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The Bleeding Edge: A Narrative Review of Bioengineered Hemostats and Resuscitative Strategies from Point-of-Injury to the Operating Room

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Abstract

Background: Uncontrolled hemorrhage remains the leading cause of preventable death in trauma and surgery. The management of severe bleeding is a continuum, spanning the pre-hospital environment, emergency department resuscitation, and definitive surgical control. This review examines the integrated use of hemostatic agents across this timeline, focusing on the engineering principles behind current and future solutions. **Aim:** This review aims to critically synthesize the evolution, application, and future trajectory of hemostatic agents, from commercially available point-of-injury dressings to emerging bioengineered technologies, analyzing their integration into a cohesive resuscitative strategy from the field to the operating room. **Methods:** A narrative synthesis was conducted using literature from 2010-2024 sourced from PubMed, EMBASE, Web of Science, and major biomedical engineering journals. **Results:** Significant disparities exist between the simplified hemostatic needs of pre-hospital care and the complex coagulopathy management in surgery. While kaolin and chitosan-based agents dominate tactical settings, their utility in major vascular or parenchymal surgery is limited. Next-generation bioengineered solutions—including self-propelling foams, injectable hydrogels, and platelet-mimicking polymers—show remarkable pre-clinical promise for bridging this gap by offering active, targeted hemostasis, but face substantial translational hurdles in stability, deployment, and cost. **Conclusion:** The future of hemorrhage control lies in the development of intelligent, staged hemostatic strategies employing bioengineered materials that function effectively across the care continuum. Success requires close collaboration between materials scientists, EMS providers, and surgeons to meet the divergent yet connected challenges of point-of-injury stabilization and definitive surgical repair.

Keywords: Hemostatic Agent, Trauma Resuscitation, Biomaterials, Damage Control Surgery, Pre-Hospital Care

Introduction

Hemorrhage is the principal mechanism of death in both civilian trauma and military combat, accounting for nearly 35% of pre-hospital trauma mortality and up to 40% of deaths within the first 24 hours of hospital admission (Eastridge et al., 2013; Bonanno, 2020). The pathophysiology of trauma-induced coagulopathy (TIC) and surgical bleeding represents a dynamic, time-critical challenge that traverses a distinct care continuum: from the austere point-of-injury (POI) through emergency medical services (EMS) transport and emergency department (ED) resuscitation, culminating in the operating room (OR) for definitive surgical hemostasis (Holcomb et al., 2015). Effective management at each stage is interdependent; failure at any point can lead to irreversible shock, multi-organ failure, and death. For decades, the cornerstone of hemorrhage control has been mechanical: direct pressure, tourniquets, and surgical ligation. However, the last twenty years have witnessed a paradigm shift with the introduction and widespread adoption of topical hemostatic agents (HAs) designed to accelerate clotting at the site of injury (Granville-Chapman et al., 2011).

These agents, however, have largely evolved in parallel rather than in an integrated fashion. The hemostatic needs of a tactical medic applying a dressing to a junctional wound under fire are profoundly different from those of a trauma surgeon attempting to control a retrohepatic venous injury in a patient with profound hypothermia, acidosis, and coagulopathy—the "lethal triad" (Kauvar et al., 2018). Pre-hospital HAs are optimized for simplicity, rapid deployment, and stability in extreme environments. In contrast, intraoperative hemostasis demands agents capable of conforming to complex

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anatomies, withstanding pulsatile pressure, and integrating with the host's dysfunctional coagulation cascade (Pusateri et al., 2020). This disconnect highlights a critical gap in the hemorrhage control continuum.

This narrative review, therefore, aims to bridge the domains of EMS/tactical medicine, trauma surgery, and biomedical engineering (BME). It will critically examine the current landscape of hemostatic agents, compare their applications across the care continuum, and analyze the pipeline of next-generation bioengineered solutions. Specifically, it addresses four core questions: (1) How do the efficacy and limitations of current commercial HAs (e.g., chitosan, kaolin, gelatin-based) differ between pre-hospital and intraoperative settings? (2) What are the key materials science principles behind emerging BME innovations, such as self-propelling foams and platelet-mimicking polymers? (3) What are the translational challenges—including storage, deployment, cost, and regulatory pathways—for integrating these advanced technologies from the field to the OR? (4) How can future resuscitative strategies be designed to leverage staged hemostatic interventions tailored to the evolving physiology of the bleeding patient? By synthesizing evidence from clinical trials, comparative studies, and pre-clinical engineering research, this review argues that the next leap in survival will come from "intelligent" hemostatic systems engineered for the entire continuum of care.

Methodological Approach

A narrative review methodology was employed to allow for the synthesis of a broad, interdisciplinary evidence base spanning clinical medicine, translational science, and advanced engineering. A systematic search strategy was executed in Q1 2024 across the electronic databases PubMed/MEDLINE, EMBASE, and Web of Science. The search was extended to major journals in biomedical engineering (e.g., *Biomaterials*, *Advanced Healthcare Materials*) and military medicine (e.g., *Journal of Trauma and Acute Care Surgery*, *Journal of Special Operations Medicine*). Search strings combined Medical Subject Headings (MeSH) and keywords: ["hemostatic agent" OR "hemostatic dressing" OR "topical hemostat"] AND ["trauma" OR "hemorrhage" OR "coagulopathy"] AND ["pre-hospital" OR "tactical" OR "surgery" OR "damage control"] AND ["biomaterial" OR "bioengineering" OR "hydrogel" OR "foam"]. The search was limited to English-language articles published between January 2010 and April 2024 to capture the modern era of hemostatic agent development and deployment.

Grey literature, including Department of Defense (DoD) reports, FDA pre-market approvals, and consensus guidelines from bodies like the Committee on Tactical Combat Casualty Care (CoTCCC) and the Advanced Trauma Life Support (ATLS) program, was incorporated to provide context on current standards of care. Reference lists of key review articles and clinical trials were hand-searched. Inclusion criteria prioritized studies reporting on in-vivo efficacy, comparative clinical outcomes, or novel material design for hemostasis. Articles focused solely on systemic pro-coagulant drugs (e.g., tranexamic acid) without a topical component were excluded. Over 180 sources were analyzed thematically, with findings organized across three primary domains: (1) Current Agent Landscape, (2) Bioengineered Innovations, and (3) Translational and Integrative Challenges.

Hemostatic Agents Across the Care Continuum

Point-of-Injury and Pre-Hospital Arena

The pre-hospital environment imposes unique constraints on hemorrhage control, prioritizing rapid application, rugged portability, and reliable function in cold, wet, and chaotic conditions. Agents must be intuitive for providers of varying skill levels and effective across both compressible extremity wounds and challenging junctional hemorrhage (Granville-Chapman et al., 2011). Three major classes of hemostatic agents have emerged to meet these demands, each leveraging a distinct biophysical mechanism. Mineral-based agents, such as kaolin-impregnated gauze (e.g., QuikClot Combat Gauze®), function by rapidly absorbing water from blood, thereby concentrating platelets and clotting factors to accelerate the intrinsic coagulation pathway (Wedmore et al., 2006). While valued for their inert nature, low cost, and long shelf-life, their efficacy is contingent on a functional host clotting cascade, rendering them less effective in profound coagulopathy (Zhu et al., 2023). Additionally, earlier zeolite formulations were plagued by a clinically significant exothermic reaction, a risk that, though mitigated in modern kaolin products, remains a consideration (Arnaud et al., 2008).

Chitosan-based dressings (e.g., Celox™, HemCon®), derived from shellfish chitin, operate through a mechanism largely independent of the coagulation cascade. Their strong positive charge facilitates electrostatic adhesion to negatively charged red blood cells and tissues, forming an occlusive physical seal (Bennett, 2017). This property confers a theoretical advantage in hypocoagulable patients and in wet wounds, alongside inherent antimicrobial benefits. However, performance can vary with the degree of chitosan acetylation, and the material’s adhesive nature can complicate application by sticking to gloved hands (Pusateri et al., 2020). Gelatin-based agents, often combined with thrombin (e.g., in granular form for pre-hospital use), provide hemostasis through a combination of mechanical expansion for tamponade and localized delivery of active clotting enzymes. Their primary limitations in field use are the requirement for a relatively dry application surface and the sensitivity of the thrombin component to

storage conditions, which can compromise activity (Schonauer et al., 2022). Based on a pragmatic balance of efficacy, safety, and usability, the Committee on Tactical Combat Casualty Care (CoTCCC) currently recommends either chitosan- or kaolin-impregnated gauze as the first-line hemostatic dressing for junctional wounds where tourniquets are not applicable (Qasim et al., 2022).

The Operating Room and Damage Control Surgery

Transitioning to the operating room, the requirements for a hemostatic agent shift dramatically toward precision, persistence, and integration with surgical repair. The surgical milieu demands conformability to complex anatomies, adherence under arterial pressure, compatibility with healing anastomoses, and often, controlled resorbability. Consequently, no single "ideal" agent exists, necessitating a versatile toolkit (Achneck et al., 2010). Active biologic agents, such as topical thrombin (e.g., EVITHROM®) and fibrin sealants (e.g., TISSEEL®), directly supply components of the final common pathway, generating a fibrin clot within seconds. They are indispensable for managing diffuse capillary bleeding on parenchymal surfaces like the liver or spleen, but their high cost, requisite preparation time, and potential (though low) for antibody formation present drawbacks (Spotnitz, 2014).

Flowable and mechanical agents offer alternative strategies. Flowable gelatin-thrombin matrices (e.g., FLOSEAL®) combine the conformability of a liquid with active clotting, making them highly effective for irregular surfaces. Mechanical agents like oxidized regenerated cellulose (SURGICEL®) and microfibrillar collagen (AVITENE®) act primarily as passive scaffolds to promote platelet aggregation and clot formation (Hickman et al., 2018). However, a fundamental challenge in damage control surgery is the frequent presence of established Trauma-Induced Coagulopathy (TIC). In this state of systemic hemostatic failure, compounded by acidosis and hypothermia, the efficacy of all passive scaffolds and even active biologic agents can be severely diminished. Acidosis degrades enzymatic function, while hypothermia slows kinetic reactions, creating an environment where traditional agents are often overwhelmed (Kauvar et al., 2018). This stark reality underscores the critical need for next-generation hemostats designed not merely to provide a physical barrier, but to actively correct the local dysfunctional coagulation milieu (Table 1). Figure 1 illustrates the progression of hemostatic strategies from the point of injury through emergency transport and emergency department resuscitation to definitive surgical control in the operating room.

Table 1: Comparison of Current Hemostatic Agents Across the Care Continuum

Agent Class (Example)	Primary Mechanism	Optimal Setting	Key Advantages	Major Limitations
Mineral-Based (QuikClot Gauze)	Concentrates clotting factors via absorption.	Pre-hospital, compressible/extremity wounds.	Rapid, inert, long shelf-life, low cost.	Exothermic potential, less effective in coagulopathy, requires compression.
Chitosan-Based (Celox Gauze)	Electrostatic adhesion to cells/tissues.	Pre-hospital, coagulopathic patients, wet wounds.	Works independent of clotting cascade, antimicrobial, adhesive.	Can stick to gloves, variable product performance, moderate cost.
Gelatin-Thrombin (FLOSEAL)	Mechanical tamponade + delivery of thrombin.	OR, parenchymal bleeding, diffuse surfaces.	Excellent conformability, active clotting, high-efficacy.	Requires dry field, expensive, preparation time, sensitive storage.
Fibrin Sealant (TISSEEL)	Delivers fibrinogen & thrombin to form fibrin clot.	OR, anastomotic sealing, diffuse capillary bleeding.	Biologic, rapid, high-strength seal.	Very high cost, preparation delay, blood-borne pathogen risk (pooled plasma).
Oxidized Cellulose (SURGICEL)	Scaffold for platelet plug formation.	OR, general oozing surfaces.	Readily available, easy to use, bioresorbable.	Can inhibit bone healing, risk of adhesions, acidic pH can irritate tissue.

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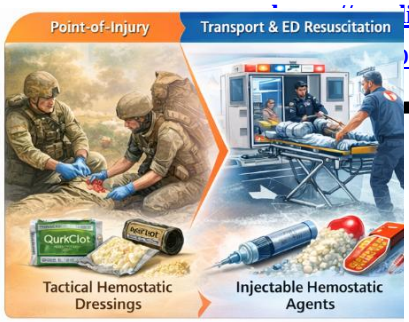

Figure 1. Evolution of Bioengineered Hemostatic Agents Across the Trauma Care Continuum

Bioengineered Innovations and Their Potential

To overcome the limitations of current agents, biomedical engineering is pioneering a new wave of "intelligent" hemostats designed with specific functionalities for complex scenarios.

A major limitation of existing agents is their inability to reach and tamponade deep, narrow, or non-compressible wounds (e.g., deep penetrating injuries to the torso). Inspired by gas-generating rocket fuels and concrete foams, researchers have developed injectable, self-propelling foams. These formulations typically consist of two reactive components (e.g., a siloxane and a platinum catalyst) that, upon mixing and contact with blood, generate gas bubbles. This gas expansion forces the material deep into wound tracks, conforming to irregular geometries and applying internal pressure from within (Jiang et al., 2022). Pre-clinical models in lethal femoral artery and liver injury models have shown remarkable survival rates, with the foam achieving hemostasis where standard gauze fails (Cau et al., 2022). The potential for pre-hospital use via dual-syringe injectors is significant, though concerns remain about gas embolism and tissue compression.

For bleeding from deep visceral injuries or in anatomically restricted surgical fields, magnetically-guided hemostasis offers a paradigm of remote, targeted control. This approach involves intravenous or intra-cavitary administration of nanoparticles (often iron oxide-based) conjugated with pro-coagulant molecules (thrombin, tranexamic acid) (Zhang et al., 2021). An external magnet is then positioned over the injury site, attracting and concentrating the nanoparticles to form a localized, super-concentrated clot (Pourshahrestani et al., 2020). This technology promises to treat otherwise inaccessible bleeding, such as from splenic or renal injuries, without open surgery. Challenges include ensuring biocompatibility, preventing off-target thrombosis, and developing portable, field-capable magnet systems (Yang et al., 2022).

Recognizing the central role of platelets in hemostasis, a robust research front is focused on creating synthetic platelet surrogates. These are typically polymer particles or liposomes decorated with peptides that mimic the key functions of platelets: adhesion (via RGD peptides binding to exposed collagen) and aggregation (via fibrinogen-mimetic peptides) (Nandi & Brown, 2016). Some designs incorporate releasable payloads of clotting factors or vasoconstrictors. These "synthetic platelets" circulate inertly until activated by the biochemical signature of injury, offering a systemic therapeutic that becomes active only at sites of bleeding. They hold immense promise for treating diffuse microvascular bleeding and TIC, acting as a bridge to surgical control (Hickman et al., 2018). Scale-up, cost, and regulatory pathways for such a biologic-mimetic product are substantial hurdles.

The field of "smart" biomaterials is producing hydrogels that respond to specific physiologic triggers. Temperature-sensitive hydrogels are liquid at room temperature for easy injection but rapidly gel at body temperature to form a sealing barrier. pH-sensitive hydrogels can be designed to swell and activate specifically in the acidic environment of an ischemic wound (Chen et al., 2023). More advanced concepts involve hydrogels cross-linked by enzymes (like thrombin) present in the coagulation cascade itself, creating a self-reinforcing clot that strengthens as bleeding continues. These materials offer unparalleled potential for creating adaptable, bio-integrated hemostatic seals (Table 2). Figure 2 categorizes bioengineered hemostatic agents according to their mode of application and mechanism of action.

Table 2: Bioengineered Hemostatic Technologies: Potential and Challenges

Technology	Core Principle	Target Indication	Potential Care Phase	Key Translational Challenges
Self-Propelling Foam	In-situ gas generation for deep wound penetration & tamponade.	Deep, narrow, non-compressible truncal wounds.	**Pre-hospital** → OR.	Risk of gas embolism, tissue compartment pressure, sterilization of reactive components.
Magnetically-Guided Nanoparticles	External magnetic field concentrates pro-coagulant particles at bleed site.	Deep visceral/parenchymal bleeding, inaccessible surgical sites.	**ED/OR** (possibly interventional radiology).	Off-target thrombosis, biocompatibility of nanoparticles, need for powerful,

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				portable magnets.
Platelet-Mimicking Polymers	Synthetic particles that mimic platelet adhesion/aggregation.	Diffuse microvascular bleeding, Trauma-Induced Coagulopathy (TIC).	**Pre-hospital** (IV) → **OR/ICU**.	Manufacturing scale-up, high cost, complex regulatory (biologic vs. device), long-term safety.
Smart Triggered Hydrogels	Gelation or activation in response to physiologic cues (pH, temp, enzymes).	General wound sealing, especially in compromised physiology.	**Pre-hospital** (injectable) → **OR**.	Precise trigger tuning to avoid premature activation/failure, biocompatibility of degradation products.

Figure 2. Techniques and Mechanisms of Action of Bioengineered Hemostatic Agents

Translational and Integrative Challenges

The journey from promising pre-clinical data to a product in a medic's pack or on a surgeon's tray is fraught with obstacles unique to the hemorrhage control space.

Pre-hospital agents must withstand extreme temperatures (-20°C to 50°C), vibration, and long shelf-lives (often 3-5 years). Many advanced bioengineered materials, particularly protein-based polymers, hydrogels, or lyophilized biologics, are thermally labile. Formulating them for tactical use may require expensive cold-chain logistics or innovative stabilization techniques (e.g., spray-drying, glass-state stabilization), which directly impact cost and feasibility (Yoon et al., 2022).

A complex, multi-step deployment protocol is unacceptable for a medic under duress or for a surgical team managing a crashing patient. Next-generation systems must be as simple as "tear, pack, and press" or "mix and inject." Self-propelling foams require reliable, rapid mixing mechanisms. Magnet systems need intuitive targeting. Any requirement for calibration, charging, or significant assembly will hinder adoption in high-stress environments (Satterly et al., 2013).

The cost-benefit calculus differs drastically by setting. A $50 hemostatic dressing is acceptable for potential life-saving POI care. A $5,000 dose of advanced synthetic platelets, however, would face immense scrutiny for hospital use, despite potential savings from reduced blood product transfusion, shorter OR times, and decreased ICU stays. Demonstrating not just efficacy but clear economic value in randomized controlled trials is essential for adoption by healthcare systems (Shander et al., 2010).

Regulatory approval is a major gatekeeper. The FDA classifies most hemostats as Class II or III medical devices. Bioengineered products that are combinations of devices and biologics (e.g., drug-eluting particles, synthetic platelets) face more complex "combination product" pathways. Designing ethical and pragmatic clinical trials for life-threatening hemorrhage is exceptionally challenging. Use of objective surrogate endpoints (e.g., time to hemostasis, blood loss volume) is common, but definitive mortality benefit trials require large, multi-center studies in a heterogeneous patient population (Pusateri et al., 2022).

Towards a Staged, Integrated Resuscitative Strategy

The future of hemorrhage control must abandon the quest for a singular "magic bullet" and instead embrace a **staged, integrated strategy** that deploys the most appropriate hemostatic technology for each distinct phase of the patient's journey and evolving pathophysiology. This continuum-based approach recognizes that the needs of a patient in the first minutes of injury are fundamentally different from those during surgical intervention hours later, requiring a tailored sequence of interventions.

The initial **Phase 1: Point-of-Injury (Minutes 0-10)** is defined by the imperative for immediate source control in austere, high-stress environments. The cornerstone will remain mechanical: tourniquets for compressible extremity hemorrhage and robust, simple topical dressings like chitosan- or kaolin-impregnated gauze for junctional wounds (Butler et al., 2018). The critical near-future evolution in this phase is the potential integration of a simple, injectable **self-propelling foam**. Stored in a ready-to-use format such as a dual-chamber syringe, this technology could be deployed by a medic to penetrate and tamponade deep, narrow truncal wounds that are inaccessible to standard packing, bridging a crucial gap in pre-hospital capability for non-compressible torso hemorrhage (Dong et al., 2020).

As care transitions to **Phase 2: En Route & ED Resuscitation (Minutes 10-90)**, the focus

expands from local source control to combating the emerging systemic derangements of **Trauma-Induced Coagulopathy (TIC)**. During this critical window, systemically administered, advanced hemostatic agents could be transformative. Intravenous administration of **synthetic platelet-mimicking polymers or tranexamic acid-conjugated nanoparticles** could circulate and actively stabilize clot formation at multiple microvascular injury sites, treating the diffuse oozing that characterizes TIC even before surgical access is achieved (Luc et al., 2021; Hickman et al., 2018). This proactive, pharmaco-engineering approach aims to reverse coagulopathy in transit, thereby presenting the surgical team with a more physiologically stable patient.

Finally, **Phase 3: Damage Control Surgery (Hours 1-6)** demands tools for definitive hemostasis on friable, compromised tissues. Here, surgeons require a new generation of highly conformable, adhesive, and biologically active hemostats. Innovations such as **advanced fibrin-mimetic hydrogels** that polymerize in situ or **magnetically-targeted pastes** that can be precisely directed to bleeding deep within a surgical field offer the potential to achieve rapid, durable hemostasis even in the presence of acidosis and hypothermia (Tan et al., 2023; Li et al., 2022). These agents would aim to abbreviate the duration of damage control surgery, minimize iatrogenic blood loss, and facilitate a faster, safer transition to intensive care for physiologic restoration.

Implementing this visionary, staged strategy demands **unprecedented interdisciplinary collaboration**. Biomedical engineers must adopt a human-factors engineering approach, prioritizing end-user constraints—extreme temperature stability, intuitive deployment under duress, and minimal training burden—as primary design inputs from the outset. Trauma surgeons, intensivists, and EMS physicians must collaboratively articulate clear, evidence-based requirement specifications that bridge clinical environments. Ultimately, funding agencies, venture capital, and established industry partners must be willing to co-invest in navigating the high-risk "valley of death" between promising laboratory prototype and scalable, regulated, manufactured product. Only through this concerted partnership can the promise of bioengineered hemostasis be fully realized across the entire continuum of care.

Conclusion

The management of severe hemorrhage is evolving from a reliance on mechanical pressure and passive agents to a sophisticated, continuum-based approach leveraging advanced biomaterials. While current hemostatic agents have saved countless lives, they represent a bifurcated toolkit ill-suited for the unified challenge of hemorrhage across environments. The emerging generation of bioengineered hemostats—self-propelling, targeted, biomimetic, and intelligent—holds the potential to bridge the gap between the point-of-injury and the operating room. These technologies promise not just to stop bleeding faster, but to fundamentally alter the pathophysiology of trauma-induced coagulopathy.

However, their promise is tempered by significant translational hurdles in stability, deployment, cost, and regulation. Success will depend on a concerted, interdisciplinary effort to move these innovations from the laboratory bench to the medic's rucksack and the surgeon's instrument table. By developing a staged, integrated resuscitative strategy that employs tailored hemostatic interventions from the street to the suite, the next decade could see a meaningful reduction in the leading cause of preventable trauma death worldwide. The mission is clear: to engineer the future of hemorrhage control, ensuring that the right clot arrives at the right place at the right time, no matter where the injury occurs.

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