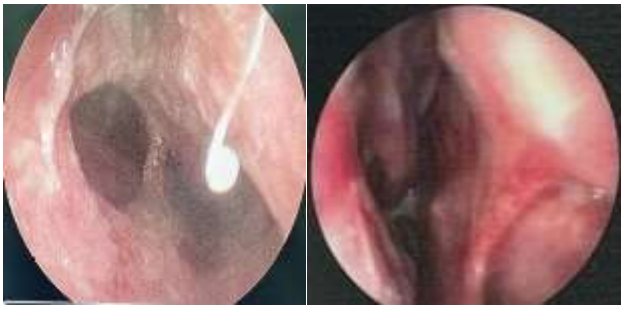

Figure 3: Pre and post MH application.

Case 4

A 31-year-old female presented to with complaints of recurrent epistaxis intermittently from both sides and crusting for 1 month. Nasal endoscopy showed crusting and ulceration of the nasal mucosa with minimal mucopurulent nasal discharge. The patient was started on oral antibiotics and nasal drops. She was advised to undergo MRI-PNS with autoimmune tests-cANCA, p-ANCA, RA factor. Nasal swab showed no pathogen growth. MRI-PNS showed left DNS with maxillary and sphenoid sinusitis. Anti-PR3-13.6, CRP-16, ANA-negative. The patient was referred to rheumatology, and a working diagnosis of granulomatosis with polyangiitis-limited disease was made. Multisystemic evaluation was done, which was negative. PTA was done which was within normal limits. Patient was started on oral Omnacortil and Septran DS for 2 weeks. Patient reported back after two weeks-epistaxis had stopped but she had persistent nasal crusting. Patient was started on MH nasal wash. A review after 2 weeks showed healthy nasal mucosa with minimal crusting.

All these 4 patients monitored with Lund and Kennedy nasal endoscopy and SNOT-22 score before treatment, at 6 weeks and 12 weeks. MH of UMF rating 30+ was used, 10%(v/v) solution of MH irrigation was prepared by mixing 24 ml of MH in 240 ml of water in a rinse bottle 120 CC of irrigation /nostril was used twice a day.

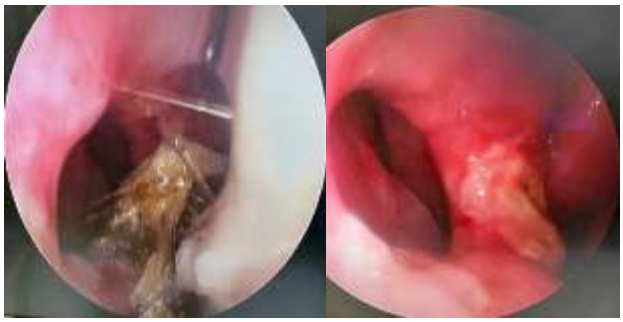

Figure 4: Pre and post MH application.

Case 5

This 55-year-old male patient presented to our OPD with history of post aural swelling for which he underwent Incision and drainage at a local hospital. Now he presented with complaints of severe pain and non-healing wound and maceration of the pinna. Cultures were taken which showed heavy growth of *P. aeruginosa*. IV antibiotics were started, and patient was put on a VAC dressing of ear. There was no significant improvement after multiple settings of the same. The decision was taken to apply MH along with VAC dressing for this. Patient had significant improvement within two settings, VAC dressing was removed, and topical application of MH continued with excellent recovery of the patient.

Figure 5: Case 5: pre and post MH application.

Table 1: Patient information.

Cases	Clinical presentation	Nasal endoscopy	Culture from the nasal swab	Treatment
Case 1	Post op FESS with nasal obstruction	Black necrotic material with purulent discharge in bilateral nasal cavity	MDR *Achromobacter Xylloxidans*	-IV cefoperazone /sulbactum for 2 weeks along with tablet minocycline -Nasal saline irrigation -Nasal irrigation with MH
Case 2	Post op FESS with nasal obstruction and mucopurulent nasal discharge	Mucopurulent nasal discharge with synechiae between the nasal septum and inferior turbinate	*Staphylococcus aureus*	-Culture sensitive oral antibiotics for 2 weeks along with -Nasal saline irrigation -Nasal irrigation with MH
Case 3	Post op FESS with septoplasty with symptoms of nasal obstruction and mucopurulent nasal discharge	Septal perforation with synechia between the middle turbinate and septum	*Staphylococcus aureus*	-Culture sensitive oral antibiotics for 2 weeks, along with -Nasal saline irrigation -Nasal irrigation with MH
Case 4	Recurrent epistaxis and crusting in nasal cavity-diagnosed with granulomatous polyangiitis	Ulceration and crusting of nasal mucosa	No growth	-Oral antibiotics and omnacortil for 2 weeks, along with -Nasal saline irrigation -Nasal irrigation with MH
Case 5	Perichondritis of PINNA post incision and drainage of post auricular abscess	Non healing wound and Skin maceration of pinna	*Pseudomonas aeruginosa*	- Culture sensitive IV antibiotics - VAC dressing - MH drops for topical application

DISCUSSION

Chronic rhinosinusitis (CRS) is a heterogeneous chronic inflammatory condition of the paranasal sinuses with multiple endotypes. The interaction of sinonasal epithelium with the outside environment leads to the activation of innate and adaptive immune pathways that causes inflammation and disruption of the normal mucociliary function.[14] Treatment for CRS typically involves a combination of medical therapies, lifestyle modifications, and surgical intervention-endoscopic sinus surgery.[15] Despite of adequate medical therapy and surgical intervention, around 6%-10% of CRS patients remain symptomatic.[16]

This has led to a strong shift in focus to understand the pathophysiology of sinus inflammation and endotyping of patients, paving the way for targeted post-operative pharmacotherapy.[16] The recurrent exacerbation and recalcitrant nature of CRS is attributed to the persistence of the pathogen in the sinonasal epithelium causing localized inflammation with higher rates of colonization leading to biofilm formation, immune dysregulation, inflammation, and barrier dysfunction.[17,18] *Staphylococcus aureus* and Pseudomonas aeruginosa associated with CRS, are frequently implicated to form biofilms.[19]

Biofilms are highly organized structures formed by communities of bacteria that are surrounded by a self-produced polymeric matrix tightly adhering them to the sinonasal mucosa. Targeting and disrupting these biofilms may help in the treatment of CRS, particularly in patients who have undergone sinus surgery but continue to experience active disease.[20,21] MH has antibacterial efficacy, which is contributed by the presence of MGO and macro-and micro-nutrients including sugars, free amino acids, proteins, enzymes, essential minerals, vitamins, and various secondary metabolites (flavonoids, phenolic acids and 1, 2-dicarbonyl compounds).[22]

A study conducted by Henriques et al described the effect of MH on *Staphylococcus aures* and pseudomonas, with both of these contrasting organisms being inhibited through different mechanisms.[25] MH inhibits *S. aureus* by interfering with the cell division process. It down-regulates murein hydrolase causing daughter cells to remain attached and ultimately resulting in cell death. MH reduced the production of key structural protein OprF required to maintain the stability of the cell envelope of *P. aeruginosa*. The instability in the outer membrane leads to blebbing of the membrane. High sugar content in MH leads to lysis and cell death.[26]

Effect of honey on biofilms

The presence of biofilm in CRS causes severe disease preoperatively and the persistence of infection and localized mucosal inflammation postoperatively. Biofilms in CRS patients are associated with significantly elevated levels of Th1-associated inflammatory mediators

and neutrophils. The propensity of biofilms to diminish innate immune response by reduced levels of the antimicrobial peptide lactoferrin further promotes microbial colonization and biofilm development. *S. aureus* biofilms have been hypothesized to facilitate the production of superantigen toxin, activating a subset of T-cells in a non–antigen-specific manner to cause inflammation.[27]

Study conducted by Lu et al which quantified cell viability of *S. aureus* in biofilm after their treatment with honey using BacTitre Glo Microbial Cell Viability Assay Kit concluded that, MGO and the sugar content of the MH not only reduced biofilm formation, but also reduced biofilm mass by killing bacterial cells entrapped in the biofilm matrix. [28]

In vitro, studies have shown that MH exhibits synergistic activity when combined with antibiotics such as oxacillin, rifampicin, and vancomycin. This means that when honey is used in conjunction with these antibiotics, their antimicrobial effects are enhanced, potentially improving treatment outcomes.[29,30]

Use of MH in post op FESS

FESS is reserved for patients who are symptomatic in spite of maximal medical therapy. The concept of FESS is the removal of tissue obstructing the osteo metal complex (OMC), reducing the local inflammatory load and the facilitation of drainage while conserving the normal non-obstructing anatomy and mucous membrane. There are 2 components to be taken into account in the post-op period- (i) Repair of the surgical site (ii) Reduction in the localized inflammatory process of the sinonasal mucosa.[31]

Meticulous follow-up is essential in the healing of the nasal mucosa and prevention of synechiae formation, which includes oral antibiotics, nasal saline irrigation, sinus debridement, and a topical steroid. There is a complex interplay between pro inflammatory, anti-inflammatory cytokines, and reactive oxygen species to promote macrophage activity for wound debridement-epithelization and angiogenesis in the early post-operative period.[32]

Manji et al conducted a study to identify the differences in cytokine expression between sinonasal tissue from patients treated with leptospermum (Manuka) honey (LH) irrigation versus normal saline irrigation twice daily for twelve weeks following sinus surgery (FESS). Compared to the saline irrigation group, five cytokines were differently expressed (CI=95%) in sinonasal tissue obtained from subjects in the LH irrigation group during the 12-week treatment period. LH may potentially act to modulate the expression of IL-6, IL-8, IL-13, MCP-1 and MIP-1β in sinonasal tissue. These cytokines are key mediators of the wound healing process and were found to be upregulated MH irrigation group.[33]

Use of MH in perichondritis

Perichondritis of pinna is inflammation of the perichondrial layer around the cartilage. If poorly managed can lead to deformity of the external ear and may progress to severe soft tissue infection. There are diverse reasons for the development of perichondritis most common being penetrating trauma to the pinna, iatrogenic infection like herpes zoster. The most common causative organism is pseudomonas, followed by *Staphylococcus aures*. Antibiotics are the mainstay of treatment.[36,37] The patient that presented to us was started on iv antipseudomonal antibiotic, and vacuum dressing was considered as there were many pockets of the micro abscess. In spite of good antibiotic coverage, the inflammation persisted. MH was topically applied before connecting the vacuum dressing in a week's time the pockets of micro abscess subsided. In the present scenario RCT was conducted by Henatsch et al for the treatment of chronically infected open mastoid cavities showed decreased discomfort and otorrhea in the group using MH, although there was no difference in the incidence of negative cultures between the groups.[38] There is no literature in relation to the use of MH in perichondritis, necessitating further studies.

Minimum inhibitory concentration of MH

A study conducted by Almasaudi et al used MH with different UMF against *S. aureus*. All honey showed bacterial inhibition at 10%- 20%(v/v). Various *in-vitro* studies have showed MIC as low as 2% (vol/vol) for *Staphylococcus aureus* and 5.5% (vol/vol) for *Pseudomonas aeruginosa*.[2,23]These variations in MIC may be related to the source of honey, the storage condition and the UMF factors. In our study, MH with UMF 30 was used. Antibacterial and anti-inflammatory properties were attained at 10% (v/v).[34]

A meta-analysis done in 2018 by Theresa and John Bent reviewing honey as treatment in otorhinolaryngology concluded the use of oral honey for treatment of cough associated with upper respiratory infection and pain control after tonsillectomy in pediatric studies. Clinical trials also suggest the usefulness of honey for exacerbations of chronic rhinosinusitis and allergic fungal rhinosinusitis, chronic infection of open mastoid cavities, radiation-induced xerostomia, and cough in adults. Evidence is insufficient to support the use of honey for post-FESS wound care, free flap or thyroidectomy postoperative wound care, or allergic rhinitis.[13]

MH is a natural antibiotic with a low toxicity profile, allowing for prolonged use when necessary. Honey is generally well-tolerated, and adverse effects are rare and may be related to intolerance due to its acidic nature.[35] Moreover, the development of bacterial resistance to honey has yet to be reported, making it an attractive alternative or adjunctive therapy, particularly in cases where AMR is a concern.

CONCLUSION

The use of honey, particularly MH, demonstrates promise in the treatment of bacterial infections, including those with AMR characteristics. However, it's essential to acknowledge that additional research, including well-designed clinical trials, is necessary to establish optimal protocols, standardize dosages, and thoroughly evaluate the long-term safety and efficacy of this approach. While MH 's antimicrobial properties have been observed in various studies, translating this knowledge into clinical practice requires rigorous investigation to ensure its effectiveness, safety, and proper integration with conventional antibiotic therapies. Collaborative efforts between researchers, healthcare professionals, and bee product specialists will be critical in advancing our understanding of MH's potential role in bacterial infection management and contributing to improved patient outcomes.

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