

RECURRENT
APHTHOUS ULCER
FACT FILE



GENGI GEL[®]
Hyaluronic Acid

HOW CAN RECURRENT APHTHOUS ULCER AFFECT ORAL HEALTH?

Recurrent Aphthous Ulcer (RAU), also recognized as Recurrent Aphthous Stomatitis (RAS) or canker sores, represents the most prevalent ulcerative condition **affecting the oral mucosa, impacting approximately 20-25% of the global population** (Akintoye and Greenberg, 2014; Manoj et al., 2023). This condition is characterized by an inflammatory state of unknown etiology, marked by the recurrent appearance of singular or multiple ulcerations within the oral mucosa, including the buccal and labial mucosa and tongue (Natah et al., 2004; Akintoye and Greenberg, 2014). These ulcers present as **painful, circular, superficial lesions featuring well-defined erythematous margins and a yellowish-gray pseudomembranous center** (Natah et al., 2004; Akintoye and Greenberg, 2014). There are three clinical subtypes of RAU, known as **Minor RAU, Major RAU, and Herpetiform RAU** (Belenguer-Guallar et al., 2014; Lau and Smith, 2022). Minor RAU,

affecting 80% of cases, is characterized by small ulcers less than 1 cm in diameter that typically resolve within 4-14 days without scarring. Major RAU represents a more severe manifestation, featuring ulcers larger than 1 cm that can persist for over 6 weeks, often resulting in scarring. Herpetiform RAU, accounting for 1-10% of cases, is distinguished by recurrent clusters of small, deep, and painful ulcers that may coalesce to form larger irregularly shaped ulcers. As highlighted by Scully (2006), the term RAU (or RAS) should be reserved for recurrent ulcers localized within the oral cavity and observed in the absence of systemic disease. This is due to the fact that ulcerations resembling RAU can be present in systemic conditions such as Behçet's syndrome, gastrointestinal disorders including Crohn's disease, celiac disease, or ulcerative

colitis, as well as immunodeficiency syndromes such as HIV infection or cyclic neutropenia (Scully, 2006; Akintoye and Greenberg, 2014; Saikaly et al., 2018).

In addition to its physical symptoms, **RAU can significantly impact the quality of life (QoL)** of affected individuals. The recurrent nature of RAU and its associated discomfort and pain can potential-

ly interfere with daily activities and routines (Rivera et al., 2022).

Maintaining oral health is paramount for individuals with RAU. Regular dental check-ups, proper oral hygiene practices, and avoidance of triggering

factors such as certain foods or stress can help manage and prevent flare-ups of RAU. Additionally, seeking professional dental care for proper diagnosis and management is essential for individuals experiencing recurrent oral ulcers.

**RAU
impacts
up to 25%
of the global
population**

WHAT ARE THE FACTORS THAT CONTRIBUTE TO RAU DEVELOPMENT?

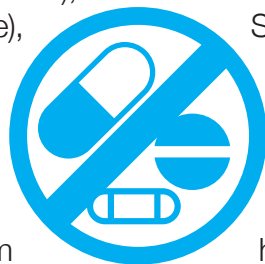
Several factors contribute to the development of Recurrent Aphthous Ulcer, reflecting a complex interplay of inherent characteristics and environmental influences. Gender and age are notable contributors, with a higher prevalence of RAU observed in women and individuals under the age of 40 (Scully, 2006). **Genetic predisposition and family history also significantly influence RAU susceptibility**, underscoring the role of genetic factors in the etiology of the condition (Scully and Porter, 2008; Natah et al., 2004). Moreover, various other factors have been identified as contributors to the occurrence of RAU. These encompass **oral trauma and oral health practices**, including the frequency of brushing and the use of dental braces, which may exacerbate mucosal irritation and predispose individuals to ulcer formation. **Microbial and immunologic factors** are also implicated, as disruptions in the oral microbiome or dysregulation

of immune responses can contribute to mucosal inflammation and ulceration. **Psychosocial stress** has been linked to RAU onset or exacerbation, suggesting a potential role of stress-related hormonal changes or immune dysregulation in ulcer development.

Additionally, **dietary habits play a role in RAU occurrence**, with factors such as the consumption of drinks or spicy and fried foods potentially triggering ulcer formation. Nutritional deficiencies in essential vitamins and minerals, including iron, zinc, folic acid, and vitamin B12, have also been associated with an increased risk of RAU (Porter et al., 1998; Akintoye and Greenberg, 2014; Wan et al., 2015; Du et al., 2018; Lau and Smith, 2022; Manoj et al., 2023). These multifactorial influences underscore the **complex nature of RAU pathogenesis and highlight the importance of comprehensive assessment and management strategies in addressing the condition.**

WHY RESORT TO NON-DRUG TREATMENTS?

RAU management involves a combination of topical and systemic medications aimed at alleviating pain, facilitating healing, and preventing recurrence (Lau and Smith, 2022). Initially, treatment typically involves the application of topical agents such as corticosteroids (e.g., triamcinolone acetonide), non-steroidal anti-inflammatory drugs (e.g., amlexanox), antiseptics (e.g., chlorhexidine gluconate), antibiotics (e.g., tetracyclines), and anesthetics (e.g., benzocaine) directly onto affected areas. Despite the variety of available topical medications, their efficacy remains uncertain due to limited success and weak evidence from various studies, resulting in the absence of a definitive and effective therapy (Casale et al., 2017; Al-Maweri et al., 2021). In cases of severe lesions or unknown causative factors, systemic treatments such as oral corticosteroids may be necessary (Bell, 2005; Belenguer-Guallar et al., 2014). However, careful consideration of potential side effects is crucial, and systemic treatments should be reserved only as a second-line therapy exclusively for patients who do not respond to



initial topical interventions (Bell, 2005; Belenguer-Guallar et al., 2014).

An alternative approach involves the use of **coating devices containing hyaluronic acid (HA)** to promote healing. These devices **act as a barrier, improving water retention and protecting the lesion from the surrounding oral environment** (Chen and Abatangelo, 1999;

Sridharan and Sivaramakrishnan, 2021).

HA exhibits no contraindications or interactions with other drugs, making it an ideal choice for all people (Casale et al., 2016). In recent

years, the topical application of HA has emerged as an excellent treatment for oral ulcers and other painful oral lesions.

Indeed, several studies have demonstrated its efficacy in relieving pain, reducing the number and size of ulcers, and alleviating inflammatory symptoms in lesions associated with Recurrent Aphthous Ulcers, without causing local or systemic pharmacological effects on the mucosa (Casale et al., 2017; Al-Maweri et al., 2021; Lau and Smith, 2022).

WHY HIGH MOLECULAR WEIGHT HYALURONIC ACID?

Hyaluronic acid (HA) is a non-sulfated glycosaminoglycan (GAG) widely distributed in neural, epithelial, and connective tissues, including the periodontium. As a significant component of the extracellular matrix (ECM), HA plays a crucial role in tissue regeneration, inflammatory response, angiogenesis, and wound healing (Graça et al., 2020). Remarkably hygroscopic, HA possesses significant viscoelastic properties, which hinder the infiltration of viruses and bacteria into tissues (Casale et al., 2016).

The properties of HA are directly influenced by its molecular weight. High molecular weight hyaluronic acid (HMW-HA) inhibits cell differentiation while promoting cell proliferation, contributing to tissue regeneration, wound healing, epithelial integrity, embryogenesis, plasma protein distribution, matrix structuring, and water homeostasis (Valachová et al., 2021).



HMW-HA exhibits remarkable hydration capacity, swelling to many times its original volume upon water uptake, thus enhancing tissue hydration and cellular resistance to mechanical damage.

This biopolymer finds common application in the treatment of gingivitis, ulcers, recession,

and periodontal pockets, as well as in grafts and implants, owing to its properties (Iviglia et al., 2019).

Moreover, **HA serves as a stable barrier against viral and bacterial invasion, promoting regeneration in oral cavity diseases** (Iviglia et al., 2019).

These attributes are critical for preventing the introduction of foreign pathogens into wounds and facilitating tissue regeneration (Casale et al., 2017) (Iviglia et al., 2019). Given its healing properties, **HA holds promise for treating RAU** (Casale et al., 2017; Al-Maweri et al., 2021).

Why Gengigel®?

Hyaluronic acid deficiency resulting from oral tissue injury leads to free water imbalance and delayed healing. **Gengigel®, with its HMW-HA-based composition, protects the oral mucosa by promoting the natural healing and recovery process of the tissue.** Thanks to its bioadhesive and film-forming properties, it forms a stable barrier that preserves the microenvironment of the mucosal surface and accelerates mucosal healing by maintaining the action of HMW-HA over a long period of time while delaying the absorption and excretion of HMW-HA. The ability of HMW-HA to retain large amounts of water helps Gengigel® maintain extracellular fluid balance and promote edema resorption in inflammatory conditions, providing rapid relief to inflamed oral tissues. Importantly, **hyaluronic acid has no local or systemic pharmacological effects on the mucosa, presenting a significant advantage for oral discomforts such as RAU.**

Indeed, **the efficacy of hyaluronic acid (HA) in managing Recurrent Aphthous Ulcers has been highlighted by various studies.** A study conducted by Lee et al. (2008) demonstrated notable improvements in 72.7% of RAU patients treated with Gengigel®, manifesting as reduced ulcer numbers, diminished ulcer size, and accelerated ulcer healing. Moreover, 75.8% of patients reported pain reduction, alongside improvements in inflammatory symptoms like swelling and local heat following treatment (Lee

et al., 2008). Another study by Nolan et al. (2006) showed the prompt pain reduction achieved with HA gel application, with patients reporting fewer ulcers and a reduced incidence of new ulcers compared to those treated with placebo. Furthermore, the HA gel exhibited a protective role, facilitating RAU healing (Nolan et al., 2006). A recent retrospective clinical study explored the efficacy of HA-containing formulations in RAU management, revealing significant improvements in lesion color normalization, pain

reduction, and lesion dimension reduction within days of treatment (Dalesandri et al., 2019). Moreover, in a comparative study involving children, HA topical gel demonstrated comparable efficacy to dexamethasone topical ointment in reducing ulcer size and pain scores among children with RAU. Notably, HA exhibited faster pain relief compared to corticosteroid ointment, with a lower risk of complications, discomfort, and drug interactions (Yang et al., 2020). A recent systematic

review underscored the promising outcomes of HA in RAU management, showcasing its efficacy in pain reduction and hastening lesion healing compared to alternative interventions, while maintaining a high level of safety and tolerability (Al-Maweri et al., 2021).

In conclusion, **Gengigel® emerges as a valuable and effective therapeutic option for recurrent aphthous ulcers**, offering symptomatic relief, inflammation modulation, and enhancement of the healing process.



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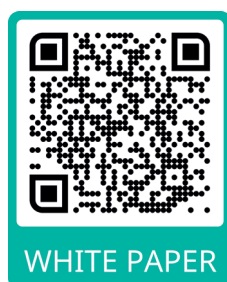
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RICERFARMA S.R.L.
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Via Egadi, 7 - 20144 Milano – Italy
info@ricerfarma.com