

BREAKING BARRIERS: THE PROMISING IMPACT OF EARLY INTERVENTION AND BIOMOLECULAR THERAPY ON PROUD FLESH

by Noxsano Animal Health

Horses are prone to injury, and for veterinarians, equine wound management is an ongoing challenge. Notably, the formation of Exuberant Granulation Tissue (EGT) or proud flesh is an all-too-common complication and most frequently occurs in distal limb injuries.¹ Where possible, suturing and healing by primary intent reduces the likelihood of EGT. However, wounds must frequently be allowed to heal by secondary intent, and these are particularly susceptible to formation of EGT.

While the causes of EGT are not fully understood, many aspects of the underlying cellular processes have been elucidated and the science of treatment and mitigation of EGT is continuing to improve. The continued improvements in understanding of physiology are pushing new treatments towards fruition. The topical application of nitric oxide to the wound bed is one such new treatment.

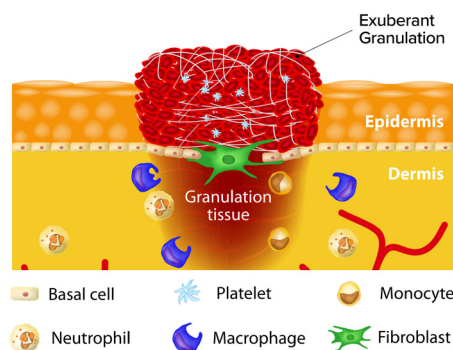
PHYSIOLOGY OF EGT

While EGT can be a thorn in the veterinarian's side, fibroplasia, the formation of granulation tissue, is a critical component of wound healing. Firstly, the granulation tissue fills in the gap left by the wounding event thus forming a barrier against environmental contamination. Further, the process produces myofibroblasts which exhibit a contractile force on the wound margins and creates a tissue bed over which epithelial

cells migrate to complete wound closure.

From this tissue also comes endothelial cells, which form the vascular network of the newly grown tissue to bring oxygen and nutrients to the area. The vascular network also brings leukocytes into the area which attack and help clear contamination and debris from the wound.

Ideally, the wound transitions out of this granulation phase as the gap in the wound is filled, allowing healthy contraction and epithelialization to proceed. When this transition does not occur, EGT begins to grow. (FIGURE 1)



Interestingly, low oxygen concentration has been shown to stimulate fibroblast proliferation and extracellular matrix formation. Oxygen is required for leukocytes to perform their antibacterial function efficiently.² Well perfused tissue is generally not hypoxic. Any veterinarian who has excised proud flesh has observed the significant bleeding that can occur due to extensive angiogenesis. While this might seem to be the

sign of well perfused tissue, the lumen, or opening, of the newly growing vessels have been shown in EGT to be significantly more occluded than those in healthy wounds.³ Hence, EGT is frequently more hypoxic than the heavy bleeding would seem to indicate.

Among the many causes of EGT, chronic inflammation stands out due to the frequency of occurrence in distal limb wounds and can be unrecognized because it often presents with a mild signature. Thus, strategies and treatments to mitigate chronic inflammation that are easy to apply and speed wound healing are also highly desirable. In hypoxic environments a prolonged response due to lack of oxygen may result in an extended period of inflammation. To further complicate the situation, hypoxia has been demonstrated to increase angiogenic and fibrogenic processes.⁴

TREATMENT, MITIGATION, AND PREVENTION

Early stage wound management can dramatically affect the wound healing process and thus, the propensity for developing EGT. Bandaging plays a critical role in successful distal limb wound healing but can result in an exacerbation of the conditions that results in EGT when done improperly. Even when done properly, multilayer bandaging with a primary dressing, an absorbent secondary layer to manage wound exudate, and a tertiary overwrap to support

the other layers can still result in EGT formation, albeit with significantly less complications than poor bandaging techniques.⁵

Bandages perform a key function of keeping wounds clean and free of irritants, such as dirt and straw, and protect the wound from additional trauma, all of which helps to reduce inflammation. Further, they allow for the placement of topical wound treatments utilized to reduce bacterial load and drive healthy wound closure. Well bandaged wounds also enable moisture management by removing exudate while keeping enough moisture in the wound bed to ensure healthy epithelialization, an important step in scar management.

When EGT does form, in most cases excision is the most effective course of action. Removal of EGT allows the wound to transition from the fibroblastic phase of wound healing into the critical phases of contraction and epithelialization.

It is advisable to be proactive and perform the procedure as soon as the granulation tissue protrudes above the wound bed while taking care to avoid damaging the migrating epithelium marching towards wound closure. Ideally, this will lead to wound closure without repeated excision, though the process may need to be repeated until wound closure proceeds normally. In most cases, when early treatment is utilized, this can be done with the horse standing and without the need for local anesthetics because the tissue is not innervated.

Beyond removing the excess, non-viable tissue, excision aids healing by removing any debris which may have entered the wound and rapidly reduces the leukocyte count in the superficial layer. This reduces stimuli present that incite chronic inflammation. When coupled with aseptic preparation of the surrounding skin, sterile bandaging, and utilizing

topical antimicrobials to reduce bioburden, dramatic improvements in the health of the granulation bed are typically observed. Even the most skilled veterinarians utilizing the best procedures and conditions will find that this process may need to be repeated.

FUTURE PROMISE – BIOMOLECULAR THERAPY NITRIC OXIDE

It is unlikely that a single silver bullet to prevent and resolve EGT will be discovered due to the wide range of underlying pathology. However, new treatments for resolution and prevention of EGT are being investigated. Biomolecular therapies, molecules produced naturally in healthy wounds, are a notable area of development in human medicines.




One notable treatment that addresses aspects of the complications above and is finding its way into veterinary medicine is

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topical nitric oxide (NO) therapies. (FIGURE 2) Nitric oxide occurs naturally in the healthy wound bed and topical application in animal models and humans has been studied over the past three decades.⁶ Importantly, among its many roles in the wound healing process, NO has anti-inflammatory properties⁷ and reduces leukocyte adhesion which drives the wound towards a healthy resolution.⁸

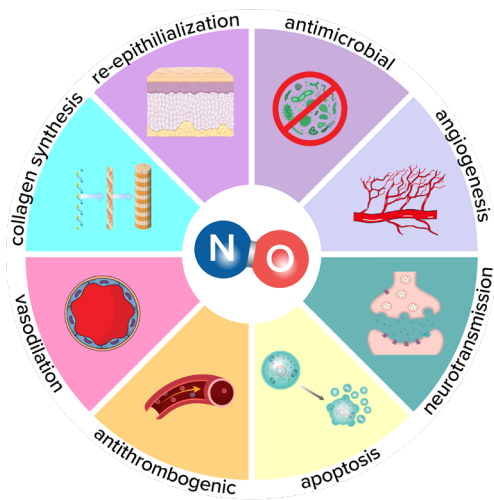
NO promotes angiogenesis AND vasodilation resulting in well oxygenated tissue. The molecule is a naturally occurring antimicrobial and signals for macrophage polarization switch, a key step in the transition from inflammatory to post-inflammatory stages of wound healing.⁹

A variety of methods to deliver this important bioactive molecule have been evaluated since its discovery. Research in a number of contexts has demonstrated that topical delivery of nitric oxide can reduce wound healing times by regulating fibroblasts, inflammatory cells, cytokines, and remodeling proteins, improving the speed of closure and improving the strength and appearance of the regrown tissue.¹⁰ All of these benefits directly help with a significant reduction in EGT.

management practices and newly developed treatments, such as Noxsano's Restore Wound Pads and Gel which effectively and efficiently deliver nitric oxide directly to the wound bed, offer a path to resolution of the condition.

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FINAL WORD

EGT continues to be a long-standing challenge for veterinarians and owners but good wound