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SHORT COMMUNICATION

Arne Simon
Kai Sofka
Gertrud Wiszniewsky
Gisela Blaser
Udo Bode
Gudrun Fleischhack

Wound care with antibacterial honey (Medihoney) in pediatric hematology–oncology

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A. Simon (✉) · K. Sofka · G. Wiszniewsky · G. Blaser · U. Bode · G. Fleischhack
Department of Pediatric Hematology and Oncology, Children's Hospital, University of Bonn,
Adenauerallee 119,
53113 Bonn, Germany
e-mail: asimon@ukb.uni-bonn.de
Tel.: +49-228-2873254
Fax: +49-228-2873301

Abstract The physiologic process of wound healing is impaired and prolonged in pediatric patients receiving chemotherapy. Due to profound immunosuppression, wound infection can easily spread and act as the source of sepsis. Referring to in vitro studies, which confirmed the antibacterial potency of special honey preparations against typical isolates of nosocomially acquired wound infections (including Methicillin-resistant *Staphylococcus aureus* and Vancomycin-resistant enterococci) and considering the encouraging reports from other groups, Medihoney has now been used in wound care at the Department of Pediatric Oncology, Children's Hospital, University of Bonn for 3 years. Supplemented with clinical data from pediatric oncology patients, this article reviews the scientific background and our promising experience with Medihoney in wound care issues at our institution. To collect and analyze the available experience, we prepare an internet-based data documentation module for pediatric wound care with Medihoney.

Keywords Wound care · Pediatric oncology · Honey · MRSA

Introduction

A functional immune system is a prerequisite for the physiological process of wound healing. In pediatric oncology patients, the immune system is often suppressed, and wound healing is impaired to a clinically significant extent for extended periods of time. Obvious reasons for this include:

- Toxicity of treatment with cytotoxic antineoplastic agents or radiation therapy to the skin and mucous membranes (i.e., high-dose methotrexate, anthracyclines)
- Persistent or intermittent profound immunosuppression (neutropenia with <500 granulocytes/μl for more than 10 days, lymphocytopenia) [1]
- Malnutrition due to nausea, vomiting and mucositis [2]
- Microbial super infections (bacteria, fungi, viruses) [3–5]

Table 1 lists a selection of common wound care situations nurses and physicians in pediatric oncology departments are confronted with. It has to be considered that in this patient population, typical clinical signs of infection except for fever can be missing due to immunosuppression [6]. At the Department of Pediatric Hematology and Oncology, Children's Hospital, Medical Center, University of Bonn, antibacterial honey is used for wound care purposes now for 3 years. Supplemented with clinical data from pediatric oncology patients, this article reviews the scientific background and the experience with Medihoney in wound care issues at our institution. To the best of our knowledge, there has not been any prior publication describing the use of honey in pediatric oncology patients. With this case reports, we would like to encourage other oncological treatment centers to use antibacterial honey for wound treatment. An overview of the 16 wound care situations in 14 patients, their underlying illnesses, and outcomes are given in Table 2.

Antibacterial honey for wound treatment

Non-heated honey, processed under controlled pharmacological conditions [7] with proven antibacterial activity, is being increasingly used for the treatment of infected wounds

Table 1 Selection of common wound care situations in pediatric oncology

- Dehiscence and infection of surgical wounds (after tumor biopsy or surgery)
- Ulcers (decubiti) due to tumor cachexia or injuries due to peripheral neuropathy induced by cytotoxic agents (like vincristin)
- Inflamed or infected catheter entry sites (Broviac, Port)
- Deep wounds after reservoir explantation, leaving an infected port pocket (prolonged secondary wound healing)
- Skin necrosis due to extravasation of cytotoxic drugs, septic infections or vasoocclusion in patients with sickle-cell anemia and acute sickle crisis
- Skin and bone necrosis due to invasive *Aspergillosis*
- Ecthyma gangraenosum in patients with *Pseudomonas* sepsis
- Impaired and prolonged wound healing after amputation of extremities
- Anorectal inflammation, dermatitis, fissures, ulcers [45]

[5, 8–12], ulcers [13, 14], scalds and burns [15–19], for herpetic skin lesions and atopic dermatitis [20, 21] as well as for protection of transplants in plastic surgery [22, 23]. Sterilization with gamma radiation inactivates *Clostridium* spores, which may be contained in honey [24].

For medical purposes, honey is used primarily from bees collecting nectar from *Leptospermum* spp. (manuka, jelly-bush), growing in the immediate vicinity of the hives in Australia and New Zealand.[1] It has been demonstrated in vitro that the antibacterial effects of this honey are superior to most others [5, 12]. Important mechanisms of antimicrobial activity are the high osmotic potential (supersaturated sugar solution[2]) [7, 25] and the continuous production of hydrogen peroxide through the enzyme glucose oxidase in low, non-cytotoxic quantities [26]. Although its effects have been documented in vitro, the chemical nature of an additional "antibacterial factor" contributing to the potent bactericidal activity of this type of honey has not yet been elucidated [7]. Among other effects, honey stimulates the secretion of cytokines from macrophages, migrating into the wound tissue [27].

In particular, the team of Dr. Rose Cooper demonstrated that antibacterial honey shows bactericidal activity against nosocomial bacterial isolates even when diluted down to 5%. Among these bacteria were Methicillin-resistant *Staphylococcus aureus* (MRSA) and Vancomycin-resistant enterococci (VRE) as well as *Pseudomonas* spp. [9, 28–31].

Therefore, medical honey appears to be an attractive option for treating MRSA-infected wounds due to its bactericidal activity, to the absence of resistance problems, to low cost, and to high acceptability and feasibility. Local treatment with antibacterial honey usually enjoys a high level of patient acceptance; local pain occurs only rarely [14].

Medihoney (http://www.medihoney.com) is a standard mixture of honeys that has been sterilized but not inactivated through irradiation [24]. Appropriate products, for which the official certification of the European Union as medical device type IIb for wound care (CE certificate) is now available, consist of 100% honey or honey gel (80% honey and hypoallergenic waxes, facilitating a more viscous consistence).

Examples of application in clinical practice

Surgical wound infection

According to an interim analysis of the "Onkopaed NKI Study" (prospective surveillance of nosocomial infections (NI) in pediatric oncology patients, status Apr 03rd 2005, covering a cumulative surveillance period of 46,368 inpatient days) [32], surgical wound infections represent 6% of all NI with an incidence density of 0.28/1,000 inpatient days. Most wounds that were treated with antibacterial honey (Medihoney) in our department were dehiscent or infected surgical wounds, drainage sites as well as secondarily healing deep wounds due to explantation of an infected port reservoir. The first patient treated with Medihoney suffered from an MRSA infection of a drainage site after resection of an abdominal lymphoma.

The postoperative phase of wound healing is prolonged in immunocompromised patients. Complete healing can often not be waited for, as the intensity of chemotherapy necessitates the cytotoxic therapy to be continued. Catheter entry sites were often treated with Medihoney Wound Gel on a daily basis and were free of irritation and clear of infection afterwards. Even in a patient suffering from a relapse of acute lymphatic leukemia subjected to high level immunosuppression lasting for months, a deep surgical site infection of a port pocket healed completely without further complications (Fig. 1a–c). In our experience, it is possible to guide the oncological patient with a chronic wound through a high-dose chemotherapy with autologous stem cell transplantation without secondary complications if Medihoney is used for wound care (Table 2, pt. No. 11 and Fig. 2a,b). Further potential indications for therapy with Medihoney are necrotic skin lesions due to ex3travasation to cytotoxic drugs and superinfected skin lesions in children with eczemas or herpetic lesions [20, 21, 33–35].

Ecthyma gangrenosum

Ecthyma gangrenosum is a septic skin infiltrate observed in at least a third of all patients suffering from *Pseudomonas*

[1] The most prominent protagonist of manuka honey from New Zealand and pioneer of investigating its medical applications is Peter C. Molan, University of Waikato, Department of Biological Sciences, see http://honey.bio.waikato.ac.nz.

[2] Due to its high osmotic potential, honey facilitates the resolution of edema and keeps the wound moist by mobilizing wound exudate.

Table 2 Survey of 15 exemplary wound care situations in pediatric oncology patients successfully managed with Medihoney

ID	Malignancy/underlying illness (Neutropenia at day 1 of Medihoney treatment1=yes, 2=no)	Age	Description of the wound (cultured pathogens)	Length of treatment with Medihoney	Systemic antibiotics during Medihoney treatment (cumulative days)	Clinical course
1	Rhabdomyosarcoma (2)	10 (8/12)	Infection of the externally growing partially necrotic tumor (*S. aureus*)	5 d	5 d	Sterile wound on day 3, healing without further complication
2	Acute lymphoblastic leukemia, Down syndrome, (1)	12 (2/12)	Ecthyma gangraenosum right femur, sepsis (*P. aeruginosa*)	19 d	18 d	Sterile wound on day 4, healing without further complication
3	Hemophilia (2)	4 (8/12)	Infection of the port pocket (CoNS)	6 d	12 d	Sterile wound healing
4	Acute lymphoblastic leukemia first relapse (2)	14 (2/12)	Infection of the port pocket (CoNS)	15 d	10 d before Medihoney	Sterile wound healing, prolonged immunosuppression
5	Wilms' tumor relapse (1)	12 (2/12)	Dehiscent thoracotomy wound after resection of pulmonary metastases	13 d	8 d	Sterile wound healing, prolonged immunosuppression
6	Abdominal B cell lymphoma (2)	12 (5/12)	Drainage wound, infected with MRSA	17 d	4 d	Sterile wound healing
7	Ewing's sarcoma of the chest wall (2)	12 (5/12)	Dehiscent thoracotomy wound after resection of the primary tumor	36 d	15 d	Sterile wound healing, small keloid
8	T-non-Hodgkin lymphoma, mediastinal (2)	2 (2/12)	Infected entrance of the Broviac CVAD	31 d	12 d	Sterile wound healing
9	T-non-Hodgkin lymphoma (2)	5 (1/12)	Dehiscent suture at the port pocket	30 d	12 d	Sterile wound healing
10	Rhabdomysosarcoma (2)	17 (9/12)	Superficial surgical wound infection (tumor resection) with MRSA	7 d (plus octenidine)	5 d	Sterile on day 2, uncomplicated wound healing
11	Rhabdomysosarcoma (2)	17 (10/12)	Dehiscent superficial wound after Broviac implantation (high-dose chemotherapy with autologous stem cell transplantation)	28 d	20 d	In spite of severe immunosuppression and grad II skin toxicity: sterile wound, no complications
12	T-cell lymphoma of the central nervous system (2)	17	Dehiscent drainage wound, after splenectomy	11 d	12 d	Sterile wound healing
13	Desmoplastic metastatic small round cell tumor (2)	24 (10/12)	Abscess (*S. aureus*), wound care after surgical drainage	24 d	8 d before and 6 d during Medihoney	Sterile wound healing
14	Acute lymphoblastic leukemia second relapse (2)	34 (8/12)	Port pocket infection with secondary bacteremia (MRSE)	72 d!	14 d	Sterile wound healing

Table 2 (continued)

ID	Malignancy/underlying illness (Neutropenia at day 1 of Medihoney treatment1=yes, 2=no)	Age	Description of the wound (cultured pathogens)	Length of treatment with Medihoney	Systemic antibiotics during Medihoney treatment (cumulative days)	Clinical course
15	Metastatic osteosarcoma of the right upper extremity after four quarter amputation (2)	10 (1/12)	Dehiscent amputation wound after postoperative chemotherapy with adriamycin	30 d	0 d	Sterile wound healing
16	Wilms' tumor relapse (1)	12 (2/12)	Deep dehiscent wound after vascular surgery in the left groin (femoral arterial access)	52 d	27 d	Sterile wound healing, prolonged immunosuppression

Neutropenia refers to $<0.5\times10^9$ granulocytes/mm^3 at day 1 of treatment with Medihoney. Port=totally implanted CVAD
CVAD central venous access device, *d* days, *CoNS* coagulase-negative staphylococci
MRSE Methicillin-resistant CoNS, *MRSA* Methicillin-resistant *S. aureus*

aeruginosa sepsis. In the early phase, it appears as a circular erythema with subcutaneous induration and a central vesicle (see Fig. 3a,b). During later stages, it causes profound pain and leads to a central necrosis and a deep ulcer. Often it is localized at multiple sites.

Severe cases result in deep wounds, which heal only after weeks of systemic antibiotic treatment. According to our experience, those wounds may be treated with antibacterial honey, which is once daily filled into the wound cavity from day 3 after surgical excision of necrotic tissue. Until then, wounds are kept open with calcium alginates soaked with Octenidin. Similar concepts of treatment are also conceivable after surgical debridement and mash graft transplants of necrotic skin lesions due to meningococcal sepsis [13].

Convenience, adverse effects, and perception by the families

Wound care with Medihoney is rather simple and convenient, as the Medihoney dressing is non-adherent, and the wound only has to be cleaned with a rinse of sterile Ringer solution, and sterile compresses before the new honey layer is applied. A sterile gauze and tape dressing is added to cover the wound for the next day and to prevent leakage of honey or wound exudate. The Medihoney dressing should extend to cover any area of inflammation surrounding the wound. Until now, we did not observe adverse effects with the exception of local pain in a single patient with a large and deep wound after abdominal laparotomy. In this patient, wound care with the liquid Medihoney Barrier was ceased, and a change to the more consistent Medihoney Gel was not considered as feasible. Our prospective observational study revealed a high acceptance of patients and their families for this treatment, which had a positive impact on patient and parent satisfaction.

Discussion

The ideal wound antiseptic (according to Kramer et al. [36]):

- shows a quick onset of activity and a remanent, broad spectrum effect against bacteria and fungi, even under the unfavorable condition of an exudating, colonized or infected wound (dilution, different protein consistence, chemical inactivation);
- enhances and accelerates the physiologic process of wound healing (debridement, granulation), even if applied for prolonged periods;
- does not cause adverse local or systemic effects (allergy, toxicity related to absorption);
- is of moderate cost even if applied two times daily.

Polyvidone iodine has the advantage of antiseptic properties and is well suited for skin disinfection prior to invasive procedures [36, 37]. However, we have decided against its use in wound care for our patients due to the adverse effects of systemic absorption of iodine on thyroid function. Furthermore, it is difficult to assess the local situation in a wound covered with Polyvidone iodine. Even though Octenidin does have some elevated cytotoxic effects in vitro relative to iodophores or polyhexanide [14, 36], it is our first choice for antiseptic treatment of infected wounds within the first 48 h. We switch to antibacterial honey (Medihoney) as soon as possible. Later on, wounds are rinsed with sterile Ringer solution during each daily dressing change with non-touch, sterile techniques and systemic analgosedation if necessary [13].

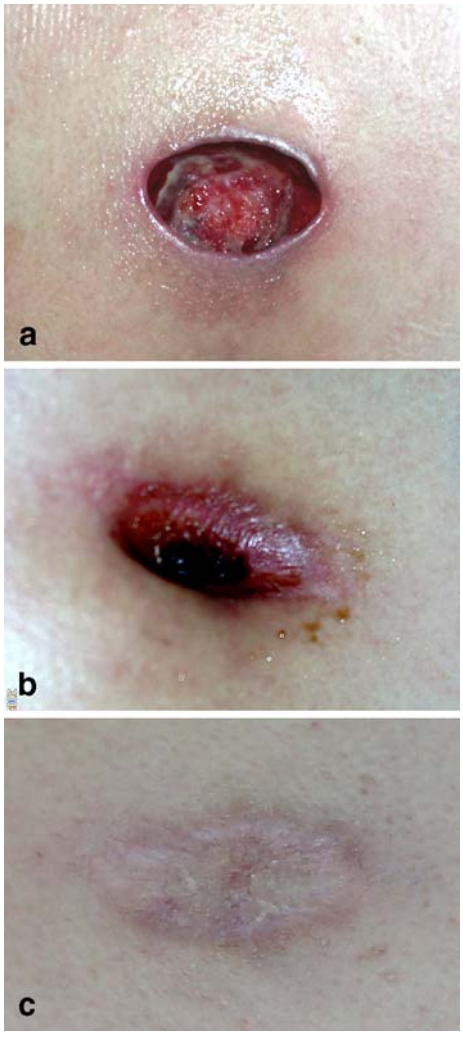

Fig. 1 **a**–**c** Deep surgical site infection of a port pocket, treated with Medihoney complete healing without further complications despite prolonged immunosuppression

According to scientific literature and clinical experience, antibacterial honey (Medihoney) seems to fulfill most of the above-mentioned requirements of an ideal antiseptic in wound care. The only open question for Medihoney is the residence time needed to kill bacteria in a colonized wound, which is supposed to be less than 5 min for Octenidin or Polyvidone iodine.

Theoretical adverse reactions such as anaphylaxis or systemic toxicity (i.e., hyperglycemia in diabetic patients) have not been reported so far. Nevertheless, meticulous clinical observation and documentation should ensure that severe adverse events related to the use of honey in wound care are immediately reported and published, when such a situation arises. Complex wounds and wounds of immunocompromised patients should only be treated under professional medical supervision. The additional administration of systemic antibiotics (see Table 2) is often necessary in pediatric

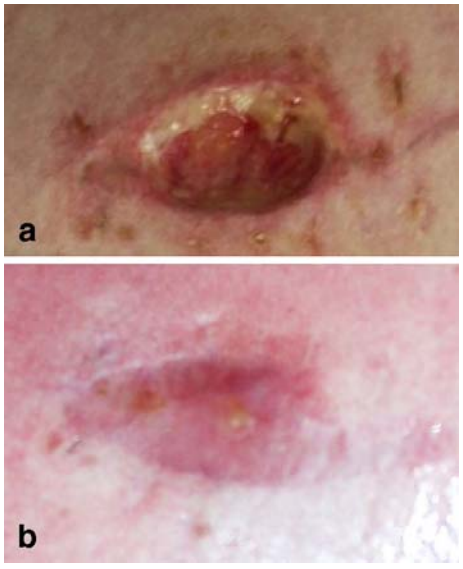

Fig. 2 **a**, **b** Chronic superficial wound (6 cm diameter), treated with Medihoney through a high-dose chemotherapy with autologous stem cell transplantation without secondary complications

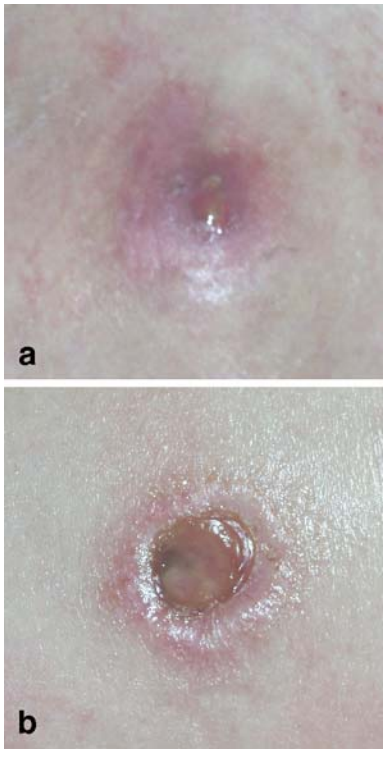

Fig. 3 **a**, **b** Ecthyma gangraenosum in a leukemia patient with *P. aeruginosa* sepsis. **a** Early phase with circular erythema, subcutaneous induration and a central vesicle. **b** Later stage central necrosis and a deep ulcer, covered with Medihoney

oncology patients during periods of profound neutropenia ($<0.5\times10^9$/l).

Even the best antiseptic, anti-edema, and granulation stimulating local treatment does not abrogate the need of early surgical drainage of retentions and the early debridement of necrotic wound areas [8, 12].

Vardi et al. observed the complete healing of complicated, deep sternal wound infections with honey in nine neonates and infants after surgical intervention for congenital heart disease within 21 days of treatment. The majority of these patients had been treated unsuccessfully with local antiseptics and systemic antibiotics for more than 14 days (*Pseudomonas*, *S. aureus*, MRSA, *Escherichia coli*, *Enterobacter* spp.). For six of nine patients, the antibiotic treatment was finished at the beginning of wound care with honey [44]. There are many impressive case studies but only a few controlled trials [10, 11, 39–41] concerning the use of honey for wound care. In superficial burn wounds, but not for deep necrotic burns [17], an advantage of honey relative to other applied remedies [18, 38] was shown.

Johnson et al. performed a randomized, controlled trial comparing the prophylactic effect of thrice-weekly exit-site application of Medihoney versus mupirocin on infection rates in patients who were receiving hemodialysis via tunneled, cuffed central venous catheters [42]. A total of 101 patients were enrolled. The incidences of catheter-associated bacteremias in honey-treated (n=51) and mupirocin-treated (n=50) patients were comparable (0.97 versus 0.85 episodes per 1,000 catheter-days, respectively; not significant). The authors concluded that thrice-weekly application of standardized antibacterial honey to hemodialysis catheter exit sites was safe, cheap, and effective and that with local Medihoney, the problem of resistance induction against mupirocin can be circumvented. Biswal et al. investigated the use of honey in 40 adult patients with head and neck cancer. In the study arm, patients were advised to stake 20 ml of pure honey 15 min before, 15 min after and 6 h post-radiation therapy. There was a significant reduction in the symptomatic grade 3/4 mucositis among honey-treated patients compared to controls; i.e., 20% versus 75% (p<0.001). Fifty-five percent of patients treated with topical honey showed no change or a positive gain in body weight compared to 25% in the control arm (p=0.053); the majority lost weight. The authors concluded that topical application of natural honey is a simple and cost-effective treatment in radiation mucositis, which warrants further investigation in a multi-center randomized trial [43].

In the near future, an internet-based documentation system with standardized items for the documentation of wound healing in children treated with Medihoney will be available. The main objective of this database will be the cumulative analysis of prospectively documented treatment experiences from many pediatric centers. The results will be sent to the participating centers and published in the medical literature. Prospective randomized and controlled studies comparing the use of Medihoney with conventional regimes of wound care are desirable, but double-blinding of honey use in wound care is not possible in clinical practice. Potential concomitant and confounding treatments such as administration of antibiotics or local antiseptics as well as the duration of neutropenia have to be carefully controlled for by randomization.

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