Successful Healing of Diabetic Foot Ulcers and Various Etiology Ulcers with Natural Honey: An Alternative Paradigm in Wound Healing

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Abstract
Hypothesis: Rapid healing or halt in progression occurs with timely intervention of natural honey in subjects with chronic diabetic foot ulcers and various etiology ulcers.

Design: In a prospective nonrandomized case series, 42 consecutive subjects were treated with natural honey after sharp surgical debridement of their ulcers.

Setting: A single (interphase) primary care teaching health center.

Patients and Methods: Forty two consecutive patients with a total of 50 wounds (1.0–6.5 cm in diameter) were treated with natural honey after sharp surgical debridement.

Main Outcome Measure: Time to 100% healing, as defined by full epithelialization of the ulcers.

Results: Twenty seven of 30 patients with diabetic foot ulcers had complete healing of all wounds. In these patients, wounds healed in an average of 46 days. In patients with decubitus ulcers, 4 of 5 wounds healed in an average of 31 days. Six varicose vein ulcer patients healed in an average four weeks. Four burn patients healed in an average of three weeks, while hydroxyurea induced ulcer healed in one month.

Conclusions: In chronic diabetic foot ulcers and ulcers of various etiologies, the utilization of natural honey with sharp surgical debridement is effective in producing full epithelization. The high healing rate with full epithelization in these various types of wounds suggests that natural honey may act as an alternative wound dressing stimulating fibroblast, keratinocyte activation, enhancing angiogenesis and wound contraction.

Keywords: Diabetic Foot ulcers; Natural Honey; Ulcers; Burns

Introduction
The morbidity and mortality from chronic wounds including those of, diabetic, venous and decubitus origin presents a huge health burden as well as pain and suffering for the patient and his family along with loss of productivity, absenteeism from work, social isolation and impaired quality of life. Patients with diabetes who undergo limb amputation have an increased risk for another limb loss, which has a 5-year mortality rate of 39% to 68% [1]. The direct financial cost of lower-limb amputation ranges from $20,000 to $60,000 in the US [2]. Financial analyses are often exceeded when the cost of failed vascular reconstruction and rehabilitation as well as lost productivity are accounted for. The dire consequences of diabetic ulcers to patients and their families make it essential to determine the best approach in managing these chronic wounds.

Pressure ulcers also cause pain, loss of productivity, and huge expenditures [3].

They commonly affect the elderly, those who are bedridden, having spinal cord injury, and post reconstructive orthopedic surgery. Stage II and greater pressure ulcers have an estimated prevalence of up to 17% among hospitalized patients [4,5], at least 12% among patients in nursing homes, and 20% to 30% [6,7] among patients with spinal cord injury and in rehabilitation units.

Additionally, increased mortality is associated with pressure ulcers when healing does not occur [8–10]. The healing rate for stage II ulcers is as low as 26% at six months.

Alternative treatments for pressure ulcers must be sought for the aging population especially in developing countries. Sequential healing occurs in acute wounds including surgical incisions without intervening on part of the clinician. Growth factors are secreted by platelets which enter the wound with ultimate recruitment of macrophages into the wound. These macrophages also release growth factors [12] that cause endothelial cells proliferation in the wound, subsequently stimulating fibroblasts to synthesize collagen [13–14]. A chronic wound is characterized by failure to heal in a timely and orderly process, compromising anatomic and functional integrity [15–20] and intervention is always needed to prevent the progression of diabetic foot ulcers and pressure ulcers into becoming chronic wounds.

Natural honey represents a credible alternative treatment for chronic ulcers because honey has been shown to exert antibacterial, antifungal and antiviral activity, even against life threatening bacteria such Methicillin-resistant *Staphylococcus aureus* (MRSA) and Vancomycin resistant enterococci. The antibacterial activity of honey is related to its release of hydrogen peroxide, lower water content (0.56–0.59); low pH (3.2–4.5); phenolic acids flavonoids are all responsible collectively for its antibacterial activity [21,22].

Honey provides an ideal medium for fibroblast proliferation, migration, and organization of collagen through its physiochemical properties (e.g., pH and viscosity). Furthermore, the newly granulating tissues are protected from exogenous pathogens due to the thick and viscous property of honey working as an external barrier for wounds.

Histological and clinical studies have demonstrated the anti-inflammatory properties of honey attracting immunocompetent cells (e.g., monocytes) within the wound bed [23,24].

Honey provides water to the wound in adequate amounts just enough to stimulate wound healing without causing maceration to the peri wound area. This is due to the fact that water represents 17–20% of honey composition depending on the floral source of honey. Fibroblasts are encouraged to proliferate and migrate as a result of drainage of fluids from capillaries and lymph due to the osmotic gradient of honey. Healthy uninfected granulation tissue is compromised by toxic rinse solutions such as hydrogen peroxide.

However, honey when it comes in contact with the wound surface releases a hydrogen peroxide at physiological concentrations (1:1000) as a result of the enzyme glucose oxidase just enough to kill the bacteria without compromising the newly forming granulation tissue [25].
Patients, Materials and Methods

In this manuscript we explain all of the consecutive chronic diabetic foot ulcers, decubitus ulcer, venous ulcers and hydroxyl urea induced ulceration that were treated with Natural honey. The subjects were treated over nine months with a follow-up period ranging from 2 to 12 months.

All ulcers were managed in a standardized fashion: The wounds were cleaned with normal saline and surgically debrided using a sharp scalpel if they had necrotic tissues or calllosities until a clean wound bed was achieved (i.e. no necrotic tissue was present). Subsequently, treatment with natural honey was commenced by applying it directly on the wound bed and covering it with a nonadherent dressing made of knitted cellulose acetate fabric (Adaptic Non-Adhering Dressing, Systagenix, San Antonio, TX) and impregnated with specially formulated petroleum emulsion. When natural honey is applied to the wound bed it becomes less viscous and is diluted through exudation. As a result, wounds were covered with a cotton wool bandage and a lightly applied cotton bandage to contain the natural honey in the wound bed environment. The natural honey dressing was changed on a daily basis and offloading was provided using a multilayered incontinence pad which was applied around the periwound area. This option was chosen since total contact or removable casts are not available at primary care level, but only if the patient is admitted to the hospital. At each daily review, wounds were debrided if necessary and assessed for signs of infection and pain level. Forty two consecutive patients were treated with Natural honey (30 patients had 38 chronic diabetic foot ulcers; 6 venous ulcers, 5 decubitus ulcers and 1 hydroxyurea induced ulcer).

There were five chronic diabetic wounds that extended to bone. The wounds ranged in diameter from 1 cm to 6.5 cm. All patients who had a probe to bone positive test (5 chronic diabetic foot ulcers) were treated with oral amoxicillin-calvulanate 1 gram twice daily and clorproflaxacin 500 mg twice daily for six weeks. Recent studies have demonstrated that minimum inhibitory concentrations (MICs) of targeted organisms in bone can be achieved by oral antibiotics in particular, fluoroquinolones, linezolid, and trimethoprim have been found to achieve bone concentrations at ~50% of serum [26-28].

In all subjects, culture specimens were obtained routinely from deep tissue after excising the superficial necrotic tissue and antibiotics were offered to those with positive cultures.

All patients were educated on how to achieve pressure relief. Therefore, we describe our initial results using natural honey for patients with chronic diabetic foot ulcers and other etiologies.

The Natural honey used in this study comes from the Russian federation from the honey bees (Apis mellifera) that originate in the Primorsky Krai region, its thick, homogenous and whitish in color keeps well on the surface of the ulcer:

- Pressure ulcers were staged in accordance with published international guidelines [35]
- Stage I: Nonblanchable erythema of intact skin
- Stage II: Partial-thickness skin loss involving epidermis or dermis or both.
- Stage III: Full-thickness skin loss involving damage or necrosis of subcutaneous tissue, which may extend down to but not through underlying fascia.
- Stage IV: Full-thickness skin loss with extensive destruction, tissue necrosis, or damage to muscle, bone, or supporting structures (such as tendon and joint capsule). Undermining and sinus tracts also may be associated with stage IV pressure ulcers.

Similarly, diabetic foot ulcers were classified according to Wagner’s classification which assesses ulcer depth and presence of osteomyelitis or gangrene by using the following grades:

- Grade 0 (pre-or post ulceration)
- Grade 1 (partial/full thickness ulcer)
- Grade 2 (reaches tendon or capsule)
- Grade 3 (probe to bone)
- Grade 4 (partial foot gangrene)
- Grade 5 (whole foot gangrene) [36]

Results

Thirty patients with chronic diabetic foot ulcers were treated. Of these, 27 had all wounds healed (Figure 1 and Figure 2); giving a healing rate of 90% in total (Table 1). Those three ulcers which have failed to heal were among patients with diabetes and suffering from severe peripheral arterial disease coupled with chronic osteomyelitis of their big hallux with purulent discharge, third toe exposed distal phalanx and the third patient was a patient undergoing kidney dialysis, with charcot foot treated by external fixation and with discharging purulent ulcer in the heel.

Of the patients with decubitus ulcers, 4 of 5 had all wounds healed in an average of 31 days except one stage 4 decubitus ulcer patient who had an ulcer depth reaching to the capsule which took three months to heal (Table 2, Figure 3-7).

Patients with burns were treated accordingly with the use of natural honey in the same manner and the patient with a whirlpool injury showed several bullae on the dorsum of the foot along with

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**Figure 1:** A. Diabetic foot post amputation of 2nd, 3rd & 4th toes secondary to wet gangrene and a dry gangrenous 5th toe. B, wound showing 50% reductions in size for weeks after natural honey application and auto amputation of 5th toe. C, Wound has completely healed and epithelialized after nine weeks.
Figure 2: A, necrotizing fasciitis post excision neglected by patient B, post sharp debridement, C, complete healing after 12 weeks.

<table>
<thead>
<tr>
<th>Patient No./Sex/age</th>
<th>No. of ulcers</th>
<th>Size of largest Ulcers (cm)</th>
<th>Location of Ulcer</th>
<th>Etiology</th>
<th>Other factors</th>
<th>Duration of natural honey applications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F/65</td>
<td>3</td>
<td>4.5 × 2.5</td>
<td>First toe, post surgical excision of 2nd, 3rd, 4th toe</td>
<td>T2DM</td>
<td>ABI, 5.5, chronic renal impairment, gangrene</td>
<td>16 weeks</td>
</tr>
<tr>
<td>2/M/45</td>
<td>1</td>
<td>6.0 × 4.5</td>
<td>6.5 × 4.0 proximal to the ankle joint</td>
<td>T2DM</td>
<td>Cellulitis, sinus formation, nicotine addiction</td>
<td>12 weeks</td>
</tr>
<tr>
<td>3/M/56</td>
<td>2</td>
<td>2.5 × 2.1</td>
<td>Right foot</td>
<td>T2DM</td>
<td>ABI, 0.6, HTN, Obesity, HTN</td>
<td>7 weeks</td>
</tr>
<tr>
<td>4/M/45</td>
<td>1</td>
<td>3.0 × 2.5</td>
<td>First toe</td>
<td>T2DM</td>
<td>HTN, Hypercholesterolemia</td>
<td>4 weeks</td>
</tr>
<tr>
<td>5/F/65</td>
<td>1</td>
<td>2.4 × 3.5</td>
<td>2nd toe</td>
<td>T2DM</td>
<td>HTN</td>
<td>3 weeks</td>
</tr>
<tr>
<td>6/F/44</td>
<td>2</td>
<td>3.1 × 1.5</td>
<td>Right big hallux</td>
<td>T2DM</td>
<td>Obesity</td>
<td>3 weeks</td>
</tr>
<tr>
<td>7/F/55</td>
<td>1</td>
<td>3.0 × 3.3</td>
<td>Base of 1st metatarsal</td>
<td>T2DM</td>
<td>Rheumatoid arthritis</td>
<td>4 weeks</td>
</tr>
<tr>
<td>8/F/54</td>
<td>1</td>
<td>6.0 × 5.5</td>
<td>Left plantar</td>
<td>T2DM</td>
<td>ABI, 0.7, Chronic nicotine addiction, failed skin graft</td>
<td>8 weeks</td>
</tr>
<tr>
<td>9/M/58</td>
<td>1</td>
<td>7.5 × 10.8</td>
<td>Left dorsum foot</td>
<td>T2DM</td>
<td>HTN, Bronchial asthma</td>
<td>12 weeks</td>
</tr>
<tr>
<td>10/F/71</td>
<td>1</td>
<td>1.0 × 0.8</td>
<td>Left first toe</td>
<td>T2DM</td>
<td>Burn injury</td>
<td>3 weeks</td>
</tr>
<tr>
<td>11/M/45</td>
<td>1</td>
<td>2.0 × 3.4</td>
<td>Base of 2nd metatarsal</td>
<td>T2DM</td>
<td>HTN, Obesity, COPD</td>
<td>3 weeks</td>
</tr>
<tr>
<td>12/F/54</td>
<td>1</td>
<td>3.0 × 2.5</td>
<td>Left plantar</td>
<td>T2DM</td>
<td>HTN, ABI, 0.9</td>
<td>4 weeks</td>
</tr>
<tr>
<td>13/M/60</td>
<td>1</td>
<td>2.0 × 1.5</td>
<td>Right plantar</td>
<td>T2DM</td>
<td>COPD, OA, Hyperlipidemia</td>
<td>3 weeks</td>
</tr>
<tr>
<td>14/M/54</td>
<td>2</td>
<td>2.4 × 3.0</td>
<td>Right big hallux</td>
<td>T2DM</td>
<td>ABI, 0.7</td>
<td>5 weeks</td>
</tr>
<tr>
<td>15/M/64</td>
<td>1</td>
<td>2.0 × 1.5</td>
<td>2nd toe</td>
<td>T2DM</td>
<td>HTN, Obesity, OA</td>
<td>3 weeks</td>
</tr>
<tr>
<td>16/F/54</td>
<td>1</td>
<td>2.1 × 1.0</td>
<td>Left plantar</td>
<td>T2DM</td>
<td>Cellulitis, HTN</td>
<td>3 weeks</td>
</tr>
<tr>
<td>17/F/50</td>
<td>1</td>
<td>3.0 × 2.6</td>
<td>Big hallux</td>
<td>T2DM</td>
<td>Obesity, HTN</td>
<td>4 weeks</td>
</tr>
<tr>
<td>18/F/64</td>
<td>1</td>
<td>1.0 × 1.3</td>
<td>Right foot</td>
<td>T2DM</td>
<td>Infected, HTN</td>
<td>5 weeks</td>
</tr>
<tr>
<td>19/F/58</td>
<td>1</td>
<td>3.3 × 2.0, toes metatarsals</td>
<td>Left foot</td>
<td>T2DM</td>
<td>Cellulitis</td>
<td>3 weeks</td>
</tr>
<tr>
<td>20/M/53</td>
<td>2</td>
<td>Toes, metatarsals</td>
<td>Left heel</td>
<td>T2DM</td>
<td>Obesity, COPD, CAD</td>
<td>6 weeks</td>
</tr>
<tr>
<td>21/M/55</td>
<td>1</td>
<td>1.9 × 1.9</td>
<td>Right heel</td>
<td>T2DM</td>
<td>HTN, Obesity, CAD</td>
<td>8 weeks</td>
</tr>
<tr>
<td>22/M/77</td>
<td>2</td>
<td>1.5 × 2.0</td>
<td>Left plantar</td>
<td>T2DM</td>
<td>Obesity, HTN, Bronchial asthma</td>
<td>3 weeks</td>
</tr>
<tr>
<td>23/F/65</td>
<td>1</td>
<td>2.0 × 2.2</td>
<td>Right plantar</td>
<td>T2DM</td>
<td>Hypercholesterolemia</td>
<td>3 weeks</td>
</tr>
<tr>
<td>25/M/63</td>
<td>1</td>
<td>2.4 × 2.2</td>
<td>Right heel</td>
<td>T2DM</td>
<td>HTN, OA, COPD</td>
<td>2 weeks</td>
</tr>
<tr>
<td>26/F/59</td>
<td>1</td>
<td>2.5 × 1.8</td>
<td>Right big hallux</td>
<td>T2DM</td>
<td>Cellulitis</td>
<td>2 weeks</td>
</tr>
<tr>
<td>27/F/57</td>
<td>1</td>
<td>3.2 × 1.5</td>
<td>Left heel</td>
<td>T2DM</td>
<td>Obesity, HTN</td>
<td>3 weeks</td>
</tr>
<tr>
<td>28/M/55</td>
<td>2</td>
<td>2.5 × 2.1</td>
<td>Left heel</td>
<td>T2DM</td>
<td>HTN, Hypercholesterolemia, obesity</td>
<td>4 weeks</td>
</tr>
<tr>
<td>29/M/66</td>
<td>1</td>
<td>2.2 × 2.1</td>
<td>Left big hallux</td>
<td>T2DM</td>
<td>Obesity, OA, HTN</td>
<td>2 weeks</td>
</tr>
<tr>
<td>30/M/52</td>
<td>1</td>
<td>3.1 × 3.3</td>
<td>Left big hallux</td>
<td>T2DM</td>
<td>HTN, ABI, 0.8</td>
<td>2 weeks</td>
</tr>
</tbody>
</table>

Table 1: Clinical characteristics of patients with chronic diabetic foot ulcers. (M: Male; T2DM: Type 2 Diabetes Mellitus; Y: Yes; F: Female; CAD: Coronary Artery Disease; HTN: Hypertension; ABI: Ankle Brachial Index; OA: Osteoarthritis; COPD: Chronic Obstructive Pulmonary Disease.)

<table>
<thead>
<tr>
<th>Patient No./Sex/ Age</th>
<th>Number of ulcers</th>
<th>Size of largest Ulcer (cm)</th>
<th>Location of Ulcer</th>
<th>Etiology</th>
<th>Other factors</th>
<th>Duration of natural honey applications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M/63</td>
<td>2</td>
<td>4.6 × 5.1 × 3.1 depth</td>
<td>Sacrum/mid back</td>
<td>Paraplegia</td>
<td>COPD</td>
<td>8 weeks</td>
</tr>
<tr>
<td>2/F/72</td>
<td>1</td>
<td>3.1 × 2.9</td>
<td>Sacrum</td>
<td>Stroke</td>
<td>T2DM</td>
<td>6 weeks</td>
</tr>
<tr>
<td>3/F/68</td>
<td>1</td>
<td>1.5 × 2.0</td>
<td>Buttock</td>
<td>Stroke</td>
<td>T2DM</td>
<td>4 weeks</td>
</tr>
<tr>
<td>4/F/59</td>
<td>1</td>
<td>1.8 × 2.4</td>
<td>Sacrum</td>
<td>Anoxic brain injury</td>
<td>T2DM, COPD</td>
<td>4 weeks</td>
</tr>
<tr>
<td>5/M/63</td>
<td>1</td>
<td>1.8 × 2.0</td>
<td>Sacrum</td>
<td>Stroke</td>
<td>Parkinson disease</td>
<td>3 weeks</td>
</tr>
</tbody>
</table>

Table 2: Clinical characteristics of patients with decubitus ulcers. (M: Male; F: Female; COPD: Chronic Obstructive Air Way Disease; T2DM: Type 2 Diabetes Mellitus.)
**Figure 3:** Neuropathic diabetic heel ulcer with ABI = 0.7, showing complete healing after seven weeks.

**Figure 4:** A, Sacral pressure ulcer; B, 6 weeks post-treatment showing 90% reduction in wound size; C, complete healing.

**Figure 5:** A, Varicose vein ulcer; B, showing 75% reduction in ulcer size 10 weeks post treatment; C, complete healing after 12 weeks.

**Figure 6:** A, Neuropathic heel ulcer; B, 75% reduction in wound size six weeks later; C, complete healing after eight weeks.

**Figure 7:** A, Post osteomyelitis 1st hallux amputation; B, 10 weeks later; C, complete healing 16 weeks later.
peeling of the skin and exhibiting injury deep into the reticular dermis measuring 2 cm width and 7 cm length and hyperaemia extending from the toes to above the ankle regions (Figure 8, Table 3). Daily natural honey application along with oral ciprofloxacin 500 mg twice daily for one week was prescribed to cover for Pseudomonas aeruginosa.

**Discussion**

In this article, we describe an efficacious, safe and enhanced healing process using natural honey for chronic diabetic foot ulcers and various other etiology ulcers. In 90% of diabetic foot ulcers, notable healing resulted after a single daily application of natural honey.

On the basis of this published evidence, we therefore began treating non-healing chronic ulcers of various etiologies present for longer than six months with Natural honey. Therefore, we hypothesized that a single daily application of Natural honey applied after proper sharp debridement, specifically in the population of patients with diabetes and in those with decubitus ulcers, could prevent the progression of these wounds and possibly accelerate their closure.

Furthermore, none of 38 wounds in patients treated with natural honey deteriorated or failed to heal under this wound healing paradigm. Therefore, the use of natural therapy should be considered by clinicians managing pressure ulcers or chronic diabetic foot ulcers in order to avoid the deterioration of these highly morbid conditions.

In physiologically impaired wounds including pressure ulcers and diabetic wounds, higher healing rates are associated with higher debridement rates [30]. In our study, subjects required no more than one debridement prior to natural honey application. This is due to extensive sharp debridement at point of entry. In our series, debridement was carried out on wound to the level at which scar and infection are no longer present, this approach has proved to be safe and effective. Likewise, viable tissue should not be excised. In particular, the wound margins should not be extended more than 1 mm or 2 mm.

Our data suggest that osteomyelitis prevents natural honey from being effective in an area in which the wound is adjacent to the area of osteomyelitis. The wounds of four patients in our series failed to heal; some of these patients had osteomyelitis and others had concurrent severe peripheral vascular disease.

In a met analysis carried out by Tian X et al. [29], a total of 4 RCTs involving 258 participants were included, and three trials involving 228 participants met the quantitative analysis and one study involving 30 participants met qualitative analysis. Results of descriptive and meta-analysis showed that total treatment time, ratio of purging germs mean purge time of ulcers, healed area of ulcers in honey dressing group are better than that of the control group, respectively reaching a difference considered to be statistically significant. Pooled differences in overall treatment time after intervention revealed a difference between the honey dressing group and control groups [SMD = −1.28, 95% CI (−2.46, −0.07), p = 0.04] [29].

One possible limitation of our study in design is that it was a nonrandomized study with no placebo group. However, authors of the systemic review assessing four randomized controlled trial which met the inclusion criteria, comprising four randomized controlled trials with a total population of 228 subjects found that natural honey was superior to traditional dressing in the management of chronic diabetic foot ulcers. In another systematic review comparing natural honey to standard wound therapies. Sosa SO [31] carried out an exhaustive search of available medical literature using search engines MEDLINE, CHINAHL, and Web of Sciences. The validity of each study was determined by the use of Jadad score. In comparison to standard wound therapy all studies point towards the value of honey in increasing the healing rate of chronic ulcers. However, only one study reached statistical significance.

It is well documented that patients with diabetes are at an increased risk for developing foot ulcers which are further hindered by both an increased susceptibility for wound infection and subsequently impairment in wound healing [32].

About 85% of all nontraumatic lower limb loss is preceded by
an ulcer, half of which are carried out in patients with diabetes [33]. A cost of a single application of natural honey in our study is around 10 US cents which is much cost saving compared to advanced wound products.

Conclusion

The data presented in this manuscript demonstrates that natural honey therapy provides an alternative choice that assures lack of progression in both diabetic and other chronic ulcers once infection is controlled by appropriate debridement and antimicrobial cover.

Certain difficult to heal wounds may require more than a single type of wound therapy. In the future, natural honey may be used in synergy with some other advanced wound products and or drugs currently available for patients in whom wounds are difficult to heal. Natural honey has demonstrated significant granulation ability, fibroblast stimulation, and enhanced anti-inflammatory activity [22–24]. In our cohort study natural honey use at primary care level represents a paradigm shift in the management of chronic wounds of various etiologies significantly enhancing granulation tissue, epithelization in healing of venous stasis ulcer, pressure, and diabetic foot ulcer and reduction in cost.

Along with advanced wound products Natural honey should be part of the armamentarium used in managing acute and chronic wounds. Treatment plans for chronic wounds should be based on the fact that chronic wounds by definition have an impaired healing physiology. Initial recognition of a diabetic ulcer should prompt an immediate visit with the patient’s first point of contact that is a family physician with special interest in diabetic foot care. A holistic management of the patient condition including metabolic control, diet, and psychological well-being, diabetic foot ulcer assessment including neurological and vascular assessment can all be done in an ideal time and place.

References


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