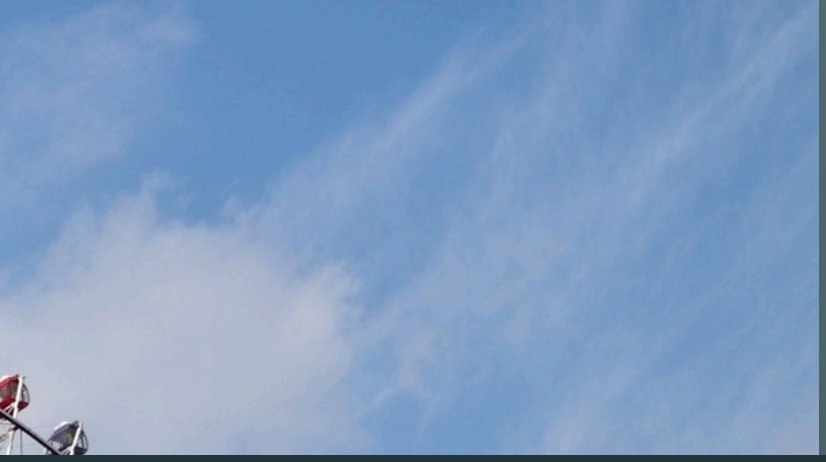

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Welcome Message

Michiaki Yamkakage

The Chair of 73rd JSA Meeting

Introductory Message

This booklet presents a selection of review articles and books published immediately before and after the 73rd Annual Meeting of the Japanese Society of Anesthesiologists.
In alignment with the theme of this meeting, “Master the Secrets of Anesthesiology,” these works address key contemporary issues in our field, including pulse oximetry, remimazolam, disaster medicine, transfusion strategy, artificial blood, sustainability in anesthesiology, and artificial intelligence in perioperative medicine.
Several articles published in Open Journal venues are provided as printed booklets. For other publications where copyright restrictions apply, QR codes are provided for immediate online access.
Recently published textbooks are also introduced for reference. These academic contributions would not have been possible without the continued collaboration, inspiration, and international partnership of the distinguished colleagues gathered here tonight. I would like to express my sincere gratitude for your support and friendship.
It is my hope that these works may serve as a small foundation for further discussion, collaboration, and shared progress in anesthesiology.
As a modest personal touch, I have also included a small 3D-printed item—one of my hobbies. I hope you may find it useful in your daily life.
With my deepest appreciation.

Michiaki Yamakage, MD, PhD
Chair, 73rd JSA Annual Meeting

fortune Journals

Review Article

ANESTHESIA AND CRITICAL CARE

ISSN: 2687-7996

The Evolution and Global Impact of Pulse Oximetry: From Innovation to Standard of Care - A Comprehensive Review for Anesthesiologists and Critical Care Physicians

Michiaki Yamakage MD, PhD[1*]

Abstract

This review examines the evolution, clinical applications, and global impact of pulse oximetry, with emphasis on its transformative role in anesthesiology and critical care medicine. Technological advancements, clinical evidence, limitations, and future directions—including educational uses, quality improvement initiatives, and implementation science - are discussed in detail.

A comprehensive literature review of PubMed, MEDLINE, and Cochrane databases (1970–2024) was conducted using terms such as "pulse oximetry," "oxygen saturation monitoring," "perioperative monitoring," and "anesthesia safety." Industrial patents, regulatory documents, and international guidelines from organizations including the WHO, ASA, and ESA were reviewed. Clinical case studies from major medical centers and quality improvement data were analyzed to highlight real-world benefits.

Since its introduction in the early 1980s, pulse oximetry has progressed from basic analog instruments to sophisticated digital systems with AI-driven analytics and wireless connectivity. It enables early detection of hypoxemic events, typically 1–2 minutes before clinical signs appear. Although large-scale randomized trials have not demonstrated significant reductions in perioperative mortality, it is universally recognized as indispensable for safe anesthetic practice. During the COVID-19 pandemic, it played a crucial role in identifying silent hypoxemia, with home monitoring programs preventing thousands of hospitalizations. Adoption exceeds 95% in high-income countries, with rapid growth in low-resource settings through targeted training and quality initiatives.

Future directions include multi-wavelength technology, AI-enhanced signal processing, and solutions to address skin pigmentation–related accuracy gaps. Integration into telemedicine, medical education, and quality frameworks will secure its role as a cornerstone of next-generation healthcare.

Keywords: Pulse oximetry; Oxygen saturation; Anesthesia monitoring; Critical care; Patient safety; COVID-19; artificial intelligence; Health equity

Introduction

The introduction of pulse oximetry into clinical practice represents a paradigm shift in patient monitoring that has fundamentally transformed anesthesiology and critical care medicine. Pulse oximeters provide continuous, non-invasive monitoring of arterial oxygen saturation (SpO_2), enabling early detection of hypoxemia before clinical signs appear. This facilitates prompt intervention and has made pulse oximetry an essential component of safe anesthetic practice,

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although definitive evidence for mortality reduction in radomized trials remains limited.

The significance of this technology extends beyond its technical capabilities. Pulse oximetry has significantly improved perioperative safety through early detection of hypoxemia, as demonstrated in large-scale institutional studies and comprehensive reviews [1,2]. The improvement in patient safety has been so profound that pulse oximetry monitoring is now recognized as a standard of care and is mandated by professional societies worldwide [3,4].

From a global health perspective, pulse oximetry has democratized access to sophisticated physiological monitoring, particularly in resource-limited settings where traditional invasive monitoring is unavailable or impractical [5,6]. The recent COVID-19 pandemic further highlighted its critical importance, as pulse oximetry became an essential tool for early detection of silent hypoxemia in patients with coronavirus disease, enabling timely intervention and resource allocation [7,8].

This comprehensive review examines the evolution of pulse oximetry technology, its clinical applications, global impact, and future directions. Particular emphasis is placed on its role in anesthesiology education, quality improvement programs, and implementation science initiatives that have driven its widespread adoption and ongoing refinement.

Historical Development and Technological Evolution

Early Pioneers and Foundational Research

The conceptual foundation of pulse oximetry dates back to the 1930s, when Karl Matthes first described the measurement of oxygen saturation using transmitted light through living tissue [9]. However, it was not until the 1970s that technological advances in light-emitting diodes (LEDs), photodiodes, and microprocessors made practical pulse oximetry possible [10,11].

A major breakthrough came in 1972, when the collaborative efforts of biomedical engineer Takuo Aoyagi at Nihon Kohden (Japan) who introduced the fundamental principle of pulse oximetry, with a patent application filed in 1974 [12]. This Japanese innovation significantly influenced the global medical device industry and established Japan as a leader in non-invasive monitoring technology.

Commercial Development and Clinical Introduction

The first commercially successful pulse oximeter was introduced simultaneously by Biox and Nellcor in 1981 [13]. Nellcor's N-100 device became particularly influential in establishing pulse oximetry as a standard monitoring tool. These early systems, while revolutionary, were limited by poor signal-to-noise ratios, motion artifacts, and the need for frequent calibration [10,11]. Their use was largely cinfined to operating rooms and intensive care units, where trained personnel could interpret the readings and manage the technical limitations [4].

Significant technological advances occurred in the 1990s with the introduction of digital signal processing and improved algorithms for artifact reduction [14]. Companies such as Masimo pioneered signal extraction technology (SET), which used advanced algorithms to isolate arterial signals from noise, dramatically improving accuracy during patient movement and low perfusion states [15,16] (Figure 1).

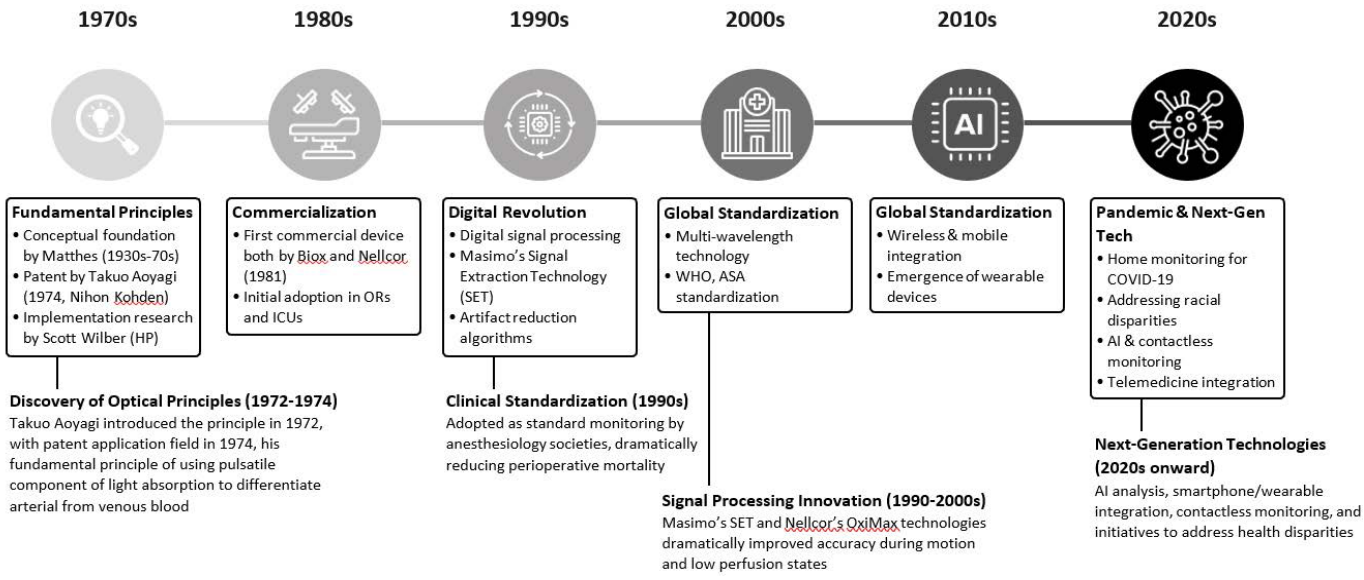

Figure 1: Timeline of Major Technological Milestones in Pulse Oximetry Development (1970–2024).

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The timeline illustrates the evolution of pulse oximetry, from Aoyagi's foundational discovery in the early 1970s to recent advances such as AI-driven algorithms and contactless monitoring.

Historical milestones are based on [9] for basic principles, [12] for Aoyagi's contributions, [13] for commercial development, and [15] for modern advances. Actual development proceeded continuously and in parallel; only key milestones are highlighted.

Studies in pediatric cardiac surgery have demonstrated the critical importance of pulse oximetry for early hypoxemia detection [17,18]. Continuous monitoring enables earlier detection of hypoxemic events compared to clinical observation alone, with particular benefits in complex congenital heart surgeries [17]. Multiple studies have demonstrated that pulse oximetry-guided interventions can improve perioperative outcomes in pediatric cardiac procedures, though the degree of benefit varies depending on procedure type and patient characteristics [18,19]

Physical Principles and Measurement Theory

Photoplethysmography and Light Absorption

Pulse oximetry is based on the principle of photoplethysmography combined with spectrophotometry. The technology exploits the differential absorption characteristics of oxygenated and deoxygenated hemoglobin at specific wavelengths of light [9,20]. Conventional pulse oximeters use two wavelengths: red light at approximately 660 nm and infrared light at 940 nm [9,10].

The fundamental principle relies on the Beer-Lambert law, which describes the relationship between light absorption and the concentration of absorbing species [9,20]. In biological tissues, the total light absorption consists of contributions from arterial blood, venous blood, and tissue. The key innovation of pulse oximetry is the use of the pulsatile component of light absorption, which corresponds primarily to arterial blood, to calculate oxygen saturation [10,11].

Advanced Signal Processing and Calibration

The ratio of pulsatile to non-pulsatile light absorption at the two wavelengths (R-value) is calculated and converted to oxygen saturation using empirically derived calibration curves [20,21]. These curves are typically established through studies involving healthy volunteers who breathe hypoxic gas mixtures while arterial blood gas measurements are obtained simultaneously [22].

Modern pulse oximeters incorporate machine learning algorithms that can adapt to individual patient characteristics, improving accuracy across diverse populations and clinical conditions [23]. These sysetems analyze multiple signal parameters simultaneously, including waveform morphology, signal strength, and noise characteristics, to generate more reliable measurements.

Industrial Innovations and Key Contributors

Nellcor (Medtronic)

Nellcor's contributions to pulse oximetry extends beyond device manufacturing to include fundamental research in sensor technology and clinical validation [14]. The company's OxiMax technology introduced multi-wavelength measurement capabilities, improving accuracy in challenging clinical scenarios such as carbon monoxide poisoning and methemoglobinemia [24].

The collaboration of Nellcor with anesthesiology societies was instrumental in establishing pulse oximetry as a standard monitoring requirement [4,19]. The company's extensive clinical studies provided the evidence base for regulatory approval and informed professional guidelines mandating pulse oximetry monitoring during anesthesia [4,19].

Masimo Corporation

Masimo's Signal Extraction Technology (SET) represents one of the most significant advances in pulse oximetry since its inception [15,16]. By using parallel processing engines and adaptive algorithms, SET technology can extract arterial signals even in the presence of significant motion artifacts and low perfusion states that would render conventional pulse oximeters unreliable [15,16].

The company's rainbow technology extends pulse oximetry beyond traditional SpO_2 monitoring to include measurements of total hemoglobin, carboxyhemoglobin, methemoglobin, and pleth variability index [16,24]. This multi-parameter approach has expanded the clinical utility of pulse oximetry in perioperative and critical care settings [16].

Emerging Technologies and Innovation

Recent innovations include smartphone-based pulse oximetry applications, wearable devices integrated into smartwatches, and contactless monitoring systems using computer vision and machine learning [25,26]. Companies such as Apple, Samsung, and various startups are developing consumer-grade pulse oximetry solutions that may democratize access to oxygen saturation monitoring [26] (Table 1).

This comparison is based on [12] for historical development, [15] for SET technology validations, [22] for accuracy studies, and [23] for mobile applications. Accuracy values are shown as standard deviations (±SD). Wearable device accuracy has been validated under limited conditions only, and should not be used for clinical decision making.

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Table 1: Comparative Analysis of Leading Pulse Oximetry Technologies.

Manufacturer/ Technology	Technical Features	Clinical Applications	Accuracy Characteristics	Motion Tolerance
Masimo Signal Extraction Technology (SET)	Parallel processing engines Adaptive algorithms Discrete saturation transform	Operating rooms Intensive care units Neonatal/pediatric care Low perfusion states	SpO_2: ±2% (70%-100%) High accuracy in low perfusion	Excellent (validated in clinical studies)
Masimo rainbow SET	Multi-wavelength measurement Multi-parameter analysis Non-invasive continuous monitoring	Perioperative monitoring Emergency medicine Carbon monoxide poisoning Methemoglobinemia	SpO_2: ±2% (70%-100%) Total Hb: ±1g/dL COHb: ±3% MetHb: ±1%	Excellent
Nellcor (Medtronic) OxiMax	Digital signal processing In-sensor memory chip OXIMART signal processing	Operating rooms Intensive care units Neonatal monitoring Apnea detection	SpO_2: ±2%~3% (70%-100%) Improved bradycardia detection	Moderate to good
Nonin Medical PureSAT	Digital signal processing Compact, power-efficient design Rapid response algorithms	Home healthcare Emergency/transport Sleep apnea Telemedicine	SpO_2: ±2% (70%-100%) Robust for portable applications	Good (optimized for portable use)
Consumer/Wearable (Apple, Samsung, etc.)	Micro-optical sensors AI-assisted analysis Wireless/cloud integration	Health monitoring Remote patient monitoring Screening Trend analysis	SpO_2: ±3%~4% (90%-100%) Limited vs medical-grade devices	Limited (optimized for normal activity)

This comparison is based on [12] for historical development, [15] for SET technology validations, [22] for accuracy studies, and [23] for mobile applications. Accuracy values are shown as standard deviations (±SD). Wearable device accuracy has been validated under limited conditions only, and should not be used for clinical decision making.

Clinical Applications in Anesthesiology and Critical Care

Perioperative Monitoring

Pulse oximetry has become an indispensable monitoring tool in anesthesiology, mandated by professional societies including the American Society of Anesthesiologists (ASA), the European Society of Anaesthesiology (ESA), and the World Federation of Societies of Anaesthesiologists (WFSA) [3,4]. The technology enables early detection of hypoxemia during induction, maintenance, and emergence from anesthesia [19,27].

Studies have demonstrated that pulse oximetry monitoring during anesthesia can detect hypoxemic events 1-2 minutes before clinical signs appear, providing critical time for intervention. Although large-scale randomized trials have not shown significant reductions in perioperative mortality, the technology's ability to detect hypoxemia early has made it an indispensable tool for ensuring safety in anesthetic practice [19,27], particularly in high-risk procedures, pediatric anesthesia, and patients with compromised respiratory function [17,18].

During the COVID-19 pandemic, home pulse oximetry monitoring proved clinically beneficial across multiple healthcare systems [8,28,29]. Studies of COVID-19 Oximetry @home programs have shown potential benefits in patient outcomes, with some research suggesting reduced mortality and readmission rates, although results varied across different healthcare systems and implementation strategies [28]. In the U.K., NHS England's virtual ward initiatives utilized pulse oximetry for remote monitoring of COVID-19 patients, enabling early detection of clinical deterioration and reducing strain on healthcare resources [8].

Critical Care Applications

In intensive care units, pulse oximetry provides continuous monitoring of critically ill patients, enabling the titration of oxygen therapy and mechanical ventilation [1,30]. It is particularly valuable in managing patients with acute respiratory distress syndrome (ARDS), where maintaining optimal oxygenation while minimizing oxygen toxicity is crucial [1,30].

Recent studies have shown that pulse oximetry-guided oxygen therapy can reduce mortality and length of stay in critically ill patients compared to standard care [30]. The technology also enables real-time assessment of responses to positioning, recruitment maneuvers, and other interventions [30].

Emergency Medicine and Prehospital Care

Portable pulse oximeters have become standard equipment in emergency medical services, providing rapid assessment of patient oxygenation in prehospital settings [31,32]. The technology is particularly useful in managing

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patients with chest pain, dyspnea, or altered mental status, where hypoxemia may not be clinically apparent.

Studies conducted in emergency departments have shown that pulse oximetry can guide triage decisions and resource allocation, particularly during mass casualty events or pandemic surges when rapid assessment of multiple patients is required [33] (Table 2, Figure 2).

The clinical benefits of pulse oximetry adoption are shown across different healthcare settings, including perioperative monitoring, emergency medicine, pediatric care, and global health applications.

Evidence is based on [2] for perioperative benefits, [14] for systematic review outcomes, [32] for emergency medicine applications, and [17] for pediatric applications.

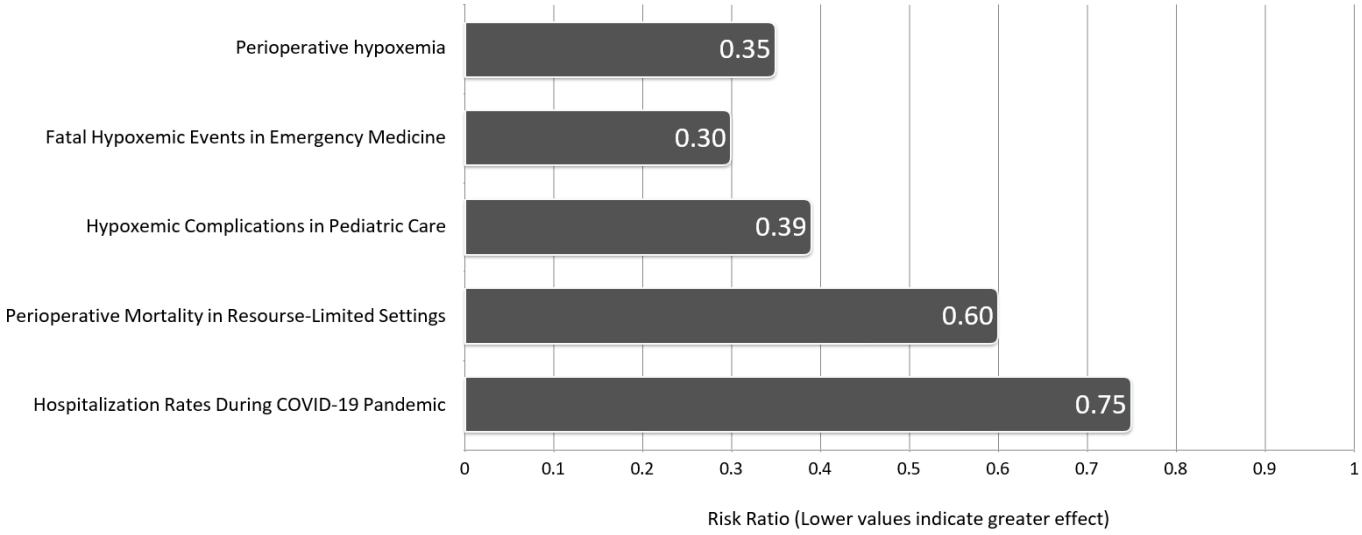

Figure 2: Clinical Impact of Pulse Oximetry on Adverse Event Reduction.

Clinical benefits represent documented improvements in patient outcomes following pulse oximetry implementation. Evidence based on [1, 2] for perioperative monitoring, [32] for emergency care, [17] for pediatric applications, [6] for low-resource settings, [8] for COVID-19 response, and [34] for telemedicine. Effects may vary depending on clinical context, patient characteristics, and equipment used.

Educational Applications in Anesthesiology and Critical Care Training

Residency Training Programs

Pulse oximetry is now an integral component of anesthesiology and critical care training programs worldwide. Educational curricula now incorporate comprehensive instruction on pulse oximetry principles, interpretation, troubleshooting, and clinical decision-making based on oxygen saturation monitoring [35].

Structured programs include hands-on training with various pulse oximetry devices, simulation-based scenarios illustrating common artifacts and limitations, and competency assessment protocols. These programs have demonstrated improved resident confidence and clinical performance in oxygen saturation monitoring [35].

Simulation-Based Education

High-fidelity simulation centers utilize pulse oximetry monitoring to create realistic clinical scenarios for training anesthesiology residents and critical care fellows. Simulations can replicate complex conditions such as motion artifacts, low perfusion states, and equipment malfunctions, providing trainees with valuable learning experiences in managing these challenges within a controlled environment [36].

Standardized simulation scenarios are used to teach recognition and management of hypoxemic events, appropriate alarm threshold settings, and integration of pulse oximetry data with other physiological parameters. These educational interventions have been shown to improve clinical performance and patient safety outcomes [36].

Interprofessional Education

Pulse oximetry education extends beyond physician training to include nurses, respiratory therapists, and other healthcare professionals. Interprofessional education programs emphasize team-based approaches to oxygen saturation monitoring, communication protocols for abnormal readings, and collaborative decision-making in clinical care [37].

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Table 2: Clinical Evidence for Pulse Oximetry Impact on Patient Outcomes

Clinical setting	Representative Studies/Evidence	Impact on Patient Outcomes
Perioperative Monitoring	Moller et al, multicenter study Randomized trial involving 20,802 patients	Early detection of hypoxemia 1-2 minutes before clinical signs Limited evidence for mortality reduction in large, randomized trials Improved perioperative safety monitoring
Emergency Medicine & Prehospital Care	Comparative studies before and after pulse oximetry implementation in emergency medical systems	Improved triage decisions Better outcomes through early intervention Optimization of oxygen therapy Reduced cardiopulmonary events during transportation
Pediatric & Neonatal Care	Fouzas et al, review Khatri et al, prospective observational study	Improved stabilization protocols for premature infants Optimization of oxygen delivery in preterm infants Early detection of undiagnosed congenital heart disease Reduced PICU admission rates
Low-Resource Settings	Comparative studies in sub-Saharan African facilities Lifebox Foundation's global implementation program	Significant reduction in perioperative mortality Greatest impact in pediatric and obstetric procedures Improved pneumonia diagnostic accuracy Optimized allocation of medical resources
COVID-19 Pandemic Response	Greenhalgh et al, study Home monitoring programs involving over 100,000 patients	Early detection of silent hypoxemia Reduced hospitalization rates and improved patient outcomes Improved severity assessment Efficient allocation of healthcare resources
Telemedicine & Home Healthcare	Home monitoring studies of COPD and heart failure patients Darwish et al, digital health research	Early detection of acute exacerbations in chronic diseases Reduced readmission rates Improved patient satisfaction Enhanced access to healthcare

Clinical benefits represent documented improvements in patient outcomes following pulse oximetry implementation. Evidence based on [1, 2] for perioperative monitoring, [32] for emergency care, [17] for pediatric applications, [6] for low-resource settings, [8] for COVID-19 response, and [34] for telemedicine. Effects may vary depending on clinical context, patient characteristics, and equipment used.

Quality Improvement Programs and Implementation Science

Patient Safety Initiatives

Healthcare institutions have implemented comprehensive quality improvement programs centered on pulse oximetry monitoring to enhance patient safety. These programs typically include standardized alarm management protocols, regular competency assessments for clinical staff, and systematic analysis of hypoxemic events [38].

Data from such initiatives have demonstrated significant reductions in preventable hypoxemic events, lower false alarm rates, and improved staff satisfaction with monitoring systems. The implementation of evidence-based pulse oximetry protocols has become a key component of hospital accreditation standards [38].

Alarm Fatigue Management

One of the major challenges in pulse oximetry implementation is alarm fatigue, in which healthcare providers become desensitized to frequent alarms, potentially delaying responses to critical events [39]. Quality improvement programs have addressed this issue through the following strategies:

- Individualized alarm threshold settings based on patient conditions
- Smart alarm algorithms that reduce false alarms
- Staff education on appropriate alarm responses
- Regular review and adjustment of alarm policies

These interventions have resulted in significant reductions in alarm frequency while maintaining sensitivity for detecting clinically relevant hypoxemic events [39].

Quality improvement programs in resource-limited settings have demonstrated substantial benefits from systematic pulse oximetry implementation [5, 6]. Studies in low- and middle-income countries have shown that introduction of pulse oximetry monitoring can significantly reduce perioperative mortality, with particularly notable impacts in pediatric and obstetric procedures [6]. The Lifebox Foundation's Safe Surgery initiative has distributed pulse oximeters to healthcare facilities globally and provided training programs, thereby contributing to improved surgical safety outcomes in resource-limited settings [40]. (Figure 3).

Cost-effective analysis showing economic benefits of pulse oximetry implementation across different healthcare settings, with improved cost-effectiveness through prevention of complications and efficient resource utilization.

Values represent the estimated annual economic benefit per facility type. Horizontal bars indicate the point estimates, and thin lines denote the 95% confidence intervals.

Data compiled from [5] for global distribution analysis, [6] for low-resource settings, and [40] for implementation outcomes.

Implementation Science Perspectives

The global adoption of pulse oximetry provides valuable

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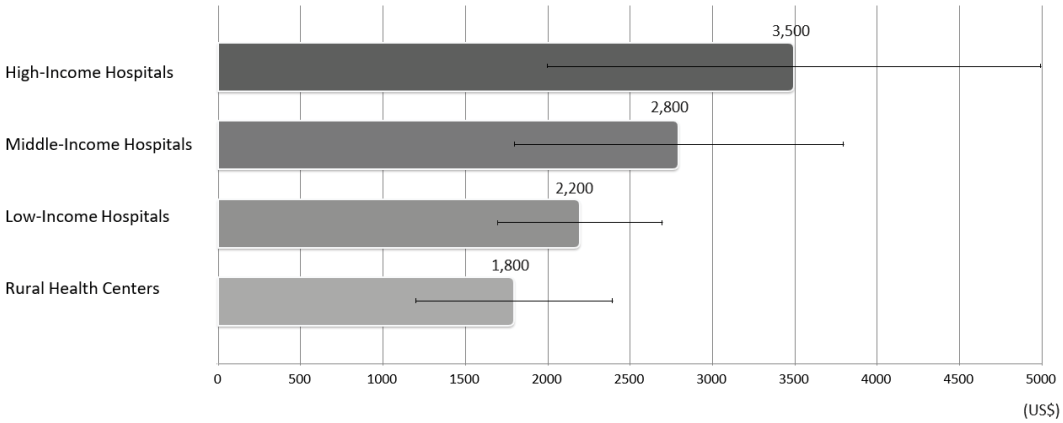

Figure 3: Economic Impact of Pulse Oximetry Implementation.

insights into medical technology implementation. Key factors contributing to successful implementation include [41]:

- **Clinical Evidence:** Strong evidence base demonstrating improved patient outcomes
- **Ease of Use:** Intuitive operation requiring minimal training
- **Cost-Effectiveness:** Favorable economic profile with clear return on investment
- **Professional Endorsement:** Support from medical societies and regulatory agencies
- **Cultural Adaptation:** Flexible implementation approaches tailored to local contexts

These principles have informed subsequent medical device implementations and continue to guide efforts to expand access to pulse oximetry in underserved populations [41].

Global Health Impact and COVID-19 Pandemic Response

Implementation in Low-resource Settings

Global efforts to implement pulse oximetry have been driven by initiatives such as the World Health Organization's Global Pulse Oximetry Project and the Lifebox Foundation's Safe Surgery programs [5,40]. These organizations have distributed thousands of pulse oximeters to hospitals in low- and middle-income countries (Figure 4), where lack of monitoring contributes to preventable perioperative deaths [5,6,40].

Map shows estimated regional implementation rates of pulse oximetry based on global surveys and WHO data. Adoption is highest in North America and Europe, moderate in Asia and Latin America, and lowest in Sub-Saharan Africa and South Asia.

Data based on [5] by global operating theater survey, [6] for LMIC implementation, and [40] by Lifebox Foundation global reports. Implementation rates represent pulse oximeter availability in major healthcare facilities.

Studies from sub-Saharan Africa have demonstrated that the introduction of pulse oximetry can significantly reduce perioperative mortality, with the greatest impact seen in pediatric and obstetric procedures [6,33]. The technology is particularly valuable in settings where blood gas analysis is unavailable or impractical [6, 20].

COVID-19 Pandemic and Home Monitoring

The COVID-19 pandemic highlighted the critical role of pulse oximetry in detecting silent hypoxemia, a phenomenon in which patients maintain normal breathing patterns despite significant oxygen desaturation [7,42]. Home monitoring programs using pulse oximeters enabled early identification of patients requiring hospitalization, potentially preventing thousands of deaths worldwide [8,28].

Large-scale studies involving over 100,000 patients demonstrated that home pulse oximetry monitoring could reduce hospital admissions while maintaining patient safety [8,28,29] (Figure 5). The technology enabled healthcare systems to manage surge capacity and allocate resources more effectively during peak pandemic periods [28,29].

Timeline shows the evolution of home pulse oximetry as a key component of COVID-19 response strategies, enabling early identification of silent hypoxemia during the pandemic.

Evidence from [7] for COVID-19 racial disparities, [8] for virtual ward programs, [28] for implementation studies, and [42] for silent hypoxemia mechanisms.

Telemedicine Integration

The integration of pulse oximetry into telemedicine platforms has expanded access to specialist care, particularly

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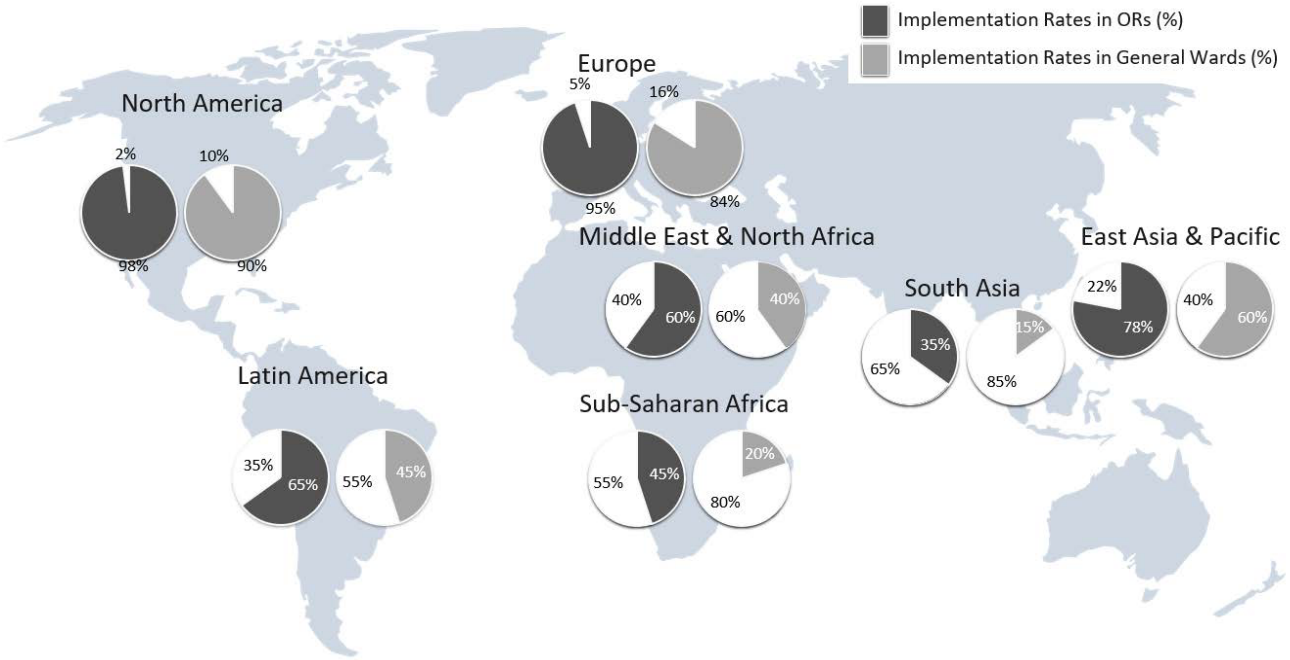

Figure 4: Global Pulse Oximetry Implementation Rates by Region.

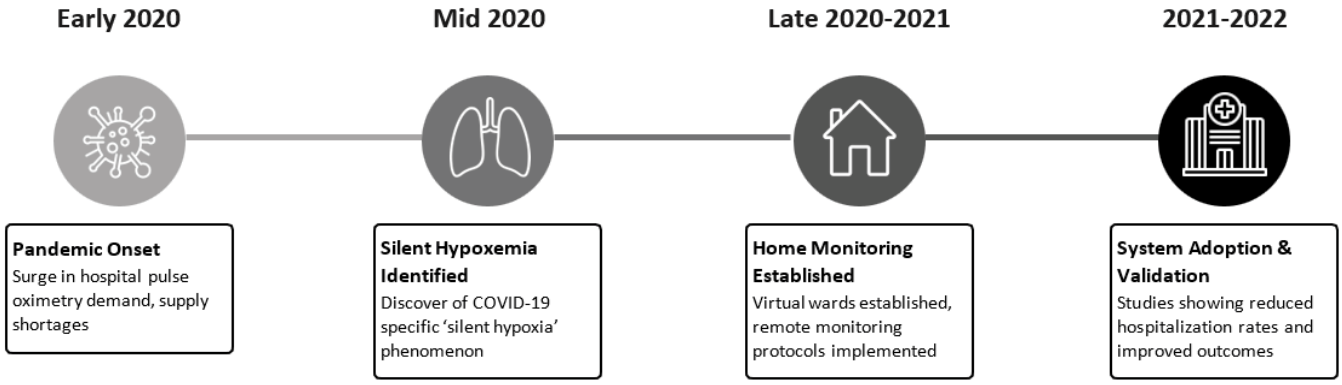

Figure 5: COVID-19 Pandemic Impact of Home Pulse Oximetry Monitoring.

in rural and underserved areas [42,43]. Patients can now transmit real-time oxygen saturation data to healthcare providers, enabling remote monitoring and management of chronic conditions such as chronic obstructive pulmonary disease (COPD) and heart failure [34,43].

Telemedicine integration studies have shown benefits of pulse oximetry-enabled remote monitoring [34,43], including reductions in emergency department visits and hospital readmissions among patients with COPD, although the magnitude of benefit varies by patient population and implementation approach [34]. Systems such as the U.S. Veterans Affairs have implemented pulse oximetry-based telehealth programs for chronic disease management, showing potential for cost savings and improved access to care [43].

Technical Limitations and Challenges

Accuracy Issues in Diverse Populations

Recent studies have identified significant accuracy limitations of pulse oximetry in patients with darker skin pigmentation [22,44,45]. Conventional pulse oximeters may overestimate oxygen saturation in Black and Hispanic patients, potentially delaying recognition of hypoxemia and contributing disparities in care.

The underlying mechanism for these inaccuravies is thought to involve differences in light scattering and absorption due to higher melanin content, which can interfere with the optical measurements [22,44]. In response, regulatory agencies have called for manufacturers to validate devices across diverse populations and develop more inclusive calibration algorithms [7,46,47].

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Motion Artifacts and Low Perfusion States

Despite advances in signal processing, motion artifacts remain a significant limitation of pulse oximetry, particularly in pediatric patients, during transportation, and in patients with tremor or seizures [15,17]. Low perfusion states, such as those caused by shock, hypothermia, or vasoconstriction can also result in unreliable readings.

Advanced signal processing algorithms and alternative sensor sites (e.g., forehead, ear, nasal ala) have been developed to address these limitations, but challenges remain in the most critically ill patients, in whom reliable monitoring is most crucial [15,48].

Interference from Abnormal Hemoglobin Variants

Conventional pulse oximeters cannot differentiate between normal oxyhemoglobin and abnormal hemoglobin variants such as carboxyhemoglobin and methemoglobin [24,49]. Consequently, pulse oximetry may overestimate oxygen saturation in case of carbon monoxide poisoning or methemoglobinemia [24,49].

To overcome this limitation, multi-wavelength pulse oximeters capable of measuring these abnormal hemoglobin variants have been developed, but are not yet widely adopted due to cost and complexity considerations [16,24].

Enhanced Conclusion

Pulse oximetry stands as one of the most transformative medical technologies of the modern era, fundamentally changing the landscape of patient monitoring and safety in anesthesiology and critical care. From its humble beginnings as a research curiosity in the 1970s to its current status as an indispensable clinical tool, pulse oximetry has saved countless lives and continues to evolve with advancing technology.

The impact of this technology extends far beyond the operating room and intensive care unit, reaching into emergency medicine, home healthcare, global health initiatives, medical education, and quality improvement programs. While definitive evidence for mortality reduction in randomized trials remains limited, the ability of pulse oximetry to detect hypoxemia early has fundamentally changed the practice of anesthesiology and critical care. The COVID-19 pandemic demonstrated the critical importance of accessible, reliable oxygen saturation monitoring, while also highlighting persistent challenges in accuracy and equity across diverse populations.

The successful implementation of pulse oximetry worldwide provides valuable lessons for medical technology adoption. The combination of strong clinical evidence, ease of use, cost-effectiveness, professional endorsement, and adaptability to diverse healthcare settings has contributed to its universal acceptance. These same principles continue to guide efforts to address remaining limitations and expand access in underserved populations.

Educational applications of pulse oximetry have transformed training in anesthesiology and critical care, providing standardized approaches to teaching physiological monitoring principles and clinical decision-making. Quality improvement programs centered on pulse oximetry have demonstrated significant gains in patient safety and healthcare delivery efficiency.

As we look toward the future, the integration of artificial intelligence, wearable technology, and contactless monitoring promises to further expand the utility and accessibility of pulse oximetry. However, realizing this potential will require continued efforts to address technical limitations, ensure equitable access, and maintain rigorous standards for accuracy and reliability.

For anesthesiologists and critical care physicians, pulse oximetry remains an essential tool that requires understanding of its capabilities and limitations. As the technology continues to evolve, clinicians must stay informed about new developments while exercising appropriate clinical judgment in interpreting and acting upon pulse oximetry data.

The journey of pulse oximetry from innovation to standard of care exemplifies the impact of biomedical engineering in transforming clinical practice. As we continue to refine and expand its application, we move closer to the goal of universal access to safe, effective patient monitoring that can save lives regardless of geographic location, socioeconomic status, or patient characteristics. Ongoing commitment to addressing health equity issues and developing bias-free monitoring technologies will be essential to ensuring that the benefits of pulse oximetry are available to all.

Author Declarations

The author acknowledges the use of artificial intelligence tools including ChatGPT (OpenAI), Genspark AI documents, and AI-powered fact-checking systems for language refinement, literature organization, and content structuring. All scientific content, clinical interpretations, and conclusions were independently verified, critically evaluated, and finalized by the author, who take full responsibility for the accuracy and integrity of this work.

The author declares that there are no conflicts of interest related to any commercial entities, including those mentioned in this manuscript.

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Remimazolam: Five Years of Clinical Experience Since Its First-in-World Approval in Japan

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Abstract

Background: Remimazolam besylate, an ultra-short-acting benzodiazepine anesthetic, received its first-in-world approval in Japan in January 2020, marking a significant milestone in anesthetic drug development. Five years of clinical experience have provided substantial evidence on its clinical utility and safety profile, offering unprecedented insights into the practical application of this novel agent across diverse patient populations and clinical scenarios. **Methods:** This narrative review synthesized published literature from PubMed-indexed sources, focusing on Japanese clinical trials, international studies, and post-marketing surveillance data to evaluate remimazolam's clinical performance over the five years since its approval. The analysis encompassed randomized controlled trials, observational studies, case reports, and pharmacovigilance data, to provide a comprehensive assessment of clinical outcomes, safety profiles, and practical considerations for its clinical use. **Results:** Clinical trials demonstrated remimazolam's non-inferiority to propofol for general anesthesia, with superior cardiovascular stability and reduced injection site pain. Japanese researchers led pivotal Phase III trials showing drug efficacy in both standard and high-risk (ASA III) patients, establishing a robust evidence base for its clinical implementation. Post-marketing surveillance revealed rare but serious adverse events, including anaphylaxis and circulatory collapse, particularly in elderly patients, while simultaneously demonstrating excellent overall tolerability. Notably, remimazolam showed no increased risk of postoperative delirium in cardiovascular surgery patients, distinguishing it from other benzodiazepines, and suggesting potential cognitive advantages. **Conclusions:** Five years of clinical experience confirm that remimazolam is a valuable addition to the anesthetic armamentarium, with particular advantages in terms of hemodynamic stability and reversibility. While the overall safety profile remains favorable, vigilance for rare, albeit serious allergic reactions is warranted, especially in older patients. The accumulated evidence supports judicious use of remimazolam in selected clinical scenarios

where traditional agents may be suboptimal.

Keywords

Remimazolam, Benzodiazepine, General Anesthesia, Japan, Clinical Experience, Safety

1. Introduction

The development and approval of new anesthetic agents represent a rare, but profoundly significant advancement in perioperative medicine, occurring perhaps once in a generation. In January 2020, Japan achieved a historic milestone by becoming the first country worldwide to approve remimazolam besylate (Anerem®) for general anesthesia, culminating decades of meticulous research and clinical development that began in the laboratories of Glaxo Wellcome in the late 1990s [1]. This ultra-short-acting benzodiazepine, bearing the original research designation CNS-7056, represents a unique pharmacological approach that successfully combines the familiar and well-understood receptor profile of benzodiazepines with revolutionary metabolic properties specifically designed to overcome the traditional limitations that have long constrained this drug class [2].

The significance of Japan's pioneering regulatory approval extends far beyond mere administrative precedence, reflecting the country's substantial intellectual contribution to the drug's development. Japanese investigators, led by distinguished researchers such as Doi, Masui, and Yamakage, conducted many of the foundational clinical studies that established remimazolam's efficacy and safety profile through rigorous scientific investigation [3] [4]. The prescient observation by Masui in his landmark 2020 editorial captures the essence of this achievement: "A novel anesthetic, remimazolam, would be desired to have advantages beyond existing anesthetics such as inhalation anesthetics, propofol, and midazolam" [1]. This statement proved remarkably prophetic as subsequent clinical experience has validated many of these anticipated advantages. The Japanese clinical development program strategically targeted patient populations and surgical contexts that were particularly relevant to Japan's healthcare landscape and demographic profile. Initial trials focused on elderly patients undergoing elective surgery, reflecting Japan's rapidly aging society where nearly 30% of the population is over 65 years old. The emphasis on cardiovascular procedures and patients with multiple comorbidities (ASA-PS class III) aligned with the prevalent healthcare challenges in Japan, where age-related cardiovascular disease represents a major perioperative risk factor. This targeted approach ensured that remimazolam's clinical evidence would be directly applicable to the patient populations most encountered in Japanese anesthetic practice, facilitating evidence-based adoption and optimal clinical implementation [3] [4].

The temporal milestone of five years since this landmark approval now provides sufficient clinical experience to conduct a comprehensive and meaningful assessment of remimazolam's place in modern anesthetic practice. The accumulated ex-

perience spans diverse patient populations, varied surgical procedures, and multiple clinical contexts, offering insights that extend well beyond the controlled conditions of initial clinical trials. The present review synthesizes this wealth of available evidence, with particular emphasis on the pioneering Japanese clinical experience, while incorporating valuable international perspectives and crucial post-marketing surveillance data that have emerged during this formative period.

2. Development History and Pharmacological Profile of Remimazolam

2.1. Historical Development and Corporate Evolution

The genesis of remimazolam can be traced to the British pharmaceutical company, Glaxo Wellcome, in the late 1990s, where researchers, buoyed by the remarkable success of remifentanil development, embarked upon an ambitious project to identify novel sedatives with short and highly predictable durations of action [5]. The pharmaceutical development landscape of this era was marked by growing recognition of the clinical limitations inherent to existing anesthetic agents, creating both scientific opportunity and commercial incentive for innovation. The compound that would eventually become remimazolam, initially designated GW502056 and subsequently CNS-7056, emerged as the lead candidate through systematic medicinal chemistry efforts, although its path to clinical reality proved both circuitous and prolonged [6].

The compound's developmental journey reflects the complex realities of modern pharmaceutical innovation, involving multiple corporate transitions and strategic realignments that are characteristic of drug development in the contemporary era. Following initial promise at Glaxo Wellcome, the project underwent various corporate transitions before ultimately reaching clinical development under the guidance of PAION AG (Aachen, Germany) in 2008, demonstrating the persistence required for novel anesthetic development [6]. Simultaneously, a parallel and strategically independent development program was initiated by Jiangsu Hengrui Pharmaceutical Co. Ltd. in China, utilizing a different salt formulation (tosylate) in what appears to have been a calculated maneuver to circumvent existing patent protection while advancing clinical availability [6]. This dual development pathway ultimately contributed to remimazolam's eventual global availability in multiple formulations, each optimized for different regulatory and clinical contexts.

2.2. Pharmacological Characteristics and Molecular Innovation

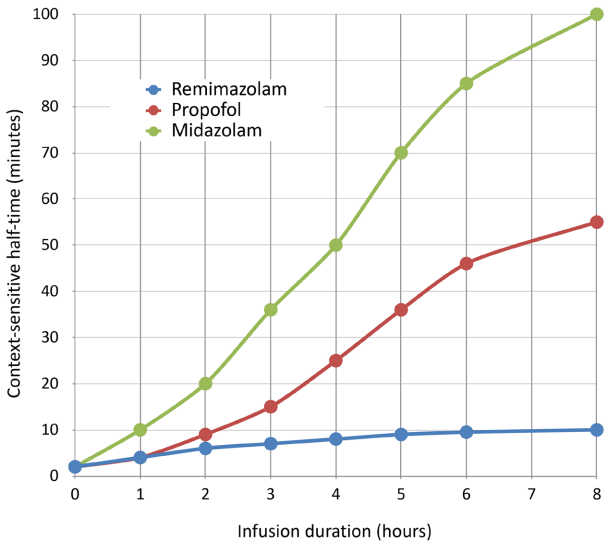
Remimazolam possesses a sophisticated imidazobenzodiazepine structure, distinguished by a carefully engineered ester side chain attached to the diazepine ring, representing a masterful example of rational drug design [2]. This structural modification, seemingly minor from a chemical perspective, enables rapid and predictable hydrolysis by tissue esterases, primarily carboxylesterase 1 (CES1), to produce CNS-7054, an inactive carboxylic acid metabolite characterized by approximately 300 - 400 fold lower receptor affinity compared to the parent compound [6]. This remarkable difference in receptor affinity ensures that metabolism truly

represents pharmacological inactivation rather than merely redistribution or chemical transformation into an equipotent metabolite.

The comprehensive pharmacological profile of remimazolam encompasses several remarkable characteristics that distinguish it from existing benzodiazepines. The compound demonstrates high affinity for GABA-A receptor benzodiazepine binding sites with a Ki value of approximately 30 nM, ensuring robust pharmacological activity at clinically relevant concentrations. The kinetic profile is characterized by rapid onset and offset, with an effect-site equilibration half-life ranging from 1 - 5 minutes, allowing clinicians to exert precise temporal control over anesthetic depth. The terminal elimination half-life of approximately 0.75 hours, combined with linear pharmacokinetics and minimal accumulation potential, ensures predictable recovery characteristics even following prolonged administration [6].

The formulation represents another triumph of pharmaceutical science, with remimazolam presented as a water-soluble besylate salt with a molecular weight of 567.5 Da, eliminating many of the formulation challenges that have historically complicated benzodiazepine administration, such as poor aqueous solubility and the need for organic solvents. The protein binding of 92% ensures appropriate tissue distribution, while maintaining sufficient free drug concentrations for pharmacological activity [6]. The metabolic pathway of remimazolam through tissue esterases represents a fundamental advantage over traditional hepatic cytochrome P450-dependent metabolism, potentially reducing drug interactions and providing more predictable pharmacokinetics across patient populations with varying hepatic function [2] (**Figure 1**).

Parameter	Remimazolam	Propofol	Midazolam
Elimination half-life (h)	0.75	4-7	1.5-2.5
Primary metabolism	Tissue esteraces (CES1)	Hepatic (CYP2B6, CYP2C9)	Hepatic (CYP3A4/5)
Active metabolites	No (CNS-7054)	No	Yes (α-hydroxymidazolam)
Context-sensitive half-life	Minimal increase	Increases with infusion time	Marked increase with infusion time
Pharmacokinetic profile	Linear	Non-linear	Linear
Recovery predictability	High	Moderate	Low
Characteristics	Organ-independent metabolism	Affected by liver dysfunction	Drug interaction & variability



Linear pharmacokinetics with predictable recovery characteristics regardless of infusion duration distinguish remimazolam from the hepatic cytochrome P450-dependent sedative midazolam. The table demonstrates the pharmacokinetic effects of the organ-independent metabolism of remimazolam versus the hepatic metabolism of propofol and midazolam, with implications for drug interactions and recovery predictability [11] [12]. The graph represents a comparison of the pharmacokinetic parameters of the three drugs, showing remimazolam's ultra-short elimination half-life (0.75 hours) and tissue esterase-mediated metabolism via CES1 to inactive metabolite CNS-7054 [2] [6].

Figure 1. Pharmacokinetic comparison: remimazolam, propofol, and midazolam.

3. Clinical Development of Remimazolam: Foundational Studies in Japan

3.1. Early Clinical Investigation and Phase I Studies

Japanese investigators assumed a crucial and ultimately decisive role in remimazolam's clinical development, contributing scientific rigor and clinical insight that proved essential for regulatory approval and clinical implementation. Doi's comprehensive 2014 review of early clinical data established many fundamental principles that remain relevant and applicable even today, providing a scientific foundation upon which subsequent clinical experience has been built [2]. The initial Phase I studies conducted in healthy volunteers demonstrated several remarkable pharmacological characteristics that would later prove clinically significant.

These early investigations revealed a single-dose elimination half-life ranging from 39 - 53 minutes, confirming the rapid clearance anticipated from the compound's molecular design. Perhaps most significantly, universal loss of consciousness occurred at the modest dose of 0.2 mg/kg, demonstrating both potency and consistency of effect across study participants. The pharmacokinetic parameters exhibited dose-independence, a characteristic that greatly simplifies clinical dosing and reduces the potential for unexpected accumulation or prolonged effect. Throughout these studies, subjects maintained a stable cardiovascular profile during anesthesia, demonstrating one of remimazolam's most clinically valuable characteristics [2].

The transition from Phase I to Phase II studies marked remimazolam's first clinical application for general anesthesia, representing a pivotal moment in anesthetic drug development. This landmark Phase II trial involved 85 carefully selected patients, comprising 55 non-elderly and 30 elderly subjects, and demonstrated average maintenance infusion rates of 1.02 mg/kg/h in non-elderly patients and 0.72 mg/kg/h in elderly patients. These findings suggested age-related pharmacokinetic differences that would require clinical consideration. Recovery times from infusion cessation to eye opening averaged 14 minutes in non-elderly and 11 minutes in elderly patients, indicating rapid and predictable emergence across age groups [2].

3.2. Landmark Phase III Trials: Establishing Clinical Efficacy

The definitive Phase IIb/III multicenter trial conducted by Doi *et al.* represents perhaps the most significant single study in remimazolam's clinical development, providing unequivocal evidence of its clinical efficacy and establishing the foundation for regulatory approval [7]. This meticulously designed study randomized 375 surgical patients to receive either remimazolam at induction doses of 6 or 12 mg/kg/h, followed by maintenance at 1 mg/kg/h, or propofol according to standard protocols. The study's primary endpoint was a composite measure designed to capture the essential elements of successful anesthesia: absence of intraoperative awakening or recall, no requirement for rescue sedatives, and absence of purposeful body movements.

The results exceeded expectations, with a remarkable 100% success rate achieved in all treatment groups for the composite endpoint, definitively establishing rem-

imazolam's clinical efficacy. The statistical demonstration of non-inferiority to propofol, confirmed by a 95% confidence interval of −0.0487 to 0.0250, provided regulatory authorities with the evidence needed for approval decisions. However, the study's most clinically significant findings may have been the safety advantages demonstrated by remimazolam compared to propofol [7].

The safety profile revealed several remarkable differences favoring remimazolam. The overall incidence of adverse events was substantially lower, with remimazolam groups experiencing rates of 39.3% - 42.7% compared to 61.3% in the propofol group. More specifically, the incidence of hypotension, a common and clinically significant adverse event associated with anesthesia induction, occurred in only 20.0% - 24.0% of remimazolam patients compared to 49.3% of propofol patients. Perhaps, most notable from a patient comfort perspective, injection site pain, reported in 18.7% of propofol patients, was completely absent in the remimazolam group [7].

The study also revealed important kinetic differences that inform clinical practice. The time to loss of consciousness was longer with remimazolam compared to propofol, reflecting different pharmacological mechanisms and suggesting the need for modified induction techniques. Similarly, extubation times were prolonged in the remimazolam group, although this difference must be interpreted in the context of overall recovery quality and patient satisfaction [7].

3.3. High-Risk Patient Populations: Studies of Remimazolam in ASA-PS Class III Patients

Building upon the success of the drug in standard patient populations, Doi *et al.* conducted a subsequent investigation specifically targeting American Society of Anesthesiologists-physical status (ASA-PS) class III patients, a population traditionally considered at elevated risk for anesthetic complications [8]. This study, involving 67 carefully selected high-risk patients, compared two remimazolam induction regimens (6 vs. 12 mg/kg/h), and proved particularly significant in establishing the agent's safety profile in vulnerable patient populations.

The study achieved a remarkable 100% anesthesia success rate across both dosing regimens, demonstrating that remimazolam's efficacy extends to patients with significant medical comorbidities. The adverse event profiles were manageable and comparable between dose groups, suggesting that higher-risk patients do not experience disproportionate complications with remimazolam use. This finding proved crucial for its clinical adoption, as it provided evidence-based support for remimazolam use in precisely those patients who might benefit most from its favorable hemodynamic profile [8].

4. International Clinical Experience and Global Regulatory Development

4.1. Regulatory Approvals and Global Implementation

Following Japan's pioneering approval, remimazolam underwent a carefully or-

chestrated global regulatory campaign that reflected both the compound's clinical promise and the complex realities of international drug development. The pattern of approvals revealed important strategic considerations, with general anesthesia indications approved in Japan in January 2020 and South Korea in 2021, while procedural sedation applications gained approval in the United States in July 2020, the European Union in 2021, and China in 2021. This staggered approval pattern reflects different regulatory priorities and clinical needs across global markets [6].

The approval for intensive care unit sedation in Belgium through compassionate use protocols represented an important expansion of remimazolam's clinical applications, although this indication remains limited compared to its general anesthesia and procedural sedation uses. These varied regulatory pathways demonstrate the flexibility of remimazolam's clinical profile and its potential applicability across different clinical contexts [6].

4.2. Procedural Sedation Applications

International clinical trials, particularly those conducted under the leadership of Rex *et al.*, established compelling evidence of remimazolam's efficacy in procedural sedation applications, complementing the general anesthesia data generated by Japanese investigators [9]. The pivotal Phase III colonoscopy study demonstrated the superior efficacy of remimazolam compared to both placebo and midazolam controls, while simultaneously revealing faster recovery times and reduced respiratory depression compared to traditional agents. These findings proved particularly significant given the large volume of colonoscopic procedures performed worldwide, and the growing emphasis on the efficiency of ambulatory care.

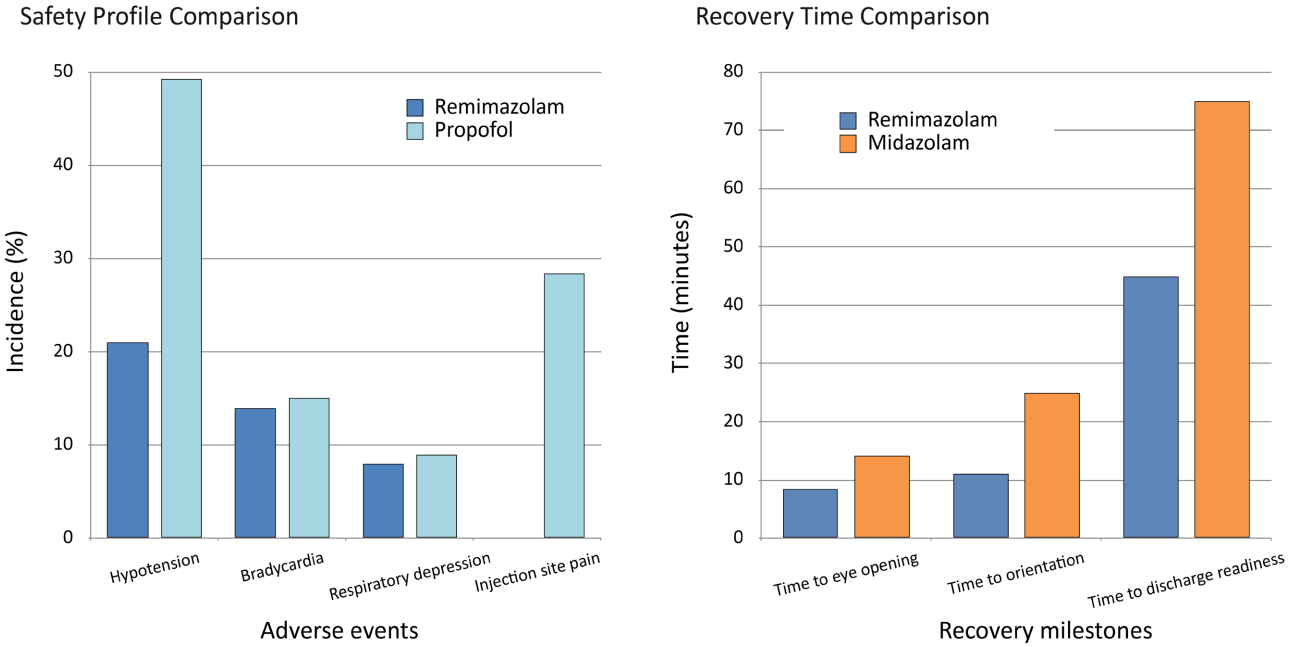
Similar benefits were observed in bronchoscopy procedures, with particular advantages noted in elderly and high-risk patients who traditionally pose greater challenges for procedural sedation [10]. The consistency of these findings across different procedures and patient populations provided strong evidence for remimazolam's versatility and reliability in ambulatory settings, where rapid, predictable recovery is paramount.

4.3. Pharmacokinetic Validation across Populations

International pharmacokinetic studies conducted by Schuttler *et al.* and other investigators provided crucial validation of remimazolam's pharmacological consistency across diverse patient populations [11] [12]. These investigations confirmed that the favorable pharmacokinetic properties observed in initial Japanese studies were maintained across different ethnic populations, with minimal effects of age, sex, race, and obesity status on drug disposition. Such consistency represents a remarkable achievement in drug development, where population-specific pharmacokinetic differences often complicate clinical implementation and dosing recommendations.

These findings proved instrumental in supporting remimazolam's global regulatory approvals and clinical implementation, providing evidence-based reassur-

ance that dosing recommendations developed in one population could be safely applied across diverse patient groups. The pharmacokinetic predictability observed across populations also supported the development of standardized dosing protocols that could be implemented globally without extensive population-specific modifications [11] [12] (**Figure 2**).



Integrated efficacy and safety outcomes were evaluated in pivotal trials. Japanese Phase III studies demonstrated 100% composite endpoint success with non-inferiority to propofol, significantly reduced hypotension (20.0% - 24.0% vs. 49.3%) and complete elimination of injection site pain [7] [8]. High-risk ASA-PS class III patients experienced equivalent efficacy of remimazolam as healthy subjects [8]. International procedural sedation trials confirmed superior outcomes of remimazolam versus midazolam, with faster and more predictable recovery profiles in bronchoscopy and colonoscopy procedures [9] [10]. Enhanced hemodynamic stability represented a consistent finding across all major clinical trials.

Figure 2. Summary of major clinical trials on remimazolam.

5. Five Years of Clinical Experience: Comprehensive Safety Assessment

5.1. Overall Safety Profile and Clinical Tolerability

Five years of increasingly widespread clinical use have provided unprecedented insight into remimazolam's safety profile under real-world conditions, confirming and extending the favorable findings observed in controlled clinical trials. The most commonly reported adverse events continue to align closely with expected benzodiazepine pharmacology, including hypotension, nausea, vomiting, and transient respiratory depression. However, the critical clinical observation is that the incidence of these events typically equals or falls below that observed with comparative agents, confirming remimazolam's favorable risk-benefit profile across diverse clinical applications [6] [13].

The accumulation of clinical experience has also provided valuable insights into patient factors that may influence adverse event risk, dosing requirements, and

clinical outcomes. Age-related differences in drug sensitivity and clearance have become more clearly defined through clinical observation, while the influence of comorbid conditions on drug response has been better characterized through case reports and clinical series.

5.2. Post-Marketing Surveillance: FAERS Database Analysis

The recent comprehensive analysis of the FDA Adverse Event Reporting System (FAERS) database, covering the period from 2020-2023, provides the most systematic assessment of remimazolam's post-marketing safety profile currently available [14]. However, it is important to acknowledge the inherent limitations of spontaneous adverse event reporting systems. FAERS data are subject to significant reporting bias, with serious and unexpected events more likely to be reported than common or well-recognized adverse effects. The database cannot establish causal relationships between drug exposure and adverse events, as temporal association does not prove causation. Additionally, underreporting is common, particularly for non-serious events, and the quality and completeness of individual reports vary considerably. Despite these limitations, this analysis, encompassing 67 cases with 161 adverse drug events, offers valuable insights into the real-world safety experience that extends beyond the controlled conditions of clinical trials [15].

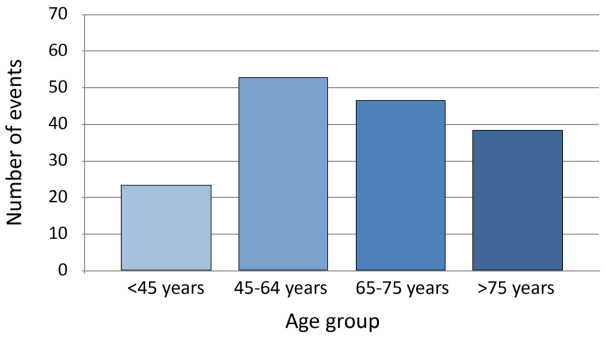
The FAERS analysis revealed several important patterns that inform clinical practice. A higher incidence of adverse events was observed in patients over 45 years of age, with particular concentration in those over 65 years, suggesting that advanced age represents a risk factor for remimazolam-related complications. The analysis identified notable signals for serious adverse events, including allergic reactions, respiratory arrest, cardiac arrest, and vascular access occlusion, emphasizing the need for enhanced monitoring protocols in elderly patients and continued post-marketing surveillance [14].

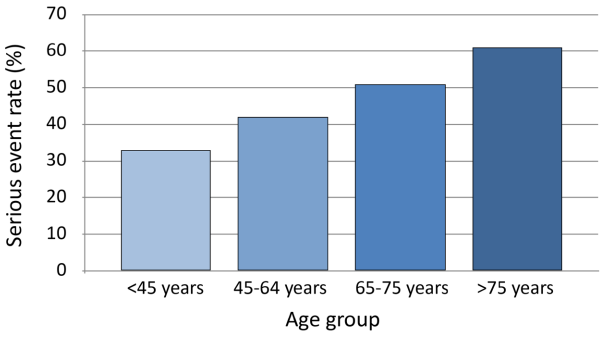
These findings underscore the importance of systematic post-marketing surveillance in detecting rare but potentially serious adverse events not evident in clinical trials, particularly in elderly patients (**Figure 3**).

5.3. Rare but Serious Adverse Events: Clinical Characterization

Japanese case reports have provided detailed clinical characterization of rare but potentially life-threatening anaphylactic reactions associated with remimazolam administration [16]. These reports describe a distinctive clinical pattern of the reaction, characterized by rapid onset within minutes of drug administration, severe hypotension with systolic blood pressure falling to 30 - 40 mmHg, and, notably, the absence of typical cutaneous or respiratory symptoms that usually characterize anaphylactic reactions. The circulatory collapse observed in these cases required aggressive management with epinephrine for hemodynamic stabilization, as other conventional vasopressors (e.g., phenylephrine or ephedrine) were ineffective.

These case reports have raised important questions about the mechanisms underlying these severe reactions, with some evidence suggesting a possible role of





Adverse Event Type	Frequency	% of Total	Age Association
Hypotension	42	26.1	Strong (>65 years)
Respiratory depression	36	22.4	Moderate
Bradycardia	29	18.0	Strong (>75 years)
Anaphylactic reaction	4	2.5	None
Other events	50	31.0	Variable

Anaphylactic reactions present as rapid-onset circulatory collapse without typical allergic manifestations

- Onset typically within minutes of remimazolam administration
- Absent or minimal cutaneous manifestations (urticaria, erythema)
- Primary presentation: Sudden hypotension and cardiovascular collapse
- Potential association with dextran component of formulation

Post-marketing surveillance analysis of 67 cases with 161 adverse events from the FDA Adverse Event Reporting System database showed clear age-related risk stratification [14]. Patients >65 years old exhibit significantly higher serious adverse event rates, with hypotension (26.1%), respiratory depression (22.4%), and bradycardia (18.0%) showing strong age associations. Rare anaphylactic reactions (2.5%) present as rapid-onset circulatory collapse without typical allergic manifestations, with onset typically within minutes of remimazolam administration, potentially associated with the dextran component of the formulation [16].

Figure 3. Adverse events profile by age group: FAERS database (2020-2023).

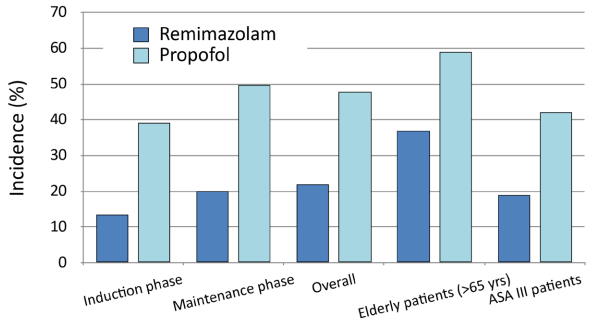
formulation additives, such as dextran 40, rather than the active pharmaceutical ingredient itself [15]. This mechanistic uncertainty has important implications for patient management and risk assessment, as conventional allergy testing may not reliably predict the risk of these severe reactions. Currently, the commercially available remimazolam formulation (Anerem®) contains dextran 40 as a stabilizing excipient, and alternative dextran-free formulations are not yet available for clinical use. However, pharmaceutical manufacturers are actively investigating alternative formulation strategies that could eliminate dextran 40 while maintaining drug stability and efficacy. Until dextran-free alternatives become available, clinicians should maintain heightened awareness of this potential risk factor, particularly in patients with known dextran sensitivity or previous unexplained intraoperative hypotensive episodes. The development of dextran-free formulations represents a high priority for improving remimazolam's safety profile and could potentially eliminate this rare but serious adverse event risk.

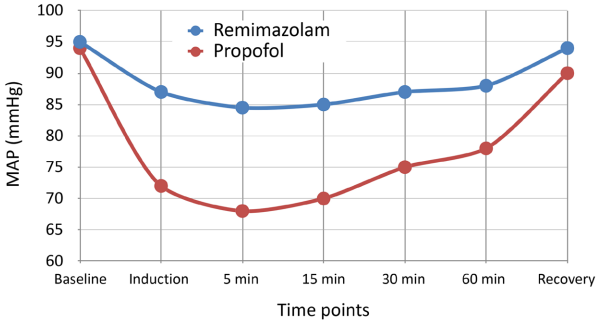
The clinical presentation of remimazolam-associated anaphylaxis, characterized primarily by cardiovascular collapse without classic allergic manifestations, represents a unique challenge for clinical recognition and management. These cases emphasize the critical importance of readiness for anaphylactic emergencies in all patients receiving remimazolam, regardless of prior allergy history, and highlight the need for immediate access to epinephrine and advanced resuscitation capabilities.

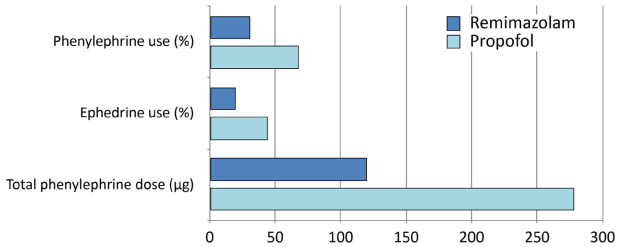
5.4. Cardiovascular Considerations and Paradoxical Responses

While remimazolam generally promotes hemodynamic stability compared to other anesthetic agents, isolated case reports have documented unexpected hypertensive responses during cardiac surgery procedures [17]. These reports suggest the potential for atypical cardiovascular reactions in specific clinical contexts, particularly in patients with underlying cardiovascular diseases, or during procedures involving significant physiological stress.

These paradoxical cardiovascular responses, while rare, underscore the importance of continuous hemodynamic monitoring during remimazolam administration, and the need for clinicians to remain vigilant for unexpected cardiovascular changes. Several mechanistic hypotheses may explain these atypical responses. First, remimazolam's selective binding to specific GABA-A receptor subunits (α_1, α_2, α_3, and α_5) may produce differential effects in patients with altered receptor expression patterns due to chronic cardiovascular disease [5]. Second, reflex sympathetic activation could occur in response to remimazolam-induced peripheral vasodilation, particularly in patients with impaired baroreceptor sensitivity or pre-existing sympathetic hyperactivity. Third, the stress of cardiac surgery may unmask latent cardiovascular instability that becomes apparent when combined with remimazolam's unique pharmacological profile. These mechanisms highlight the complex interactions between remimazolam's pharmacological effects and the underlying cardiovascular pathophysiology in susceptible patients (**Figure 4**).







Procedure Type	Remimazolam	Propofol	P-value
Cardiopulmonary bypass	87.3% stable	62.1% stable	P < 0.01
Transcatheter interventions	92.5% stable	76.8% stable	P < 0.01
ASA III-IV patients	18.2% hypotension	42.7% hypotension	P < 0.01

Hemodynamic outcomes demonstrating remimazolam's cardiovascular advantages with superior hemodynamic stability during high-risk procedures compared to propofol [7] [8]. Hemodynamic stability was seen in 87.3% of cardiopulmonary bypass procedures with remimazolam versus 62.1% with propofol ($P < 0.01$), while stability was seen in 92.5% versus 76.8% transcatheter interventions, respectively ($P < 0.01$). ASA III-IV patients experienced significantly reduced hypotension rates (18.2% vs. 42.7%, $P < 0.001$), supporting remimazolam's utility in cardiac surgery and high-risk cardiovascular procedures [19]-[21].

Figure 4. Hemodynamic stability: remimazolam versus propofol.

6. Remimazolam in Specialized Populations and for Advanced Clinical Applications

6.1. Elderly Patient Management and Super-Elderly Experience

Japanese investigators have made particularly significant contributions to understanding remimazolam's clinical performance in elderly patients, including groundbreaking case reports documenting its successful use in super-elderly patients exceeding 90 years of age [18]. These reports demonstrate that remimazolam can provide safe and effective anesthesia management in this challenging population without significant hemodynamic perturbation, supporting its potential value in geriatric anesthesia where traditional agents may pose excessive risks.

However, post-marketing surveillance data suggest that increased vigilance is warranted in elderly populations due to reports of higher adverse event rates, creating a nuanced clinical picture that requires careful balance between the potential benefits and recognized risks of remimazolam [14]. This apparent contradiction between case report successes and surveillance data highlights the complexity of elderly patient management and the importance of individualized risk assessment.

Clinical experience in elderly patients has also provided valuable insights into age-related pharmacokinetic and pharmacodynamic differences that influence dosing requirements and recovery characteristics. While the fundamental pharmacological profile remains consistent across age groups, subtle differences in drug sensitivity and clearance may require clinical consideration and potentially modified dosing protocols in very elderly patients.

6.2. Cardiac Surgery Applications and Hemodynamic Advantages

Multiple Japanese case series have documented successful remimazolam implementation across a broad spectrum of cardiac surgical procedures, providing compelling evidence for its utility in this demanding clinical context [19]-[21]. These applications have encompassed complex procedures, including cardiopulmonary bypass operations, transcatheter aortic valve implantations, and MitraClip implantations in patients with advanced heart failure.

The consistent theme emerging from these cardiac surgery reports is remimazolam's primary clinical advantage of maintenance of hemodynamic stability, although the reports also emphasize that careful monitoring remains essential despite this favorable profile [19]-[21]. The hemodynamic stability observed in cardiac surgery patients represents a particularly valuable characteristic, as these procedures often involve patients with compromised cardiovascular reserve who have poor tolerance for anesthesia-induced hypotension or cardiac depression.

The success of remimazolam in cardiac surgery applications has important implications for anesthesia management in high-risk cardiovascular patients across a broader range of procedures. The demonstrated hemodynamic stability in these challenging cases also provides evidence-based support for remimazolam use in other clinical contexts where cardiovascular stability is paramount.

6.3. Postoperative Delirium: A Distinguishing Safety Feature

One of the most clinically significant findings to emerge from the five-year experience with remimazolam usage is the evidence regarding the risk of postoperative delirium. A landmark prospective cohort study involving 200 elderly cardiovascular surgery patients demonstrated that remimazolam administration was not associated with an increased risk of postoperative delirium compared to other anesthetic agents, with delirium rates of 30.3% versus 26.6% respectively ($P = 0.63$) [22].

This finding represents a potentially paradigm-shifting observation that distinguishes remimazolam from other benzodiazepines, which have traditionally been associated with an increased delirium risk in vulnerable populations. The clinical implications of this finding are profound, as postoperative delirium represents a serious complication associated with increased morbidity, mortality, duration of hospitalization, and healthcare costs. The ability to utilize a benzodiazepine-based anesthetic without increased delirium risk could represent a significant clinical advantage of remimazolam, particularly in elderly patients undergoing major surgery [22].

The mechanism underlying this apparent protection against delirium remains unclear, but may relate to remimazolam's unique pharmacokinetic profile and rapid clearance, which may minimize the prolonged central nervous system effects associated with the development of delirium. This finding warrants further investigation through larger, randomized studies to confirm and extend these preliminary observations.

6.4. Complex Medical Conditions: Case Study Evidence

Japanese case reports have documented successful remimazolam implementation across an impressive range of complex medical conditions, providing valuable evidence for its safety and efficacy in challenging clinical scenarios. These conditions have included myotonic dystrophy type 1, where neuromuscular dysfunction creates significant anesthetic challenges [23], amyotrophic lateral sclerosis, where respiratory compromise is a constant concern [24], and hemodialysis patients with compromised fluid and electrolyte balance [25].

Additional case reports have documented successful use of remimazolam in patients with Child-Pugh C liver cirrhosis, where altered drug metabolism creates significant pharmacokinetic concerns [26], MELAS syndrome, where mitochondrial dysfunction affects multiple organ systems [27], and suspected malignant hyperthermia susceptibility, where avoidance of triggers is paramount [28]. The consistent success reported across these diverse and challenging conditions suggests that remimazolam's favorable pharmacological profile translates into clinical benefits across a broad spectrum of medical complexity.

These case reports consistently emphasize hemodynamic stability and predictable recovery as key advantages of the drug in medically complex patients, supporting the theoretical expectations derived from remimazolam's pharmacologi-

cal profile. While individual case reports cannot establish definitive clinical recommendations, the accumulated experience across diverse conditions provides reassuring evidence of remimazolam's safety and utility in challenging clinical scenarios where traditional anesthetic agents might pose excessive risks.

6.5. Considerations in Pediatric Patients and Gaps in Clinical Development

Despite five years of extensive adult clinical experience, the pediatric applications of remimazolam remain significantly limited, representing one of the most important gaps in current clinical knowledge. A recent comprehensive review emphasized that while remimazolam's fundamental pharmacological properties suggest potential pediatric advantages, "routine use in pediatric populations remains underexplored and unestablished" [29]. This limitation reflects both regulatory requirements for pediatric-specific clinical trials, and the challenges inherent to conducting anesthetic research in vulnerable pediatric populations.

Due to the limited availability of pediatric data, the effects of age-related differences in drug metabolism that might significantly influence remimazolam's clinical performance in children are unclear. Particularly concerning is the reduced carboxylesterase 1 (CES1) activity observed in neonates, which may substantially affect remimazolam pharmacokinetics, necessitating age-specific dosing strategies that have yet to be systematically investigated [29]. These metabolic differences could potentially lead to prolonged drug effects or altered recovery characteristics in very young patients, emphasizing the importance of systematic pediatric pharmacokinetic studies before widespread clinical application of the drug in pediatric populations.

The pediatric knowledge gap represents both a clinical limitation and a significant research opportunity. Given remimazolam's favorable safety profile in adult populations and its theoretical advantages in pediatric applications, systematic investigation of its pharmacology and clinical performance in pediatric patients represents a high priority for future research efforts. Such studies could potentially expand remimazolam's clinical utility to encompass the full age spectrum of patients requiring anesthetic care.

7. Comparative Analysis with Existing Anesthetic Agents

7.1. Advantages over Propofol: Clinical Validation

Five years of clinical experience have comprehensively validated the theoretical advantages of remimazolam over propofol that were initially proposed based on pharmacological considerations. The clinical reality has confirmed reduced cardiovascular depression, with a significantly lower incidence of hypotension during anesthesia induction and maintenance. Complete elimination of the injection site pain associated with propofol injection represents a substantial improvement in patient comfort and satisfaction, particularly important in ambulatory settings where patient experience directly influences procedure acceptance [1] [7].

Absence of the risk of propofol infusion syndrome-like effects with remimazolam has proven clinically significant, particularly in intensive care applications where prolonged anesthetic infusions are sometimes required. The water-soluble formulation of remimazolam eliminates the lipid load associated with propofol administration, reducing complications related to hyperlipidemia and bacterial contamination risk. Most significantly, perhaps, availability of a specific antagonist (flumazenil) to remimazolam provides a safety advantage that has proven valuable in clinical practice, offering the ability to rapidly reverse anesthetic effects when clinically indicated [1] [7]. However, clinical use of flumazenil requires careful consideration of several important factors. Flumazenil has a shorter elimination half-life (approximately 1 hour) compared to remimazolam, creating the potential risk of re-sedation if remimazolam plasma concentrations remain elevated after flumazenil effects dissipate. This risk is particularly relevant following prolonged remimazolam infusions or in patients with impaired drug clearance. Additionally, flumazenil administration may precipitate withdrawal symptoms in patients with chronic benzodiazepine use, and can potentially lower the seizure threshold in susceptible individuals. Therefore, while flumazenil represents a valuable safety advantage, its use requires ongoing patient monitoring and readiness for repeat administration if re-sedation occurs [30].

7.2. Advantages over Midazolam: Kinetic Superiority

Compared to midazolam, remimazolam offers substantial pharmacokinetic advantages that have been consistently confirmed through clinical experience. The significantly shorter context-sensitive half-time, approximately one-fifth that of midazolam, ensures more predictable offset characteristics regardless of infusion duration. This kinetic advantage translates into reduced individual variability in recovery times and lower potential for drug interactions, both clinically significant benefits [1] [2].

The clinical implications of these kinetic differences extend beyond simple recovery times to encompass broader aspects of perioperative care efficiency and patient flow in busy surgical and procedural environments. The predictable recovery characteristics associated with remimazolam use facilitate more accurate scheduling and resource allocation, while reducing the risk of prolonged recovery that can complicate ambulatory care pathways.

7.3. Environmental and Sustainability Considerations

As healthcare systems increasingly focus on environmental sustainability and carbon footprint reduction, remimazolam's profile as an intravenous agent offers significant advantages over volatile anesthetics. Elimination of volatile agent emissions reduces the environmental impact and aligns with growing sustainability initiatives within healthcare organizations [1]. This environmental advantage, while perhaps secondary to clinical considerations, represents an important additional benefit that supports remimazolam adoption in environmentally conscious

healthcare systems.

8. Future Directions and Emerging Clinical Applications

8.1. Ongoing Research Initiatives and Clinical Questions

Current research efforts are focused on addressing the most significant knowledge gaps that have emerged during the five years of clinical experience with remimazolam. Pediatric pharmacokinetics and safety studies represent the highest priority, given the substantial pediatric patient population that could potentially benefit from remimazolam's favorable characteristics. Separately, intensive care unit sedation protocols with remimazolam are under active investigation, building upon the favorable hemodynamic profile of the drug observed in surgical applications, to explore its utility in critically ill patients requiring prolonged sedation.

Combination techniques with other anesthetic agents represent another area of active investigation, as clinicians explore methods to optimize anesthetic protocols by leveraging remimazolam's unique properties in conjunction with complementary agents. Health economic evaluations are increasingly important, as healthcare systems seek evidence-based justification for adoption of higher-cost agents, requiring systematic assessment of remimazolam's cost-effectiveness relative to established alternatives.

Long-term neurocognitive effects also represent a particularly important area of ongoing investigation, given the growing recognition of perioperative neurocognitive disorders and the potential for anesthetic agents to influence long-term cognitive outcomes. The preliminary evidence suggesting reduced delirium risk with remimazolam warrants extensive investigation to determine whether this benefit extends to longer-term cognitive outcomes.

8.2. Clinical Practice Integration and Optimal Utilization

Five years of clinical experience have begun to define optimal utilization patterns for remimazolam, identifying specific clinical scenarios where its unique properties provide maximum benefit. Hemodynamically unstable patients represent a primary target population, where remimazolam's cardiovascular stability offers clear advantages over alternatives. Elderly patients requiring rapid and predictable recovery constitute another important application, although the use of remimazolam in geriatric patients should be balanced against the increased vigilance required due to an elevated adverse event risk in this population.

Ambulatory procedures requiring predictable offset characteristics represent an ideal application for remimazolam, where the rapid and consistent recovery facilitates efficient patient flow and reduces the risk of delayed discharge. Patients at elevated risk for propofol-related complications, including those with cardiovascular compromise or propofol allergy, represent another important target population in whom remimazolam may offer superior safety profiles.

Cases requiring potential anesthetic reversal represent a unique application of remimazolam, since its reversibility with flumazenil provides a safety advantage

unavailable with other anesthetic agents. This capability may prove particularly valuable in diagnostic procedures where rapid awakening is desired, or in emergency situations where anesthetic reversal might be clinically necessary (Figure 5).

Timeline of major developments since Japan's first-in-world approval in January 2020 [1] [13]. Key regulatory milestones included US FDA approval for procedural sedation (July 2020), EU approval (March 2021), Chinese NMPA approval (September 2021), and South Korean approval (June 2022). Critical safety findings included the FAERS analysis revealing age-related adverse event patterns (January 2022) [14] and documentation of rare anaphylactic reactions (May 2023) [16]. Clinical evidence milestones included hemodynamic advantages during cardiac surgery (December 2022) and confirmation of no increase in postoperative delirium risk (April 2024) [22]. The timeline demonstrates successful translation from pharmacological innovation to established clinical utility across diverse patient populations and clinical applications.

Figure 5. Five years of remimazolam: clinical and regulatory milestones.

8.3. Limitations and Clinical Constraints

Clinical experience has also identified relative limitations that constrain remimazolam's optimal utilization. The slower onset compared to propofol requires modification of standard induction techniques, and may limit its applicability in rapid sequence induction scenarios where immediate loss of consciousness is paramount. The potential for rare anaphylactic reactions, while uncommon, requires preparedness for emergency management, and may influence risk-benefit calculations in certain patient populations.

Its higher acquisition cost compared to generic alternatives may initially appear to limit its adoption in resource-constrained environments, but this must be evaluated within the broader context of healthcare economics and value-based care. The drug's benefits, including faster and more predictable recovery, reduced injection site pain, superior hemodynamic stability, and decreased risk of complications, may translate into significant cost savings through improved operating

room efficiency, reduced recovery time, decreased need for post-operative monitoring, and enhanced patient satisfaction scores. In ambulatory surgery settings, where rapid patient turnover and predictable discharge times are economically critical, remimazolam's reliable pharmacokinetic profile may offset its higher acquisition cost through improved facility utilization and reduced staffing requirements. Therefore, comprehensive health economic evaluations considering total cost of care, rather than drug acquisition cost alone, are necessary to accurately assess remimazolam's cost-effectiveness in specific clinical contexts [31] [32].

9. Conclusions

The five-year milestone since Japan's pioneering approval of remimazolam provides an appropriate temporal vantage point from which to assess this agent's impact on anesthetic practice, and its evolving role in modern perioperative care. The accumulated clinical experience, spanning diverse patient populations, varied surgical procedures, and multiple clinical contexts, has established remimazolam as a valuable and distinctive addition to the anesthetic pharmacopeia. Japanese investigators who pioneered remimazolam's clinical development deserve particular recognition for their foundational contributions to both, initial drug development and the ongoing expansion of clinical understanding through systematic post-marketing investigation.

The evidence strongly supports remimazolam's particular value in clinical scenarios requiring hemodynamic stability, predictable recovery characteristics, and potential for anesthetic reversal. The demonstrated non-inferiority to propofol in terms of anesthetic efficacy, combined with superior cardiovascular stability and elimination of injection site pain, provides compelling clinical advantages that have been consistently validated across multiple studies and diverse patient populations. The unique finding of no increased postoperative delirium risk distinguishes remimazolam from other benzodiazepines, and suggests potential cognitive advantages that warrant further investigation.

Conversely, while the overall safety profile of remimazolam has proven favorable across five years of clinical experience, post-marketing surveillance has identified rare but serious adverse events that require clinical attention and ongoing vigilance. Of particular concern is anaphylactic reactions in elderly patients, which emphasizes the importance of appropriate patient selection, preparation for emergency management, and continued pharmacovigilance efforts. These safety considerations do not negate remimazolam's clinical utility, but rather inform appropriate risk management strategies that can minimize potential complications while preserving its clinical benefits.

The unique pharmacological properties of remimazolam, successfully combining the familiar benzodiazepine receptor profile with ultra-short duration characteristics, have fulfilled the promise articulated by Masui in 2020, of providing "advantages beyond existing anesthetics". The clinical reality has validated these theoretical expectations, demonstrating that rational drug design can successfully ad-

dress long-standing limitations of existing agents while preserving their beneficial characteristics.

As clinical experience continues to accumulate and expand to encompass additional patient populations and clinical applications, remimazolam's role in modern anesthetic practice will likely continue to evolve and expand. The five-year milestone does not represent an endpoint in clinical development, but rather a solid foundation upon which continued advancement in anesthetic care can be built. Future research priorities should emphasize pediatric applications, health economic evaluations, and optimization of clinical protocols to maximize the clinical benefits of remimazolam, while minimizing rare but serious risks.

The success of remimazolam development and implementation also provides valuable lessons for future anesthetic drug development, demonstrating that systematic clinical investigation, international collaboration, and careful post-marketing surveillance can successfully translate pharmacological innovation into meaningful clinical advancement. The Japanese experience with remimazolam serves as a model for evidence-based drug development and implementation that has global relevance and applicability.

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Conflicts of Interest

The author declares that there are no conflicts of interest related to any commercial entities, including those mentioned in this manuscript.

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Role of Anesthesiologists in Disaster Medicine: Lessons from Japan and Future Perspectives

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Abstract

Japan's unique geographical position at the intersection of four tectonic plates makes it one of the world's most disaster-prone nations. The country has experienced numerous catastrophic events, including the 2011 Great East Japan Earthquake, the 2016 Kumamoto Earthquakes, and various typhoons and floods. These disasters have provided invaluable insights into the critical role of anesthesiologists in disaster medicine. This comprehensive review examines the multifaceted contributions of anesthesiologists to disaster responses in Japan, analyzing their role beyond traditional perioperative care, and identifying key lessons for global disaster preparedness. We conducted a systematic review of the published literature on anesthesiologist involvement in Japanese disaster responses from 1995 to 2024, including peer-reviewed articles, official reports, and case studies from major disasters. Evaluation showed that Japanese anesthesiologists have performed critical roles in multiple disaster scenarios, such as: emergency airway management and hemodynamic stabilization in field conditions, coordination of hospital evacuations for critically ill patients, leadership in Disaster Medical Assistance Teams (DMAT), provision of regional anesthesia and pain management in resource-limited settings, and development of disaster-resilient perioperative protocols. Their key competencies include adaptability, interdisciplinary collaboration, and expertise in austere medical environments. The Japanese experience demonstrates that anesthesiologists are indispensable in disaster medicine, contributing skills that extend far beyond the operating room. Their unique combination of abilities related to airway expertise, hemodynamic management, pharmacological knowledge, and critical care training positions them as essential members of disaster response teams. Future preparedness strategies should formally integrate anesthesiologists into disaster planning, enhance their training in disaster medicine, and develop specialized protocols for perioperative care under extreme conditions.

Keywords

Disaster Medicine, Anesthesiologists, Japan, Disaster Medical Assistance Team (DMAT), Emergency Preparedness

1. Introduction

Japan's position at the convergence of the Pacific, Philippine Sea, Eurasian, and North American tectonic plates creates a geological environment of extraordinary seismic activity and natural disaster frequency. This unique geography has subjected the nation to recurring catastrophic events throughout its history, including the devastating 1995 Great Hanshin-Awaji Earthquake, the unprecedented 2011 Great East Japan Earthquake and tsunami, and numerous typhoons, floods, and volcanic eruptions. The cumulative impact of these disasters has been profound, with tens of thousands of casualties, widespread infrastructure destruction, and economic losses exceeding hundreds of billions of dollars.

In response to these recurring challenges, Japan has developed one of the world's most sophisticated disaster response systems, anchored by the Disaster Medical Assistance Team (DMAT) system established following the Great Hanshin earthquake. This paradigm shift created rapid deployment capabilities for specialized medical teams, complemented by robust hospital preparedness protocols and infrastructure strengthening measures.

Within this ecosystem, anesthesiologists have emerged as critical contributors to emergency medical care, bringing unique competencies that translate directly to disaster medicine: advanced airway management, hemodynamic monitoring and support, comprehensive pharmacological knowledge, critical care training, and experience in high-stress clinical decision-making. These skills prove invaluable when providers must work in austere environments—defined as resource-limited settings with damaged infrastructure, minimal equipment, and challenging operational conditions—while managing critically ill and injured patients.

The role of anesthesiologists in disaster response extends beyond individual patient care to system-level contributions, including hospital evacuation coordination, infrastructure resilience planning, interdisciplinary team leadership, and policy development for disaster preparedness. Their involvement in Japan's disaster responses has provided valuable insights into both, the potential contributions and the specific challenges faced by anesthesiologists in emergency situations.

This comprehensive review synthesizes the extensive experience of Japanese anesthesiologists in disaster medicine, drawing from their documented responses to major earthquakes, tsunamis, typhoons, floods, and volcanic eruptions over the past three decades. In this review, we examine the specific roles anesthesiologists have played in various disaster scenarios, analyze the clinical protocols and adap-

tations developed for emergency situations as a result of their contributions, and identify key lessons learned from these experiences. Additionally, we explore the educational and training implications for anesthesiology practice, discuss infrastructure and policy considerations, and propose recommendations for enhancing anesthesiologist involvement in disaster response systems both in Japan and internationally.

2. Methodology

This review employed a comprehensive search strategy to identify relevant literature on anesthesiologist involvement in disaster medicine in Japan. We searched PubMed, EMBASE, and Japanese medical databases, including Ichushi-Web and CiNii, using terms related to anesthesiology, disaster medicine, emergency response, and specific Japanese disasters from 1995 to 2024.

Inclusion criteria encompassed peer-reviewed articles, case reports, official disaster response reports, and conference proceedings that described anesthesiologists' roles in Japanese disaster responses. We also reviewed policy documents from the Japanese Society of Anesthesiologists (JSA), DMAT guidelines, and hospital disaster preparedness protocols. Articles were categorized by disaster type, anesthesiologist role, and clinical setting to facilitate systematic analysis.

2.1. Historical Context and Evolution of Disaster Response

2.1.1. The Great Hanshin-Awaji Earthquake: Catalyst for Change

The 1995 Great Hanshin-Awaji Earthquake marked a watershed moment in Japanese disaster medicine, exposing critical deficiencies in the country's emergency medical response capabilities. The disaster claimed over 6400 lives and injured more than 43,000 people, with many fatalities attributed to delayed or inadequate medical care rather than direct trauma. The medical response was characterized by poor coordination between hospitals, inadequate communication systems, and insufficient rapid deployment capabilities for medical personnel.

Anesthesiologists in affected hospitals faced unprecedented challenges during this disaster. Operating rooms were damaged or rendered inoperable due to structural damage and utility failures. Many anesthesiologists found themselves providing care outside their traditional domains, managing patients in hospital corridors, parking lots, and temporary shelters. The experience highlighted both, the adaptability of anesthesiologists and the need for formal disaster training and protocols.

The lessons learned from Kobe directly influenced the subsequent development of Japan's modern disaster response infrastructure, including creation of the DMAT system and establishment of formal disaster medicine training programs for medical professionals (**Figure 1**).

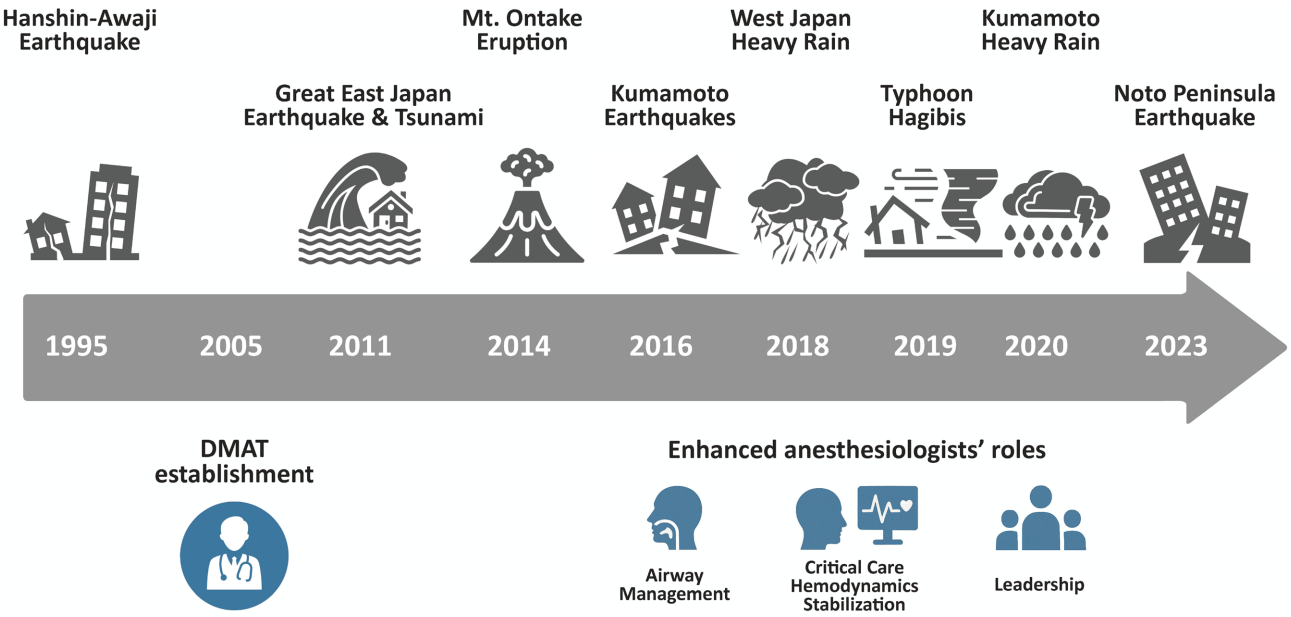
2.1.2. Development of the DMAT System

The DMAT system, established in 2005, represents Japan's primary rapid-re-

sponse medical capability for disasters. As documented by Kondo and colleagues, the DMAT system was designed to address the critical gaps in medical response capability identified during the Kobe earthquake [1]. DMAT teams consist of physicians, nurses, and logistical coordinators specially trained for disaster response, with the capability to deploy within hours of a disaster declaration and operate independently for up to 48 - 72 hours under austere conditions.

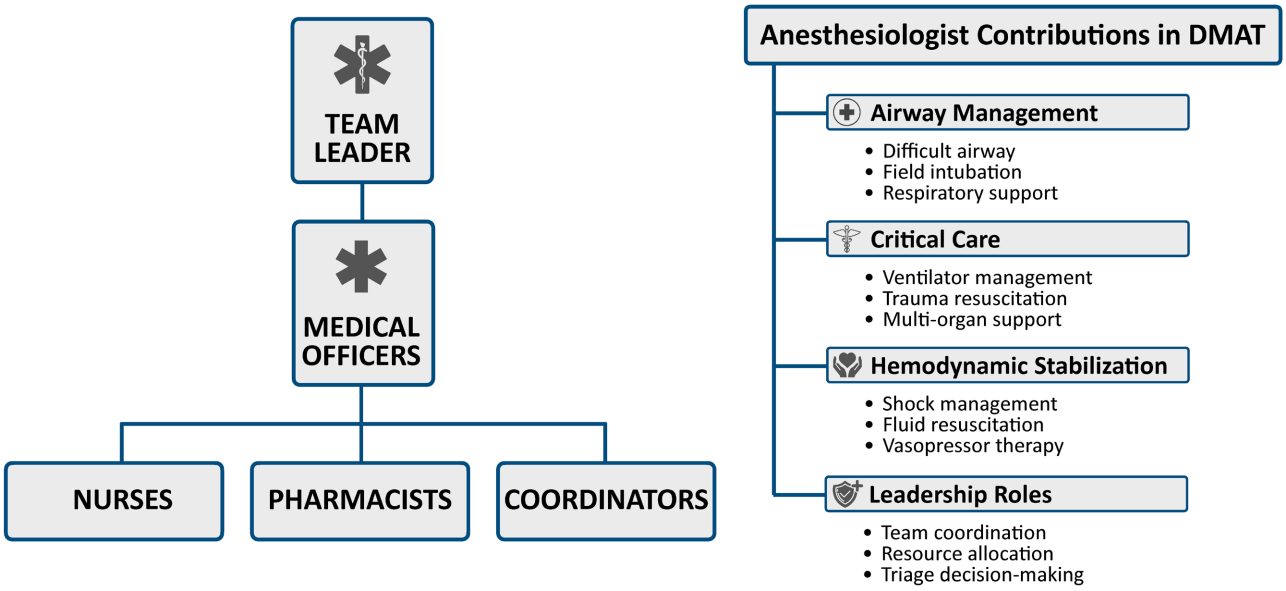
Anesthesiologists have been integral to the development and operation of the DMAT from its inception. Their skills in airway management, procedural sedation, and critical care make them highly valued team members, particularly for operations involving severely injured patients or complex medical evacuations. Matsumoto and colleagues described the critical role of anesthesiologists in aeromedical disaster relief operations following the Great East Japan Earthquake, demonstrating their importance in complex patient transport scenarios [2]. Many DMAT medical leaders are anesthesiologists, reflecting the specialty's natural fit for emergency response leadership roles.

The continuous evolution of DMAT capabilities reflects ongoing learning from disaster experiences. Anan and colleagues documented investigations into DMAT response guidelines for catastrophic scenarios, such as a potential Nankai Trough earthquake, highlighting the need for scalable response capabilities [3]. Subsequently, the same research group reported on revisions to DMAT training programs, incorporating lessons learned from actual deployments to enhance preparedness and adaptability [4] (**Figure 2**).



Timeline showing major disasters since 1995 and corresponding developments in anesthesiologists' roles in disaster medicine. Key events included the 1995 Hanshin-Awaji Earthquake that catalyzed development of the DMAT system [1], the 2011 Great East Japan Earthquake demonstrating anesthesiologist adaptability [5]-[7], the 2016 Kumamoto Earthquakes highlighting evacuation coordination [8] [9], and recent extreme weather events, which expanded their scope of practice [10]-[15]. The timeline illustrates the progressive integration of anesthesiologists into disaster response systems and the evolution of specialized protocols.

Figure 1. Timeline of major disasters in Japan and evolution of anesthesiologists' roles.



The figure shows the organizational structure of the DMAT, highlighting anesthesiologists' roles in team leadership, clinical care, and operational coordination, and demonstrating the multi-disciplinary composition of teams with physicians, nurses, and logistical coordinators [1], emphasizing anesthesiologists' contributions to airway management, critical care, and aeromedical transport [2]. Their roles include training program evolution [3] [4] and leadership responsibilities in complex disaster scenarios.

Figure 2. Anesthesiologists' roles in disaster medical assistance team (DMAT) structure.

2.2. Major Disaster Responses: Anesthesiologists' Contributions

2.2.1. The 2011 Great East Japan Earthquake and Tsunami

The March 11, 2011, earthquake and tsunami represented the most severe natural disaster in Japan's modern history, with a magnitude 9.0 earthquake generating tsunami waves reaching heights of over 40 meters in some coastal areas. The disaster resulted in nearly 20,000 deaths and missing persons, widespread infrastructure destruction, and the Fukushima nuclear accident, creating a complex multi-hazard emergency requiring unprecedented medical response coordination.

Anesthesiologists played critical roles throughout the disaster response, from immediate emergency care to long-term recovery support. Murakawa's detailed account of anesthesia department preparedness during the Fukushima nuclear disaster provides valuable insights into the challenges faced by anesthesiologists in the immediate aftermath of the disaster [5]. The nuclear emergency created unique complications, requiring evacuation of patients from hospitals within the exclusion zone while maintaining critical care for those too unstable to be transported.

Suzuki and colleagues documented the specific challenges of maintaining surgical services during the earthquake, describing how anesthesiologists adapted to power outages, equipment failure, and structural damage, while continuing to provide care for trauma patients [6]. Their report highlighted the importance of backup power systems, emergency drug supplies, and portable monitoring equipment for maintaining anesthesia services during disasters.

The experience of anesthesiologists in Minamisoma city, one of the areas that suffered the most severe damage, illustrates the expanded scope of practice re-

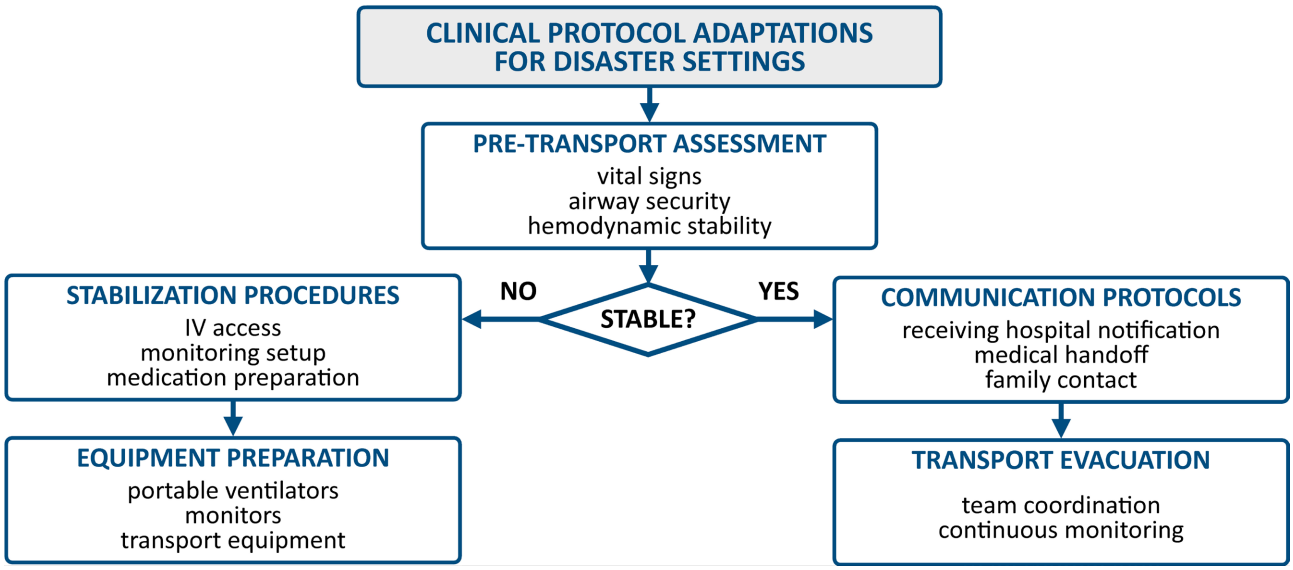
quired during disasters, documented by Akatsu and colleagues [7]. In that report, anesthesiologists provided not only traditional perioperative care, but also served as emergency physicians, managed critically ill patients in improvised intensive care units, and coordinated medical evacuations under extremely challenging conditions, including radiation exposure concerns.

2.2.2. The 2016 Kumamoto Earthquakes

The Kumamoto earthquake sequence, featuring two major earthquakes (magnitude 6.2 and 7.0) occurring within 28 hours, presented unique challenges for disaster response. Unlike single-event disasters, the repeated major earthquakes created ongoing safety concerns, complicated evacuation decisions, and required sustained emergency responses over an extended time period.

Hospital evacuation operations during the Kumamoto earthquakes, as documented by Nagata and colleagues, demonstrated the critical importance of anesthesiologists in managing complex patient transfers [8]. Successful evacuation of Kumamoto Medical Center, involving over 500 patients, including many in critical condition, required extensive coordination between anesthesiologists, emergency physicians, and transport teams.

Anesthesiologists were responsible for pre-transport stabilization of critically ill patients, including those on mechanical ventilation, patients with hemodynamic instability, and postoperative cases requiring ongoing monitoring. The evacuation process revealed the need for specialized transport protocols, portable monitoring equipment, and enhanced training in patient stabilization for helicopter and ground ambulance transportation (**Figure 3**).



The figure shows critical care transport protocols for hospital evacuations, emphasizing anesthesiologists' roles in patient stabilization and monitoring. The protocol is based on experiences from Kumamoto earthquake evacuations [8] [9], and addresses pre-transport assessment procedures, stabilization protocols for mechanically ventilated patients, equipment preparation requirements, and communication processes during large-scale evacuations involving over 500 patients.

Figure 3. Hospital evacuation protocol for critically ill patients.

Shimoto and colleagues' subsequent analysis of the evacuation also highlighted ethical considerations in patient prioritization, resource allocation, and family communication during mass evacuations [9]. Anesthesiologists were involved not only in clinical decision-making, but also in ethical deliberations about patient care priorities under extreme resource constraints.

2.2.3. Extreme Weather Events: Typhoons and Floods

Japan's increasing experience with extreme weather events, exacerbated by climate change, has expanded the scope of disaster medicine beyond seismic events. The 2018 heavy rain in West Japan, 2019 Typhoon Hagibis, and 2020 heavy rain in Kumamoto collectively demonstrated that meteorological disasters could generate medical needs comparable to major earthquakes, also presenting unique challenges for anesthesiologists.

Emergency medical team responses to these events, as analyzed through Japan Surveillance in Post-Extreme Emergencies and Disasters (J-SPEED) data, revealed distinct patterns of medical needs during disastrous floods [10]-[12]. Unlike earthquake-related trauma, flood disasters generated high rates of infectious complications, exacerbation of chronic diseases, and mental health issues, requiring different clinical approaches from anesthesiologists.

Regional anesthesia and pain management became particularly important during flood responses, as many patients required wound care and debridement in temporary medical facilities with limited resources. Anesthesiologists' expertise in regional blocks, procedural sedation, and pain management proved invaluable for providing humane care in challenging environments, such as evacuation shelters and temporary clinics.

The impact of extreme weather events extends beyond immediate trauma care. Komatsu and colleagues demonstrated a significant increase in cardiovascular and cerebrovascular events following Typhoon Hagibis, highlighting the physiological stress that disasters impose on vulnerable populations [13]. This finding emphasizes the need for anesthesiologists to be prepared for managing not only direct disaster-related injuries, but also acute exacerbations of chronic medical conditions during disaster responses.

Analysis of typhoon-related fatalities by Yoshida and colleagues revealed important patterns in flood-related deaths, linking many fatalities to both acute trauma and exacerbations of underlying medical conditions [14]. These findings raise awareness among anesthesiologists about the types of clinical scenarios they may encounter during flood disaster responses, emphasizing the importance of comprehensive medical assessment beyond obvious traumatic injuries.

Infectious complications represent another significant concern during flood disasters. Ozaki and colleagues reported cases of cellulitis and serious infections from nail puncture wounds sustained during Typhoon Hagibis, demonstrating the importance of wound care and infection prevention in flood disaster response [15]. Anesthesiologists' expertise in procedural sedation and regional anesthesia becomes particularly valuable for managing these types of injuries in resource-

limited temporary medical facilities.

2.2.4. Volcanic Disasters: The Mount Ontake Eruption

The sudden eruption of Mount Ontake in 2014 presented unique challenges for disaster medical response, combining wilderness medicine requirements with volcanic hazard management. The eruption occurred during the peak hiking season, resulting in 63 fatalities and numerous injuries from falling volcanic rocks and ash inhalation.

Anesthesiologists involved in the Mount Ontake response, as documented by Oshiro and colleagues, faced the challenge of providing advanced medical care in remote, hazardous mountain terrain while managing both direct casualties and rescue team members suffering from ash exposure and physical exhaustion [16]. The event highlighted the need for anesthesiologists to develop competencies in wilderness medicine and collaborate effectively with mountain rescue teams.

Key lessons from the volcanic eruption response included the importance of portable airway management equipment suitable for austere conditions, protocols for managing respiratory complications from ash inhalation, and specialized training related to medical operations in hazardous volcanic environments.

3. Ethical Considerations in Disaster Anesthesiology

The extreme conditions and resource limitations inherent in disaster responses create complex ethical dilemmas that require anesthesiologists to make difficult decisions regarding patient care priorities and resource allocation. Japanese disaster experiences have highlighted several critical ethical domains where anesthesiologists play essential roles.

3.1. Triage and Resource Allocation

Anesthesiologists frequently serve as triage officers in disaster scenarios, making decisions about which patients receive priority access to limited resources such as operating rooms, mechanical ventilators, and critical medications. The ethical framework for these decisions must balance utilitarian principles of maximizing overall benefit with respect for individual patient dignity and rights. Japanese anesthesiologists have developed triage protocols that consider both clinical factors and resource availability while maintaining transparency in decision-making processes [17].

3.2. Care Withdrawal and Limitation

In mass casualty incidents, anesthesiologists may face decisions about withdrawing or withholding life-sustaining treatments to reallocate resources to patients with better survival prospects. These decisions require careful consideration of medical futility, family wishes, and cultural values. The Japanese experience emphasizes the importance of clear communication with families and documentation of decision-making rationales [17].

3.3. Informed Consent in Crisis Conditions

Traditional informed consent processes may be impractical during disasters, requiring anesthesiologists to adapt consent procedures while maintaining respect for patient autonomy. This includes developing abbreviated consent protocols for emergency procedures and establishing proxy decision-making pathways when patients are incapacitated and families are unavailable.

3.4. Professional Duty and Personal Risk

Anesthesiologists must balance their professional obligations to provide care with considerations of personal safety, particularly during ongoing disasters such as earthquakes with continuing aftershocks or nuclear emergencies. The ethical principle of proportionate risk guides these decisions, recognizing that healthcare providers have duties both to patients and to their own families and communities.

4. Clinical Protocols and Adaptations (Table 1)

4.1. Airway Management in Disaster Settings

Airway management represents one of the most critical skills anesthesiologists contribute to the disaster response. However, disaster conditions often require significant adaptations from standard operating room protocols. Environmental challenges include limited lighting, unstable surfaces, noise interference, and restricted access to patients in confined spaces, such as collapsed buildings or damaged vehicles.

Table 1. Comparative medical needs across different disaster types.

Disaster Type	Primary Medical Needs	Anesthesiologists' Roles	Key Challenges
Earthquake	• Trauma management • Crush injuries • Surgical emergencies • Acute pain management	• Emergency surgery • Airway management • Critical care supervision • Triage support	• Infrastructure damage • Equipment failure • Resource limitations • Multiple casualty management
Tsunami	• Drowning • Contaminated wounds • Hypothermia • Aspiration pneumonia	• Resuscitation • Infection control • Warming protocols • Respiratory support	• Contaminated environment • Resource depletion • Water-borne diseases • Delayed medical access
Floods	• Infectious diseases • Chronic disease exacerbation • Soft tissue injuries • Medical shortages	• Regional anesthesia • Pain management • Sedation • Chronic disease stabilization	• Limited facility access • Equipment limitations • Supply chain disruption • Prolonged disaster period
Volcanic eruption	• Respiratory injuries • Burns • Trauma • Eye injuries	• Airway protection • Fluid and electrolyte management • Evacuation support • Respiratory therapy	• Hazardous environment • Access restrictions • Ongoing eruption risk • Ash-related complications

Medical needs and anesthesiologists' roles vary by disaster type, requiring tailored clinical approaches and protocols. The table compares earthquake trauma management [5]-[9], tsunami resuscitation and contamination control [5]-[7], flood-related infectious disease response [10]-[15], and volcanic eruption-related respiratory injury management [16]. It also shows how the anesthesiologists' role can be adapted based on specific disaster characteristics and the associated medical challenges.

Japanese anesthesiologists have developed specialized protocols for disaster airway management that emphasize simplicity, reliability, and minimal equipment requirements. These protocols prioritize supraglottic airway devices for initial airway control, given their ease of insertion and lower skill requirements for non-anesthesiologist providers. However, anesthesiologists are uniquely capable of performing definitive airway management with endotracheal intubation when conditions permit.

4.2. Hemodynamic Management and Shock Resuscitation

Casualties of disasters frequently present with various forms of shock, including hemorrhagic shock from trauma, distributive shock from sepsis, and cardiogenic shock from stress-related cardiac events. Anesthesiologists' expertise in hemodynamic monitoring and vasoactive drug management becomes crucial in these scenarios, particularly when intensive care unit resources are limited or unavailable.

Japanese disaster management protocols emphasize early recognition of shock states and aggressive resuscitation using simplified monitoring approaches suitable for field conditions. Point-of-care ultrasound has become increasingly important for rapid assessment of cardiac function, volume status, and identification of pneumothorax or internal bleeding.

4.3. Pain Management and Regional Anesthesia

Pain management in disaster settings presents unique challenges, including large numbers of patients with acute pain, limited pharmaceutical resources, and the need to preserve the patient's mental clarity for evacuation and family reunification. Regional anesthesia techniques have proven particularly valuable in disaster medicine, providing effective pain relief while minimizing systemic effects and preserving patient awareness. Equally important is the anesthesiologists' expertise in procedural sedation and anxiolysis, which helps mitigate psychological trauma for patients experiencing procedures in chaotic and frightening disaster environments. The ability to provide appropriate anxiolytic therapy and procedural sedation not only facilitates necessary medical interventions but also reduces the lasting psychological impact of traumatic medical experiences during disasters, contributing to both immediate patient comfort and long-term mental health outcomes [18].

Anesthesiologists involved in Japanese disaster responses have successfully implemented simplified regional anesthesia protocols using landmark-based techniques that can be performed without ultrasound guidance when necessary. These techniques have been particularly valuable for managing extremity fractures, wound care procedures, and pain control during extended transport periods.

4.4. Perioperative Care under Austere Conditions

Maintaining surgical capabilities during disasters requires significant adaptations of standard perioperative protocols. Power outages, equipment damage, and supply shortages necessitate creative solutions and simplified approaches to anesthesia care.

Japanese anesthesiologists have developed contingency protocols that prioritize patient safety while maintaining surgical capability under challenging conditions.

Key adaptations include simplified monitoring approaches using battery-powered devices, standardized drug protocols to minimize medication errors in stressful conditions, and enhanced communication procedures to coordinate care among multiple providers in chaotic environments (Figure 4).

5. Infrastructure and Equipment Considerations

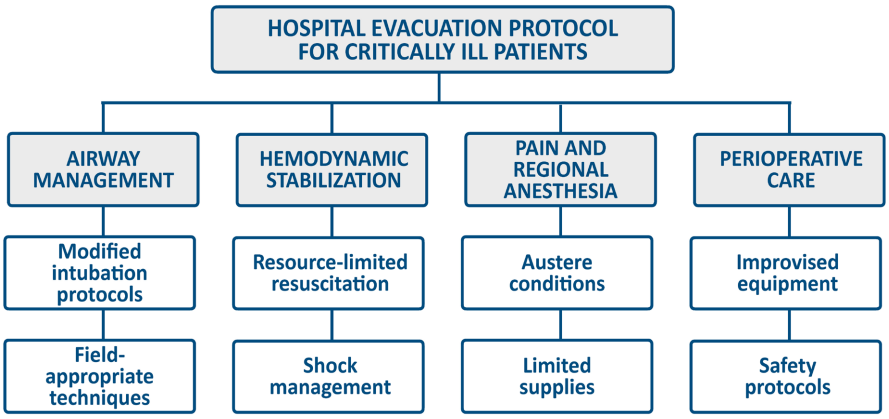
5.1. Seismic Resilience of Operating Rooms

The investigation by Tsutsumi and colleagues into operating table stability during earthquakes highlighted critical infrastructure vulnerabilities in the perioperative environment [19]. Their research demonstrated that standard operating tables could become unstable during seismic events, potentially endangering patients undergoing surgery when earthquakes occur.

These findings have prompted recommendations for seismic retrofitting of operating rooms, including anchoring systems for large equipment, emergency lighting systems, and backup power supplies specifically designed for perioperative areas. Anesthesiologists have been instrumental in developing these recommendations, drawing on their understanding of both equipment requirements and patient safety needs (Figure 5).

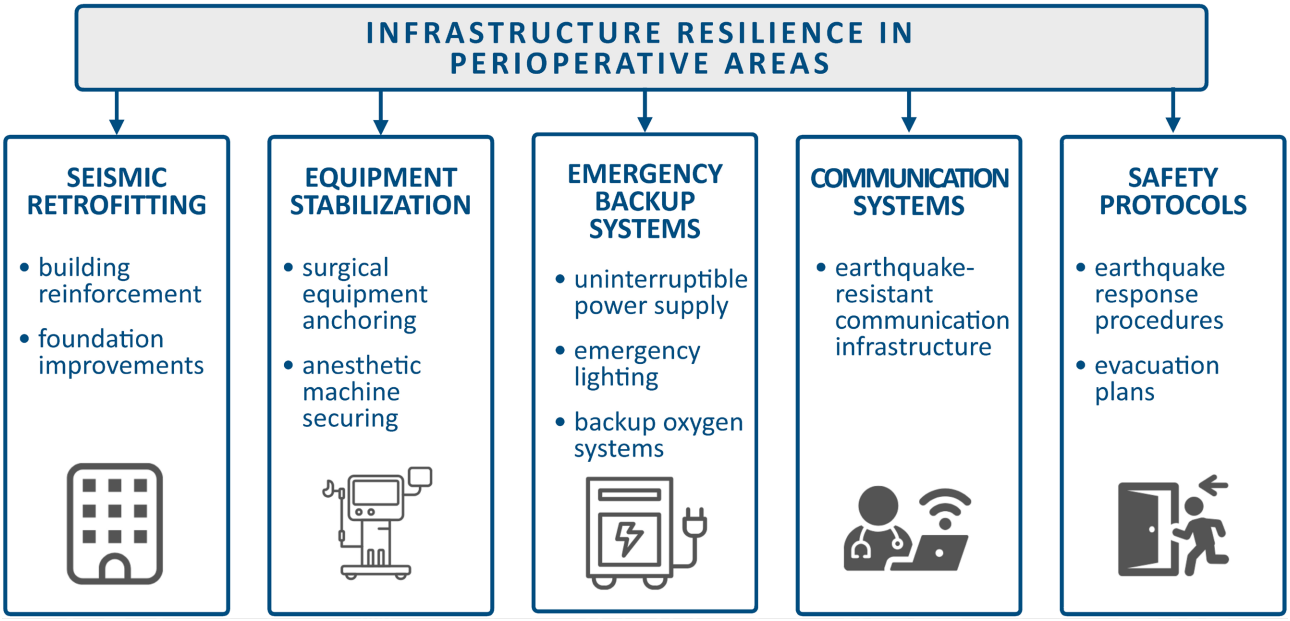
5.2. Emergency Equipment and Supply Management

Disaster response requires specialized equipment designed for portability, durability, and battery operation. Japanese anesthesiologists have contributed to the development of disaster-specific equipment caches that include portable ventilators,



Adaptation of standard anesthesiology protocols are required under disaster conditions, including simplified monitoring and equipment requirements. The protocol incorporates modifications for airway management under austere conditions [5]-[7], hemodynamic stabilization using portable equipment [2], pain management and regional anesthesia in limited resource settings [10]-[12] [15], and perioperative care protocols adapted for power outages and equipment limitations [6] [19].

Figure 4. Adaptations in clinical protocols in various disaster settings.



The figure shows the infrastructure modifications and safety systems required for maintaining perioperative capabilities during seismic events. The protocol is based on operating table stability research [19], and recommends seismic retrofitting, including equipment anchoring systems, emergency lighting, backup power supplies, and redundancy in communication. The figure also illustrates anesthesiologists' contributions to infrastructure planning and patient safety protocols during earthquakes.

Figure 5. Infrastructure resilience in perioperative areas.

battery-powered monitors, and simplified anesthesia delivery systems suitable for field operations.

Supply chain considerations have become increasingly important, with hospitals developing strategic reserves of critical medications and equipment. Anesthesiologists play key roles in determining appropriate medication stockpiles, considering factors such as shelf life, storage requirements, and anticipated usage patterns during various disaster scenarios.

5.3. Communication and Coordination Systems

Effective disaster responses require robust communication systems that can function despite infrastructure damage. Anesthesiologists have been involved in developing hospital communication protocols that ensure coordination between operating rooms, intensive care units, and emergency departments during disasters.

These systems include backup communication methods, standardized reporting protocols, and integration with regional disaster response networks. The experience of Japanese anesthesiologists has demonstrated the importance of redundant communication systems and regular testing of emergency protocols.

6. DMAT Operations and Aeromedical Transport

6.1. Anesthesiologist Leadership in DMAT Operations

The role of anesthesiologists in DMAT operations extends beyond clinical care, to include team leadership and operational coordination. The comprehensive train-

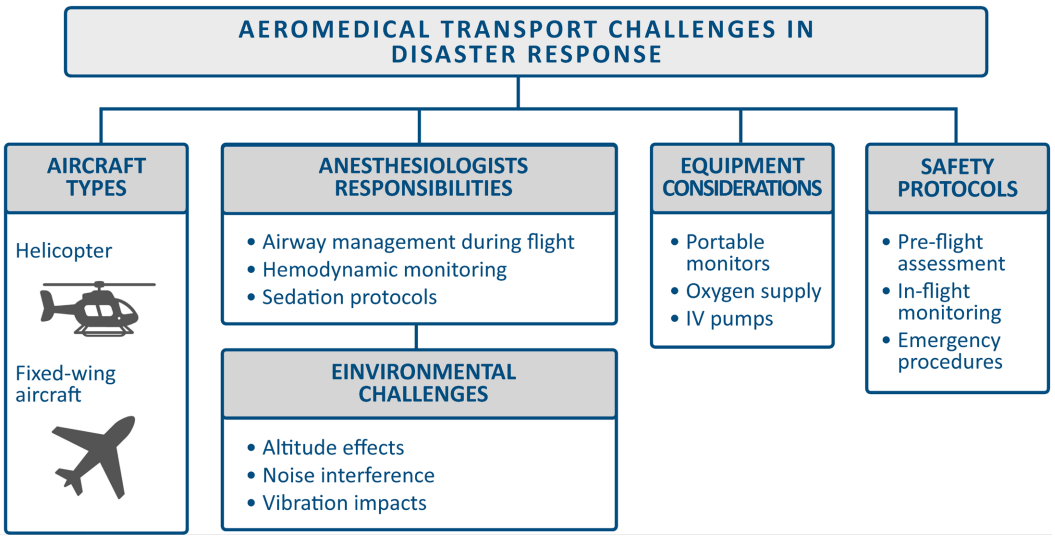
ing program described by Anan and colleagues emphasizes the development of leadership skills alongside clinical competencies [14]. Anesthesiologists serving as DMAT team leaders must coordinate with multiple agencies, manage resource allocation, and make critical decisions about patient triage and evacuation priorities.

An investigation of DMAT response guidelines for catastrophic scenarios, such as the anticipated Nankai Trough earthquake, demonstrated the scalability requirements for disaster medical responses [13]. Anesthesiologists contribute to strategic planning by providing expertise on critical care capabilities, evacuation protocols, and resource requirements for sustained operations during prolonged disasters.

6.2. Aeromedical Transport and Critical Care

Aeromedical transport represents one of the most challenging aspects of disaster medical responses, requiring specialized skills in aviation medicine combined with critical care expertise. The experience documented by Matsumoto and colleagues following the Great East Japan Earthquake highlighted the critical role of anesthesiologists in managing severely injured patients during helicopter and fixed-wing aircraft transportation [2].

Key challenges in aeromedical transport include altitude-related physiological changes, limited space for medical equipment, interference with monitoring by the vibration and noise, and the need for simplified yet effective treatment protocols. Anesthesiologists' expertise in hemodynamic management, airway control, and sedation makes them ideal care providers in these complex transportation scenarios (Figure 6).



The figure presents the unique challenges involved in aeromedical transportation that require specialized anesthesiology skills and adapted protocols. The protocol documents experiences from Great East Japan Earthquake relief operations [2], and considers altitude-related physiological effects, space limitations for medical equipment, vibration and noise interference with monitoring, and simplified treatment protocols. The protocol also emphasizes anesthesiologists' expertise in airway management, hemodynamic control, and sedation for complex transport scenarios.

Figure 6. Aeromedical transport challenges in disaster responses.

7. Education and Training Programs

7.1. Integration of Disaster Medicine Training into Anesthesiology Residency Programs

The Japanese experience has highlighted the need for systematic integration of disaster medicine training into anesthesiology residency programs. Current training initiatives include simulation-based exercises, DMAT participation opportunities, and formal coursework in disaster medicine principles. However, while international evidence supports this approach, Wilson-Raybould and colleagues demonstrated that few anesthesiologists receive sufficient education and training in disaster medicine, although over 85% believe their programs should provide such preparation [20].

Simulation training has proven particularly valuable for disaster preparedness, allowing residents to practice clinical skills under simulated austere conditions. Japanese experience has identified several particularly effective simulation modalities: high-fidelity manikin-based scenarios that replicate earthquake damage with simulated power outages and equipment failures; table-top exercises focusing on hospital evacuation decision-making and resource allocation; hybrid simulations combining standardized patients with task trainers for regional anesthesia procedures under field conditions; and multi-disciplinary team-based simulations that include anesthesiologists, emergency physicians, nurses, and logistics coordinators working together in realistic disaster scenarios. These exercises include specific scenarios such as providing anesthesia during power outages, managing multiple trauma patients with limited resources, coordinating patient evacuations, and performing airway management in confined spaces with minimal lighting [21]. Pfenninger and colleagues developed a comprehensive 14-module disaster medicine curriculum that demonstrates the effectiveness of structured, multi-experiential training approaches for medical students [22]. A recent study by Barsac and colleagues highlighted the need for improved teaching approaches in anesthesiology and emergency medicine residency programs, with trainees expressing a strong desire for more professional guidance, mentoring, and interactive educational experiences, including simulation and virtual reality [23].

7.2. Continuing Education for Practicing Anesthesiologists

Professional development in disaster medicine requires ongoing education beyond residency training. The JSA has developed continuing medical education programs that address disaster-specific clinical scenarios, infrastructure planning, and leadership roles in emergency response. Evidence from the United States demonstrates that only 31% of anesthesiologists feel their hospitals provide adequate disaster preparation and training for natural disasters, highlighting the global need for enhanced continuing education programs [20].

These programs emphasize practical skill development, including hands-on training with portable equipment, interdisciplinary collaboration exercises, and policy development workshops. The goal is to prepare anesthesiologists not only

for clinical roles, but also for leadership positions in disaster management planning and response coordination.

Modern approaches increasingly incorporate high-fidelity simulation and immersive educational experiences to enhance learning outcomes [23].

7.3. Interprofessional Training and Collaboration

Effective disaster responses require seamless collaboration between multiple medical specialties and healthcare professions. Training programs increasingly emphasize interprofessional education, bringing together anesthesiologists, emergency physicians, surgeons, nurses, and emergency medical technicians for joint training exercises.

These collaborative training programs help establish working relationships and communication protocols before disasters occur, improving coordination and efficiency during responses to actual emergencies. Japanese experience has demonstrated that prior interprofessional training significantly improves team performance during real-world disaster situations.

8. Policy Development and Professional Advocacy

8.1. Professional Society Guidelines and Recommendations

The JSA has played an increasingly active role in developing professional guidelines for disaster response. These guidelines address clinical protocols, training requirements, equipment specifications, and ethical considerations specific to anesthesiology practice during disasters. Internationally, the Helsinki Declaration on Patient Safety in Anaesthesiology provides fundamental principles for maintaining anesthesia safety standards, including during emergencies and disasters [24].

Key policy areas include standards for disaster training in residency programs, requirements for hospital disaster preparedness, and guidelines for anesthesiologist participation in DMAT and other emergency response teams. These policies help ensure consistent preparation and response capabilities across Japan's healthcare system. The Helsinki Declaration emphasizes the importance of maintaining professional competencies, appropriate facilities and equipment, and monitoring capabilities even under challenging conditions [24].

8.2. Integration with National Disaster Response Planning

Anesthesiologists have become increasingly involved in national-level disaster response planning, contributing their clinical expertise to policy development and resource allocation decisions. This involvement includes participation in government advisory committees, contribution to national medical response protocols, and input on healthcare infrastructure resilience planning.

Integration of anesthesiologist perspectives into national planning has improved the effectiveness of medical response capabilities, and ensured that specialized clinical needs in disaster preparedness strategies are addressed.

8.3. International Collaboration and Knowledge Sharing

Japan's extensive disaster experience has positioned the country as a leader in disaster medicine, with Japanese anesthesiologists contributing to international knowledge sharing through professional organizations such as the WFSA.

International collaboration efforts include participation in global disaster response exercises, sharing of training curricula and protocols, and contribution to international disaster medicine research initiatives. These activities help disseminate the lessons learned in Japan, to improve global disaster preparedness capabilities.

9. Future Challenges and Opportunities

9.1. Climate Change and Evolving Disaster Patterns

Climate change is altering the frequency and severity of natural disasters in Japan, with increasing intensity of typhoons, more frequent extreme precipitation events, and changing patterns of seasonal disasters. These changes require adaptation of disaster response strategies and training programs to address evolving threat patterns.

Anesthesiologists must prepare for longer-duration disasters, more complex multi-hazard events, and increased frequency of extreme weather emergencies. This preparation includes developing protocols for sustained operations, managing resource utilization over extended periods, and coordinating care during cascading disaster scenarios.

9.2. Aging Population and Complex Medical Needs

Japan's rapidly aging population presents increasing challenges for disaster response, with growing numbers of elderly patients requiring complex medical care during emergencies. Research demonstrates that older adults face heightened risks during disasters due to impaired mobility, cognitive deficits, and chronic medical conditions [25]. Anesthesiologists must, therefore, develop specialized protocols for managing elderly patients with multiple comorbidities, cognitive impairment, and high dependency needs during disasters.

These challenges include managing patients on chronic medications, providing care for those with advanced directives, and coordinating care transitions for elderly patients during prolonged evacuations. Specialized training in geriatric disaster medicine is becoming increasingly important for anesthesiologists. Climate change further exacerbates these challenges, with compound disasters potentially increasing cardiovascular and cerebrovascular risks in elderly populations [26].

9.3. Technology Integration and Innovation

Advancing technology offers new opportunities for improving disaster response capabilities. Consultations via telemedicine systems can provide remote support to anesthesiologists working in isolated disaster areas. Portable diagnostic equipment continues to improve, offering enhanced monitoring capabilities in field

conditions.

Artificial intelligence and decision support systems may also help optimize resource allocation and clinical decision-making during disasters, when cognitive load is high and time pressures are intense. Anesthesiologists must stay current with technological advances, while maintaining proficiency in low-technology approaches for situations where advanced systems are unavailable.

9.4. Research and Evidence Development

Despite extensive disaster experience, many aspects of disaster anesthesiology lack robust research evidence. Future research priorities include studies comparing the outcomes of different clinical approaches, effectiveness research on training programs, and health economics analyses of investments in disaster preparedness.

Collaborative research networks can help standardize data collection during disasters, enabling more comprehensive analysis of clinical outcomes and system performance. International research collaboration can accelerate knowledge development and improve evidence-based practice in disaster anesthesiology.

10. International Implications and Global Applications

10.1. Transferability of Japanese Lessons

While Japan's disaster experience is extensive, transferability of the lessons to other countries requires careful consideration of the differences in healthcare systems, resource levels, and disaster risk profiles. A comparison with California's disaster medical response system illustrates both similarities and key differences that help contextualize the applicability of Japanese lessons.

Structural Comparison: California's Disaster Medical Assistance Teams (CalMAT) share Japan's DMAT emphasis on rapid deployment and specialized training, but operate within a more decentralized healthcare system [27]. California relies heavily on hospital-based disaster preparedness and mutual aid agreements between counties, integrating with federal Disaster Medical Assistance Teams (DMAT) when needed. In contrast, Japan's model features centralized national coordination through the Cabinet Office and Ministry of Health, with standardized protocols implemented uniformly across all prefectures. This centralization enables more consistent training standards and deployment procedures but requires greater governmental coordination.

Role of Anesthesiologists: Both systems recognize anesthesiologists as valuable disaster response team members, but their roles differ in emphasis. California's approach relies more heavily on emergency physicians for medical team leadership, with anesthesiologists serving primarily in clinical support roles for complex airway management and perioperative care. Japan has increasingly embraced anesthesiologist leadership across multiple disaster response domains, including field medicine, hospital evacuation coordination, and DMAT team command. This difference partly reflects Japan's recognition that anesthesiologists' critical care training and experience with high-stress decision-making translate effectively

to disaster leadership roles.

Training and Certification: Japan's DMAT certification requires intensive multi-day training courses with regular recertification and participation in actual disaster response exercises. California's system emphasizes hospital-specific disaster drills and county-level exercises, with less standardized national certification requirements for individual responders. Both approaches have merit: Japan's model ensures consistent competency but requires significant time investment, while California's approach allows greater flexibility but may result in variable preparedness levels.

Resource Allocation: Japan's universal healthcare system facilitates more uniform resource distribution and disaster preparedness across facilities, whereas California's mixed public-private healthcare system creates variation in institutional disaster readiness. However, California's system benefits from substantial private sector resources and innovation, while Japan's approach ensures baseline preparedness even in resource-limited rural facilities.

Lessons for Transferability: This comparison suggests that while specific organizational structures must be adapted to local healthcare systems and governance models, several core principles remain universally applicable: the critical importance of specialized disaster medicine training for anesthesiologists, the value of systematic integration of anesthesiologists into disaster response planning, the need for regular simulation exercises and skills maintenance, and the benefit of formal recognition of anesthesiologists' expanded roles in disaster scenarios [28]. Countries adapting Japanese lessons should consider their existing healthcare infrastructure, regulatory environment, and disaster risk profiles while maintaining these fundamental principles.

10.2. Global Professional Development

International anesthesiology organizations can benefit from incorporating Japanese disaster medicine experiences into global professional development programs. Training curricula, simulation scenarios, and clinical protocols developed in Japan can serve as models for international adaptation.

Professional exchange programs and international training opportunities can help disseminate Japanese expertise, while allowing for cultural and system-specific adaptations. These programs can accelerate global improvement in disaster preparedness capabilities.

10.3. Humanitarian Response Applications

The skills and protocols developed for domestic disaster response in Japan have direct applications to international humanitarian medical responses. Japanese anesthesiologists have successfully applied their disaster medicine expertise to international relief operations, demonstrating the global relevance of their training and experience.

International humanitarian organizations can benefit from incorporating Jap-

anese disaster anesthesiology protocols into their medical response capabilities, particularly for complex emergencies requiring sustained medical operations under challenging conditions.

11. Clinical Practice Recommendations

11.1. Individual Practitioner Development

Anesthesiologists should pursue disaster medicine training through available programs, such as DMAT certification, simulation-based training courses, and continuing education opportunities. Individual preparedness includes maintaining current knowledge of disaster protocols, practicing skills with portable equipment, and developing personal emergency response plans.

Professional development should include interdisciplinary collaboration skills, leadership training, and communication skills for high-stress environments. Regular participation in disaster drills and exercises helps maintain readiness and identifies areas of improvement.

11.2. Institutional Preparedness

Healthcare institutions should formally integrate anesthesiologists into disaster planning committees and for establishing emergency response protocols. This integration includes developing anesthesiology-specific disaster protocols, ensuring adequate equipment and supply reserves, and establishing communication systems for emergency coordination.

Regular disaster preparedness exercises should include perioperative scenarios and test the functionality of backup systems for operating rooms and intensive care units. Staff training programs should address disaster-specific clinical scenarios and emphasize interdisciplinary collaboration.

11.3. Professional Society Leadership

Anesthesiology professional societies should develop and maintain disaster medicine guidelines, support training program development, and advocate for appropriate integration of anesthesiologists into disaster response systems. International collaboration can help share best practices and accelerate improvement in global disaster preparedness.

Professional societies should also support research initiatives to develop evidence-based practices in disaster anesthesiology and promote quality improvement through systematic evaluation of disaster response experiences.

12. Conclusions

Extensive disaster experience in Japan has clearly demonstrated that anesthesiologists play critical and multifaceted roles in disaster medicine that extend far beyond traditional perioperative care. Their unique combination of technical skills, clinical knowledge, and experience in high-pressure environments makes them invaluable contributors to disaster response teams. The Japanese experience pro-

vides compelling evidence for the systematic integration of anesthesiologists into disaster preparedness and response systems.

Key lessons from Japan include the importance of adaptability in clinical practice, the value of interdisciplinary collaboration, and the need for specialized training in disaster medicine. Anesthesiologists have demonstrated capability in diverse roles, including field medicine, hospital evacuation coordination, DMAT leadership, and infrastructure planning. These experiences have led to development of specialized protocols, training programs, and equipment designed specifically for disaster response.

The evolving nature of disaster risks, including the impact of climate change and demographic transitions, requires continued adaptation and improvement of disaster medicine capabilities. Anesthesiologists must remain engaged in professional development, research activities, and policy discussions to ensure continued effectiveness in disaster response roles.

Table 2. Key lessons learned and future directions.

Category	Key Lessons Learned	Future Directions	Implementation Strategies
Adaptability & Scope Expansion	• Anesthesiologists demonstrated remarkable flexibility in disaster settings • Expanded roles beyond traditional perioperative care • Rapid integration into DMAT structures	• Develop standardized disaster anesthesia training programs • Create specialized disaster response teams • Formalize an expanded scope of practice	• Establish a national disaster anesthesia curriculum • Implement mandatory simulation training • Integrate disaster response into anesthesiology residency programs
Interdisciplinary Collaboration	• Critical importance of teamwork with emergency physicians, surgeons, nurses • Improved outcomes through coordinated approaches • Communication challenges in crisis settings	• Strengthen inter-professional disaster training • Develop unified communication protocols • Create collaborative disaster leadership models	• Joint training exercises across specialties • Standardized communication systems • Multi-disciplinary disaster response committees
Aging Population Considerations	• Unique challenges in managing elderly patients in disasters • Increased comorbidities and medication requirements • Special evacuation and transportation needs	• Develop age-specific disaster protocols • Enhance geriatric disaster medicine training • Research on medication management during disasters	• Specialized elderly care protocols • Targeted training programs • Partnership with long-term care facilities
Infrastructure & Technology	• Importance of equipment resilience • Backup systems critical for continuity • Need for portable, durable medical devices	• Invest in seismic-resistant medical infrastructure • Develop portable advanced monitoring • Improve telemedicine capabilities for remote support	• Building code improvements • Mobile medical technology advancement • Cloud-based medical record systems with offline capabilities

Key insights and future directions for anesthesiologists' integration into disaster medicine, including demographic challenges and educational needs. The table summarizes adaptability requirements and expanded scopes of practice [5]-[9], importance of interdisciplinary collaboration across all disaster types [1]-[16], considerations for aging populations and climate change impacts [13]-[15] [25] [26], infrastructure and technology improvements [3] [4] [19].

The international implications of Japanese experience are significant, offering models for training, protocols, and system integration that can be adapted to different healthcare systems and resource levels. Global collaboration in disaster medicine research and training can accelerate improvement in worldwide disaster preparedness capabilities.

Moving forward, integration of anesthesiologists into disaster medicine should be viewed not as an additional responsibility, but as a natural extension of their clinical expertise and professional commitment to patient care under all circumstances. The Japanese experience demonstrates that with appropriate training, equipment, and system support, anesthesiologists can make extraordinary contributions to disaster responses and community resilience.

The future of disaster medicine requires continued innovation, adaptation, and collaboration among all healthcare professionals. Anesthesiologists, with their unique skill set and proven efficacy in disaster settings, must continue to play leadership roles in this critical area of medical practice. The lessons learned from Japan's disaster experiences provide a foundation for continued improvement and global application of these important capabilities (Table 2).

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Conflicts of Interest

The author declares that there are no conflicts of interest related to any commercial entities, including those mentioned in this manuscript.

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Historical Evolution of Fluid Therapy and Contemporary Challenges: From Intravenous Injection to Artificial Blood

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Abstract

Fluid therapy has evolved dramatically from its origins in 17th-century blood transfusion experiments to sophisticated, modern, perioperative fluid management protocols. This comprehensive review traces the historical development of intravenous fluid administration, beginning with William Harvey's circulation theory and Christopher Wren's pioneering venous injections, through the cholera epidemics that necessitated early fluid replacement therapy, to Sydney Ringer's groundbreaking electrolyte solutions. The evolution of blood transfusion from dangerous animal-to-human experiments to safe ABO-compatible transfusions paralleled the development of plasma substitutes and colloid solutions. Pediatric fluid therapy emerged as a specialized field in the early 20th century, with contributions from researchers like James Gamble and Daniel Darrow establishing the fundamental principles of water and electrolyte balance. Modern perioperative fluid management has been revolutionized by Enhanced Recovery After Surgery (ERAS) protocols, goal-directed fluid therapy, and evidence-based approaches that optimize patient outcomes. Contemporary challenges include the ongoing debate over crystalloid versus colloid solutions, the safety concerns surrounding hydroxyethyl starch preparations, and the continued quest for effective artificial blood substitutes. Recent advances in artificial oxygen carriers, particularly Professor Hiromi Sakai's hemoglobin vesicles (HbV) developed through three decades of research at Nara Medical University, have demonstrated promising Phase 1 trial results with acceptable safety profiles, offering potential solutions to blood supply shortages and compatibility issues with anticipated clinical implementation by 2030. This historical perspective illuminates how empirical observations evolved into evidence-based practice, while highlighting persistent challenges in optimizing fluid therapy for diverse clinical scenarios.

Keywords

Fluid Therapy, Blood Transfusion, Plasma Substitutes, Ringer's Solution, Enhanced Recovery After Surgery (ERAS), Perioperative Management, Artificial Blood

1. Introduction

Administration of intravenous fluids represents one of the most fundamental interventions in modern medicine, yet its evolution spans centuries of scientific discovery, clinical observation, and technological advancement. From the first tentative experiments with venous injection in the 17th century, to today's sophisticated perioperative fluid management protocols, the history of fluid therapy reflects humanity's growing understanding of physiology, pathophysiology, and the delicate balance required to maintain life.

The journey began with William Harvey's revolutionary description of blood circulation in 1628, which laid the theoretical foundation for intravenous therapy [1]. However, it took nearly two centuries before fluid replacement therapy found its first major clinical application during the cholera epidemics of the 1830s [2]. The subsequent development of blood transfusion, electrolyte solutions, and plasma substitutes represents a convergence of scientific inquiry, clinical necessity, and technological innovation that continues to this day.

Modern fluid therapy encompasses not merely the replacement of lost volume, but the precise management of electrolyte balance, acid-base status, and hemodynamic optimization. The emergence of Enhanced Recovery After Surgery (ERAS) protocols, goal-directed fluid therapy, and personalized medicine approaches reflects our current understanding that fluid management must be tailored to individual patient needs and clinical circumstances.

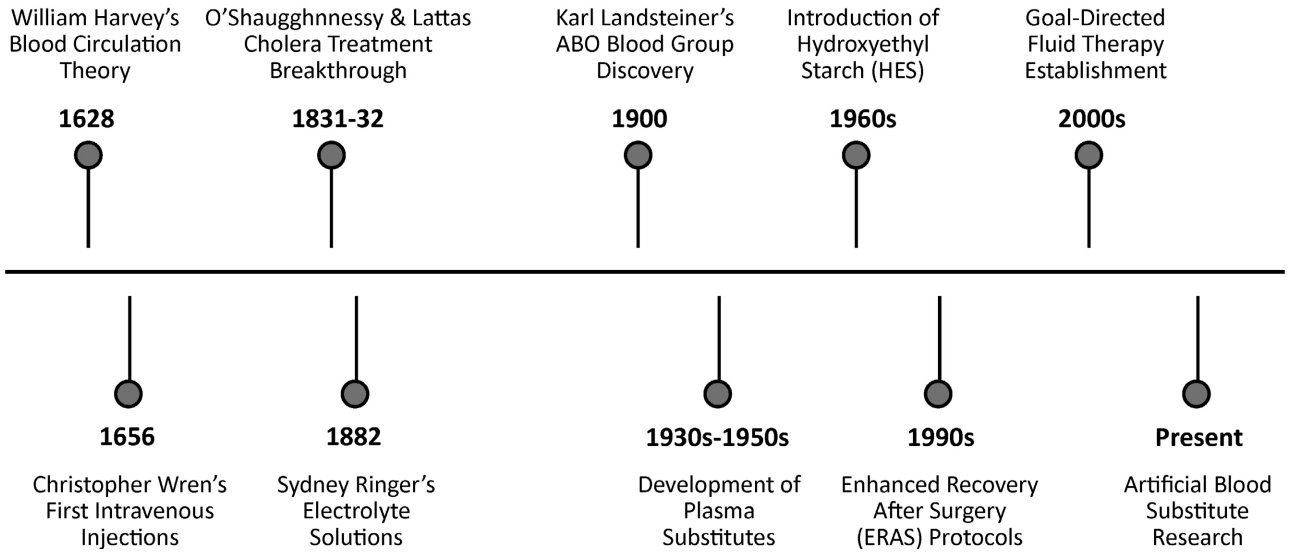
This historical analysis reveals that fluid therapy advancement has been predominantly driven by urgent clinical necessity—from cholera epidemics to battlefield medicine—which catalyzed scientific inquiry and accelerated technological innovation, demonstrating how medical crises serve as powerful catalysts for therapeutic breakthroughs.

2. History of Fluid Therapy (Figure 1)

2.1. Ancient and Medieval Foundations

The earliest recorded medical practices involving fluid therapy can be traced to ancient Egyptian medicine (3000 BCE), where physicians used rectal infusions and bladder irrigation techniques, as documented in the Edwin Smith Papyrus and Ebers Papyrus [3] [4]. These early practitioners recognized the importance of maintaining fluid balance, though their understanding was limited to observable symptoms rather than physiological mechanisms.

Islamic physicians during the medieval period made significant advances to our



Key milestones in the evolution of fluid therapy from the discovery of blood circulation to modern artificial blood research. Major discoveries include Harvey's circulation theory (1628) [1], Wren's pioneering intravenous injections (1656) [10], the cholera treatment breakthrough by O'Shaughnessy and Latta (1831-1832) [2] [89]-[92], Ringer's electrolyte solutions (1882) [109] [110], Landsteiner's ABO blood groups (1900) [46] [47], development of plasma substitutes (1930s-1950s) [67]-[74], introduction of hydroxyethyl starch (1960s) [75] [76], Enhanced Recovery After Surgery protocols (1990s) [154]-[157], establishment of goal-directed fluid therapy (2000s) [165] [166], and current artificial blood substitute research, including hemoglobin-based oxygen carriers (HBOCs), PFCs, and hemoglobin (Hb)-vesicles [215]-[217].

Figure 1. Historical timeline of the development of fluid therapy.

understanding of circulation and fluid dynamics. Al-Razi (854-925 CE) described detailed observations of fluid loss in fever patients, while Ibn Sina (Avicenna, 980-1037 CE) proposed sophisticated theories about blood circulation and fluid distribution that predated European understanding by centuries [5] [6]. Their works, preserved in Arabic texts and later translated into Latin, influenced European medical thought for over 500 years.

The Renaissance brought renewed interest in anatomical studies and physiological understanding. Andreas Vesalius (1514-1564) corrected numerous Galenic errors through systematic dissection, while Michael Servetus (1511-1553) described pulmonary circulation decades before Harvey's comprehensive theory [7] [8]. These anatomical advances laid the groundwork for understanding the circulatory system as a closed-loop network capable of supporting therapeutic interventions.

The concept of intravenous fluid administration emerged from ancient medical theories about bodily humors (fluids) and fluid balance. Hippocrates (460-370 BCE) proposed that health depended on the equilibrium of four bodily fluids: blood, phlegm, yellow bile and black bile. This "humoral pathology" theory, later refined by Galen (129-216 CE), suggested that disease resulted from imbalances in these fluids, leading to treatments involving bloodletting and purgation.

The scientific foundation for modern fluid therapy began with William Harvey's (1578-1657) groundbreaking work "De Motu Cordis" (1628), which demonstrated that blood circulates throughout the body rather than being consumed by

tissues, as previously believed [1] [9]. This discovery contradicted Galenic doctrine and established the theoretical basis for intravenous injection and transfusion.

2.2. Early Intravenous Experiments

The first recorded intravenous injection was performed by Christopher Wren (1632-1723) in 1656 [10]. Using a hollow goose quill attached to a pig's bladder, Wren injected wine, ale and opium into dogs' veins, observing their effects on behavior and physiology. While these experiments demonstrated the feasibility of intravenous administration, they also revealed the potential dangers, as several animals died from the procedures [11] [12].

Robert Boyle (1627-1691), working alongside Wren at the Royal Society, conducted parallel experiments using different substances and injection techniques [13]. Their collaborative work, documented in the Philosophical Transactions of the Royal Society, established basic principles of dose-response relationships and the importance of injection site selection [14] [15]. These early experiments also noted the rapid onset of action compared to oral administration, establishing intravenous delivery as a route for emergency interventions.

Johann Daniel Major (1634-1693) performed the first human intravenous injection in 1662, documenting his techniques in "Chirurgia Infusoria" (1664) [16]. His careful documentation included detailed drawings of injection apparatus, patient positioning, and the adverse reactions observed [17]. Major's work influenced German medical practice for decades, and established protocols that remained largely unchanged until the 19th century.

Simultaneously, Johann Sigismund Elsholtz (1623-1688) conducted similar experiments in Brandenburg, publishing "Clysmatica Nova" (1665) with detailed illustrations of injection apparatus and techniques [18] [19]. Elsholtz's contributions included the development of improved syringes, recognition of venous anatomical variations, and early descriptions of what we now recognize as anaphylactic reactions [20]. His work was more widely distributed than Major's, and influenced medical practice across German-speaking regions.

2.3. 17th and 18th Century Developments

These early experiments, while crude by modern standards, established several important principles: the need for sterile techniques (although germ theory was unknown), the importance of controlling injection speed, and the potential for both therapeutic benefit and serious harm [21] [22]. However, limited understanding about infection, blood compatibility and appropriate solutions limited the clinical application of intravenous fluid infusions for nearly two centuries.

The 18th century saw sporadic attempts to revive intravenous therapy, particularly in France, where physicians like François Magendie (1783-1855) conducted systematic studies on drug absorption and distribution [23]. Magendie's work on strychnine and other alkaloids demonstrated that intravenous administration

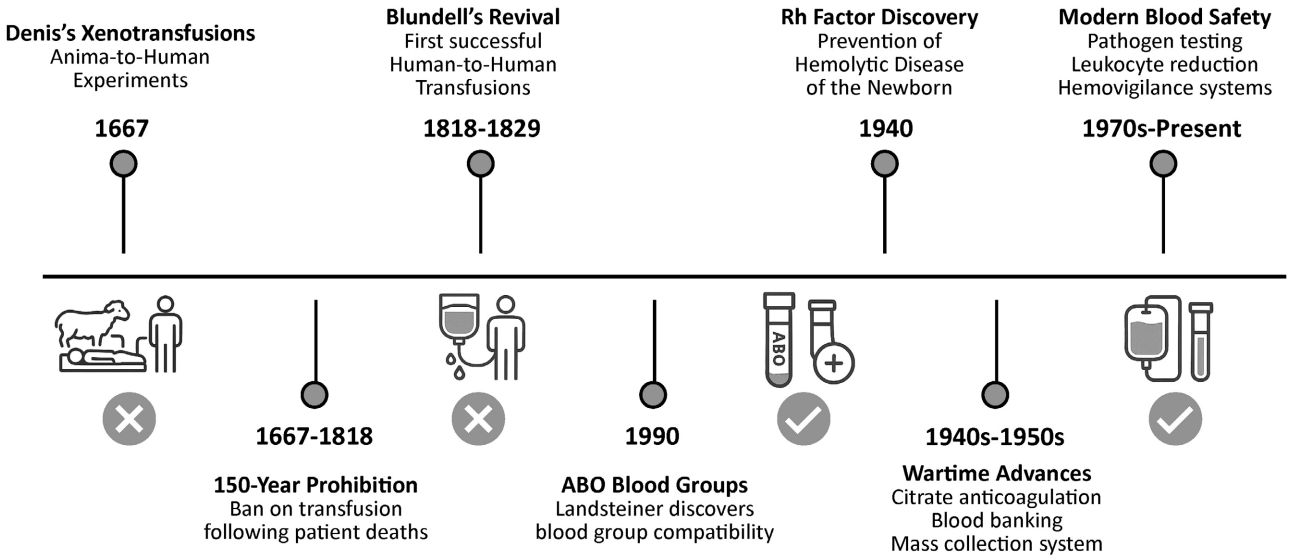
produced more predictable effects than other routes, laying the groundwork for modern pharmacokinetics [24] [25].

In England, Stephen Hales (1677-1761) made crucial contributions to understanding blood pressure and circulatory dynamics [26]. His experiments measuring arterial pressure in horses using glass tubes provided quantitative data about circulatory physiology that would later inform fluid resuscitation strategies [27] [28]. Hales also investigated the effects of different solutions on blood flow and pressure, noting that certain substances could restore circulation in moribund animals.

3. History of Blood Transfusion (Figure 2)

3.1. Ancient Beliefs and Early Concepts

Throughout history, blood has been viewed as carrying life force, personality traits, and healing properties. Ancient Egyptian texts describe drinking blood for therapeutic purposes, while Roman gladiatorial practices included consuming the blood of fallen warriors to transfer their courage and strength [29] [30]. These beliefs, while scientifically unfounded, demonstrate the early recognition of blood's vital importance, and foreshadow attempts at therapeutic blood replacement.



Development of blood transfusion from dangerous animal-to-human experiments to modern safe practice. Denis's xenotransfusions (1667) [33] [36] led to mortality and prohibition of blood transfusions lasting 150 years [40]. Blundell's revival (1818-1829) established human-to-human transfusion principles [39]-[45]. Landsteiner's ABO discovery (1900) [46] [47] and Rh factor identification (1940) [51]-[54] revolutionized compatibility testing. World Wars accelerated developments in transfusion medicine, including citrate anticoagulation, blood banking, and component therapy [57]-[65].

Figure 2. Evolution of blood transfusion safety.

Blood transfusion emerged as a logical extension of intravenous injection techniques, driven by observations that blood loss was often fatal and that replacing blood might restore life. The history of transfusion reveals both the promise and

peril of medical innovation when applied before the existence of adequate scientific understanding.

3.2. Animal-to-Human Transfusions

Richard Lower's animal experiments at Oxford University represent the first systematic investigation of blood transfusion [31]. Working with Robert Hooke and other members of the Royal Society, Lower developed techniques for direct vessel-to-vessel connections using quills and silver tubes [32] [33]. His experiments in 1665 resulted in successful transfusion of blood from one dog's carotid artery to another's jugular vein, with the recipient dog surviving and showing no apparent adverse effects.

Lower's success encouraged attempts at therapeutic transfusion in humans. His detailed documentation in Philosophical Transactions included observations about blood coagulation, the importance of matching donor and recipient sizes, and early recognition that some animals tolerated the procedure better than others [34]. These observations, while limited in comparison with contemporary understanding, established fundamental principles that remained valid for centuries.

3.3. The Denis Era and Early Human Transfusions

Jean-Baptiste Denis (1643-1704) performed the first recorded animal-to-human transfusion in Paris on June 15, 1667 [35]. The patient, a 15-year-old boy suffering from prolonged fever and weakened by repeated bloodletting, received approximately 9 ounces of lamb's blood through a silver tube connected to the lamb's carotid artery and the boy's brachial vein. The immediate improvement—restoration of consciousness, improved pulse, and return of appetite—encouraged Denis to attempt additional transfusions.

Denis performed at least four documented xenotransfusions between June and December 1667, with mixed results [36] [37]. His second patient, a laborer named Mauroy, received multiple transfusions of calf's blood for what Denis described as "madness" [29]. After initial apparent improvement, Mauroy died following a third transfusion, leading to accusations of murder and a highly publicized trial. The case ended in Denis's acquittal when investigation revealed that Mauroy's wife had poisoned him with arsenic, but the controversy effectively ended early transfusion experiments.

In London, Edmund King performed the first xenotransfusion in England on November 23, 1667, assisted by Richard Lower [38] [39]. Their patient, a Cambridge scholar suffering from mental illness, received 6 - 7 ounces of sheep's blood. While the patient initially improved, the procedure's association with the Denis controversy led to growing opposition. The Royal Society of London effectively banned transfusion experiments in 1678, followed by similar prohibition by the French Parliament, ending systematic transfusion research for nearly 150 years.

The ban on transfusion effectively halted advances in transfusions for nearly 150 years, demonstrating how premature application of new techniques can im-

pede medical advancement when safety concerns overshadow potential benefits [40].

3.4. Revival and Human-to-Human Transfusion

James Blundell (1791-1878), a London obstetrician, revived transfusion in the early 19th century, recognizing that species compatibility was crucial [41]. His experiments demonstrated that animal blood was incompatible with humans, and developed techniques for human-to-human transfusion using syringes and funnels.

Blundell's revival of transfusion was motivated by his obstetric practice, where he frequently witnessed deaths from postpartum hemorrhage [42]. His systematic animal experiments demonstrated that only blood from the same species was effective, leading him to conclude that "the blood of mammals is not so circumstanced that we can employ, with advantage to the human subject, that of lower animals" [43] [44].

Blundell's first human transfusion on December 22, 1818, involved a patient with severe gastric bleeding who had lost approximately 14 ounces of blood through vomiting [45]. Using a syringe and silver tube, Blundell slowly infused 12 - 14 ounces of fresh human blood from multiple donors. Although the patient showed temporary improvement—improved pulse, restored warmth, and regained consciousness—he died 56 hours later from continued bleeding. Despite the ultimate failure, Blundell had demonstrated the feasibility and immediate benefits of human blood transfusion.

Between 1818 and 1829, Blundell performed ten documented human transfusions with five survivals, establishing basic principles that remained valid for decades [45]. His innovations included the "Gravitator" (1824), a funnel-shaped apparatus that used gravity to drive blood flow, and the "Impellor" (1829), which employed atmospheric pressure. These devices reduced the complexity of transfusion and made the procedure more practical for emergency use.

3.5. ABO Blood Groups and Modern Transfusion

The discovery of ABO blood groups by Karl Landsteiner (1868-1943) in 1900 revolutionized transfusion medicine [46] [47]. Landsteiner's identification of A, B and O blood types (AB was discovered by his colleagues in 1902) explained the variable success of transfusions and provided a scientific basis for compatibility testing [48] [49].

Landsteiner's discovery emerged from his investigation of why blood from different individuals sometimes clumped together when mixed. Using blood samples from himself and five colleagues, he identified three distinct patterns of agglutination, leading to the classification of blood types A, B and C (later renamed O). His colleagues Alfred von Decastello and Adriano Sturli identified the fourth blood type, AB, in 1902 [50]. This work earned Landsteiner the 1930 Nobel Prize in Physiology or Medicine and established the foundation for safe transfusion

practice.

Discovery of the Rh factor by Landsteiner and Alexander Wiener in 1940 further refined compatibility testing and explained hemolytic disease of the newborn [51]-[53]. Their work with rhesus monkey blood led to identification of the Rh antigen system, adding another crucial layer to transfusion safety. Development of the Coombs test by Robin Coombs in 1945 provided a method for detecting incomplete antibodies, further improving the accuracy of compatibility testing [54].

3.6. World Wars and Advancements in Transfusion

World War I catalyzed rapid advances in blood storage and transfusion techniques. Albert Hustin's use of sodium citrate as an anticoagulant in 1914 enabled blood collection and storage, while Geoffrey Keynes developed portable transfusion apparatus for battlefield use [55]. The establishment of blood depots near the front lines demonstrated the feasibility of organized blood banking and saved thousands of lives.

World War II brought further innovations, including the development of plasma fractionation by Edwin Cohn, establishment of blood banks by Bernard Fantus at Cook County Hospital (1937), and the first systematic use of blood substitutes [56] [57]. The American Red Cross, under Charles Drew's leadership, organized massive blood collection programs that revolutionized blood banking and established principles still used today [58]-[61].

Post-war developments included the discovery of additional blood group systems, development of plastic blood bags by Carl Walter and W.P. Murphy (1950), and establishment of volunteer blood donation systems [62]. The introduction of component therapy in the 1960s—separating whole blood into red cells, plasma, platelets and clotting factors—maximized the utility of each donation and reduced transfusion reactions [63].

4. History of Blood Substitutes and Plasma Expanders

4.1. Early Development and Theoretical Foundations

The limitations and risks of blood transfusion drove the search for artificial alternatives that could provide volume expansion without the complications of blood compatibility, infectious disease transmission, and limited availability. This quest has spanned over 150 years with mixed success.

The concept of colloid osmotic pressure, described by Ernest Starling in 1896, provided the theoretical foundation for plasma substitutes [64]. Starling's principle explained how proteins in blood maintain intravascular volume by creating osmotic gradients that prevent fluid loss to tissues [65].

Early attempts at plasma substitution included various protein solutions and synthetic polymers. During the Spanish Civil War (1936-1939), Frederic Duran-Jorda pioneered the use of preserved blood and plasma, while simultaneously investigating protein hydrolysates as blood substitutes [66]. These early efforts established the principle that effective plasma substitutes must maintain oncotic

pressure, while avoiding toxicity and immune reactions [67].

4.2. First Generation Plasma Expanders

The first plasma substitute was developed in 1863 when Carl Ludwig used gum arabic dissolved in electrolyte solution for organ perfusion experiments. During World War I, William Bayliss used gum Arabic solutions to treat hemorrhagic shock, although toxicity reactions and edema limited its utility. The urgent need for blood substitutes during World War II accelerated the development of various plasma expanders [68].

4.3. Gelatin Solutions and Second-Generation Products

Modified gelatin solutions were developed in the 1950s to overcome the limitations of earlier substitutes. Gelofusine (B. Braun, 1962) and Haemaccel (Hoechst, 1968) became widely used in Europe for perioperative fluid management and trauma resuscitation [69]. These urea-linked gelatin solutions provided effective volume expansion with molecular weights of 30,000 - 35,000 daltons, although their short intravascular half-life of 3 - 4 hours required their repeated administration.

Clinical studies comparing gelatin solutions to crystalloids demonstrated the superior hemodynamic stability and reduced fluid requirements with gelatin, although higher costs and occasional anaphylactoid reactions limited their widespread adoption [69]. The development of modified fluid gelatin (Gelafusal) and polygeline (Haemaccel) provided alternatives with different safety profiles, although fundamental limitations of the short duration of effect and moderate allergic potential persisted [69].

4.4. Synthetic Colloids

Dextran solutions, developed in Sweden in the 1940 s, provided better safety profiles and became widely used for volume expansion and improvement of the flow properties of blood [70] [71]. Dextran development by Anders Grönwall and Björn Ingelman at the Pharmacia company represented a major advance in synthetic plasma expanders [71]. Dextran 70 (molecular weight 70,000) provided optimal volume expansion for a duration of 4 - 6 hours, while Dextran 40 (molecular weight 40,000) offered improved microcirculatory flow, but for a shorter duration [72]. Clinical trials demonstrated the effectiveness of dextran in surgical patients and trauma victims, although maximum dose limitations (1.5 g/kg/day) were established due to bleeding complications and renal toxicity [73] [74].

4.5. Third Generation Products: Hydroxyethyl Starch

Hydroxyethyl starch (HES) solutions, first developed by Thompson and Walton in 1963, represent the most sophisticated synthetic plasma substitute to date [75] [76]. The first-generation high molecular weight HES (450/0.7) provided excellent volume expansion lasting 8 - 12 hours, but caused significant coagulation abnor-

malities due to interference with factor VIII/von Willebrand factor complex [77] [78].

Second-generation medium molecular weight HES preparations (200/0.5) offered improved safety profiles with reduced coagulation effects, while maintaining good volume expansion properties [79]. The third-generation lower molecular weight HES (130/0.4) promised further safety improvements with minimal coagulation impact and reduced tissue storage, leading to widespread adoption in Europe and clinical trials worldwide [80].

However, the VISEP (2008), 6S (2012), and CHEST (2013) trials revealed increased mortality and acute kidney injury in septic patients receiving HES compared to crystalloids, leading to regulatory restrictions [81]-[83]. The European Medicines Agency subsequently suspended the use of HES products in 2013, although it later allowed its restricted use in 2018, while other jurisdictions maintained varying policies reflecting ongoing controversies about its risk-benefit ratio [84]. Current European guidelines permit restricted HES use in specific non-septic contexts, including elective cardiac surgery, liver transplantation, and major orthopedic procedures, where the risk-benefit ratio may favor its volume expansion properties, provided patients have normal renal function and coagulation status.

5. Fluid Therapy in Cholera Treatment

The cholera pandemics of the 19th century represented the first major test of intravenous fluid therapy, establishing fundamental principles of fluid resuscitation, while revealing both the potential benefits and limitations of early medical intervention [2]. The global impact of cholera and the development of fluid replacement therapy during these epidemics laid the groundwork for modern emergency medicine and critical care.

5.1. Cholera Pandemics and Epidemiology

Cholera, endemic to the Bengal region of India, spread globally during the 19th century due to increased trade and travel, causing six major pandemics between 1817 and 1923 [85] [86]. The first pandemic (1817-1824) remained largely confined to Asia, but subsequent waves reached Europe, North America and Africa, with devastating mortality rates. The second pandemic (1829-1837) killed over one million people in Russia alone, and prompted the first systematic medical investigations of the disease.

Cholera's pathophysiology involves massive fluid and electrolyte losses—up to 20 liters daily in severe cases—due to the effects of the cholera toxin on intestinal epithelium [87]. Without treatment, case fatality rates exceed 50%, but with appropriate fluid replacement, mortality can be reduced to less than 1%. This dramatic difference established fluid therapy as one of medicine's most effective interventions, and demonstrated the importance of understanding disease mechanisms for developing rational treatments.

Traditional treatments during early cholera outbreaks were not only ineffective, but often harmful [88]. Bloodletting, the dominant therapy based on the humoral theory, further depleted already volume-depleted patients. Mercury-based calomel purgatives worsened diarrhea, while opium-based compounds provided symptomatic relief, but did nothing to address the underlying fluid losses. These failures created desperation among physicians and opened minds to innovative approaches, such as intravenous fluid therapy.

5.2. O'Shaughnessy's Proposal

William Brooke O'Shaughnessy (1809-1889), a 22-year-old Irish physician sent to investigate cholera outbreaks, conducted detailed blood analyses of cholera patients and discovered massive losses of water and salts [89]. In 1831, he published his findings in The Lancet, proposing that intravenous injection of warm saline solutions that matched blood salt concentrations could restore normal physiology. Although O'Shaughnessy tested his theories in animal experiments, he did not attempt human treatment.

O'Shaughnessy's analytical work was groundbreaking in its precision and scientific rigor [89] [90]. Using chemical analysis techniques, he demonstrated that cholera patients lost approximately one-third of their normal water content and massive quantities of sodium salts. His proposal for treatment was remarkably prescient: "What is wanted is to restore the blood to its natural specific gravity, to restore its deficient saline matters, and to increase its temperature." The composition of the solution he recommended—containing sodium chloride and sodium carbonate—closely resembled modern oral rehydration solutions [90].

5.3. Latta's Clinical Application

Thomas Aitchison Latta (1796-1833), a Scottish physician, became the first to apply O'Shaughnessy's theories clinically [91]. Latta's technique involved inserting a silver cannula into the basilic vein and slowly injecting a saline solution warmed to approximately 112˚F (44˚C). His first patient received six pints of the solution (3.4 liters) over 30 minutes, with dramatic improvements in pulse rate, respiration and consciousness. However, when treatment was discontinued and the patient was transferred to another physician, continuing vomiting and diarrhea led to death within hours. This established a pattern that would be repeated throughout the cholera epidemic—temporary improvement during fluid administration, followed by relapse when treatment was stopped.

Subsequent patients treated by Latta and his colleagues demonstrated both the potential and limitations of early fluid therapy [92]. A 50-year-old woman received 330 ounces (9.3 liters) of the saline solution over 12 hours and made a complete recovery. However, other patients died despite treatment, leading to questions about appropriate patient selection, the timing of intervention, and adequacy of fluid replacement. Latta's detailed case reports, published in The Lancet, provided the first systematic documentation of the results of intravenous fluid

therapy [92].

5.4. Other Physicians' Contributions

John MacKintosh, working at the London Cholera Hospital, expanded on Latta's work with systematic treatment of 156 patients, achieving a 16% survival rate compared to 0% with conventional therapy [93] [94]. His detailed analysis identified factors associated with successful treatment: early intervention before complete collapse, adequate fluid volumes, and maintenance therapy to prevent relapse.

In continental Europe, physicians such as Hermann Klencke in Germany and Charles-Emmanuel Sédillot in France adapted Latta's techniques with varying degrees of success [95] [96]. The French Academy of Medicine initially opposed intravenous therapy, but gradually accepted its utility as evidence accumulated. Italian physician Arnaldo Cantani later developed subcutaneous saline infusion techniques that were safer and easier to perform, although less effective than intravenous routes [97].

The end of the cholera outbreak in 1833 and Latta's death from tuberculosis ended this early chapter in fluid therapy [88]. It was another 50 years before intravenous fluid therapy was widely adopted, although the principles established during the cholera epidemic—rapid volume replacement, electrolyte correction, and careful monitoring—remain fundamental to modern resuscitation [98] [99].

5.5. Modern Oral Rehydration Therapy

The development of oral rehydration therapy (ORT) in the 1960s represented a return to cholera's origins and vindicated O'Shaughnessy's original insights [100] [101]. Work by Robert Phillips in Dhaka and Norbert Hirschhorn at Johns Hopkins demonstrated that glucose-enhanced sodium absorption could match intravenous therapy's effectiveness, while being safer and more practical in resource-limited settings [102] [103]. The World Health Organization's standardized formula for oral rehydration solution (ORS), introduced in 1978 and refined in 2003, has, to date, prevented millions of deaths from diarrheal diseases worldwide [104] [105].

5.6. Birth of Ringer's Solution

The development of Ringer's solution represents one of the most serendipitous discoveries in medicine, arising from accidental observation and leading to fundamental understanding of electrolyte physiology and optimal fluid composition.

The serendipitous discovery of electrolyte requirements for optimal physiological function represents one of medicine's most fortunate accidents, fundamentally changing our understanding of cellular physiology and establishing the foundation for modern fluid therapy [106]. Ringer's work bridged the gap between empirical observation and scientific understanding, providing mechanistic in-

sights that remain relevant even today.

5.7. Sydney Ringer's Experiments

Sydney Ringer (1835-1910), a professor of physiology at University College London, was conducting experiments on isolated frog hearts in 1882, using them to study the effects of various substances on cardiac function [107]. When perfused with what Ringer believed was a pure saline solution, frog hearts typically stopped beating within 20 minutes. However, on one occasion, a heart continued beating for over four hours [108].

Investigation revealed that his laboratory assistant had mistakenly prepared the saline solution by using tap water from the New River Water Company rather than distilled water [108]. Analysis showed that the tap water contained small amounts of calcium and other minerals. This discovery led Ringer to systematically investigate the effects of various ions on cardiac function [106].

Ringer's investigation involved preparing solutions with precisely controlled ionic compositions and measuring cardiac contractile force, rate and rhythm using mechanical recording devices [106]. His apparatus included lever systems to measure the force of contraction, and timing mechanisms to assess rhythm changes. These experiments represented some of the earliest quantitative studies in cardiac physiology, and established experimental methods that would be used for decades.

5.8. Electrolyte Functions

Ringer's subsequent experiments, published in 1883, demonstrated that calcium was essential for cardiac contractility, while excessive potassium caused cardiac arrest [109]. He showed that sodium, calcium and potassium worked together to maintain normal cardiac rhythm and contractility—a discovery that laid the foundation for understanding cardiac electrophysiology [110].

The original experiments revealed the fundamental principles of cardiac electrophysiology that were decades ahead of their time [110]. Ringer demonstrated that calcium removal eliminated contractility without affecting electrical activity, while excess potassium caused progressive bradycardia and eventual asystole [110]. His work established the concept of calcium-sodium antagonism, and predicted findings that were not fully understood until the discovery of cellular ion channels and calcium-handling mechanisms in the mid-20th century [111].

The original Ringer's solution contained 0.75% sodium chloride, 0.014% potassium chloride, 0.012% calcium chloride, and 0.02% sodium bicarbonate [111]. This composition, while different from modern formulations, established the principle that physiological solutions should contain multiple electrolytes in appropriate concentrations.

5.9. Contemporary Research and Validation

Ringer's work was simultaneously validated and extended by other physiologists across Europe [112]. Walter Holbrook Gaskell at Cambridge University con-

firmed Ringer's findings using different experimental preparations, while Henry Pickering Bowditch at Harvard University demonstrated similar principles in mammalian cardiac tissue [113]. These independent confirmations established the universality of Ringer's discoveries and accelerated their clinical application.

5.10. Evolution of and Modifications to Ringer's Original Solution

Ringer's work inspired numerous modifications and improvements [106]. Frank Locke added glucose to create Locke's solution in 1901 [114] [115], while Maurice Tyrode developed Tyrode's solution in 1910, adding magnesium and phosphate for tissue culture applications [107] [116].

Locke's solution incorporated 0.1% glucose to provide a metabolic substrate for prolonged tissue survival, extending the viability of isolated tissues from hours to days [114] [115]. This modification proved crucial for early organ transplantation experiments, and established glucose as an essential component of physiological solutions. Tyrode's solution further refined electrolyte composition by adding magnesium chloride and monosodium phosphate, creating a solution that closely approximated the composition of extracellular fluid [107].

Development of Krebs-Henseleit solution by Hans Krebs and Kurt Henseleit in 1932 represented another major advance in intravenous solutions, optimizing the composition for metabolic studies and introducing systematic bicarbonate buffering [117] [118]. This solution became the standard for physiological research and influenced the development of the modern balanced crystalloid solutions used clinically today.

The most clinically significant modification came in 1932, when Alexis Frank Hartmann added lactate to create lactated Ringer's solution (Hartmann's solution) [119]. Working at Washington University, Hartmann was investigating the treatment of acidosis in pediatric diarrheal diseases when he discovered that lactate could serve as a metabolizable base, providing an alkali without the instability of bicarbonate solutions.

Hartmann's innovation solved multiple problems simultaneously: lactate provided buffering capacity, could be autoclaved without decomposition, and was metabolized to bicarbonate by the liver [99]. Clinical trials in children with acidotic diarrheal diseases demonstrated superior outcomes with lactated solutions compared to bicarbonate-containing solutions, leading to its rapid adoption worldwide. Modern lactated Ringer's solution remains essentially unchanged from Hartmann's original formulation, and is now the most widely used balanced crystalloid solution globally [120] [121].

6. Development of Pediatric Fluid Therapy

Pediatric fluid therapy developed as a distinct specialty in the early 20th century, driven by the enormous mortality from diarrheal diseases in children and recognition that children have unique physiological requirements that differ significantly from adults.

The recognition that children are not simply small adults represented a paradigm shift in medical thinking that occurred gradually throughout the early 20th century [122] [123].

6.1. Early Pioneers

John Howland (1873-1926) established the first academic pediatric department at Johns Hopkins University, emphasizing research alongside clinical care [124]. His work with William McKim Marriott on infantile diarrhea demonstrated that acidosis resulted from excessive bicarbonate loss, establishing the fundamental principles of acid-base physiology in children [125] [126].

James Lawder Gamble (1883-1959) revolutionized the understanding of fluid and electrolyte balance in hospitalized children [127]. His introduction of the "Gamblogram"—a graphical representation of plasma electrolyte composition using milliequivalents—provided a conceptual framework for understanding fluid and electrolyte disorders that remains valuable today [128] [129].

Marriott's detailed studies of infantile diarrhea in Baltimore revealed that acidosis was the primary cause of death, and not dehydration alone [130]. His systematic measurement of blood chemistry in sick infants demonstrated specific patterns of electrolyte loss and established the scientific foundation for replacement therapy. Marriott's work influenced a generation of pediatricians and established Johns Hopkins as the leading center for pediatric research globally.

Gamble's conceptual contributions extended far beyond clinical practice to fundamental understanding of cellular physiology and kidney function [131]. His studies of fasting and refeeding established the concept of intracellular versus extracellular fluid compartments, and demonstrated how different disease states affect fluid distribution. The Gamblogram visualization technique made complex electrolyte abnormalities comprehensible to practicing physicians, and established the use of milliequivalents as standard units for clinical chemistry [132].

6.2. Physiological Discoveries and Clinical Applications

Nathan Talbot's work at Massachusetts General Hospital established safety limits for pediatric fluid administration and developed the concept of "homeostatic limits" for fluid therapy [133] [134]. His mathematical models predicted the consequences of various fluid compositions and volumes, providing a scientific basis for safe practice limits that prevented both dehydration and water intoxication.

Allan Butler's metabolic studies at Boston Children's Hospital revealed the unique nutritional requirements of sick children, and led to the development of maintenance solutions containing appropriate ratios of glucose, electrolytes and amino acids [135] [136]. Butler's solutions were among the first designed specifically for pediatric metabolism rather than simple extrapolation of adult requirements.

6.3. Maintenance Fluid Requirements (Table 1)

Malcolm Holliday and William Segar's 1957 publication established standard formulas for calculating pediatric maintenance fluid requirements based on metabolic

Table 1. Pediatric maintenance fluid calculations.

Holliday-Segar Methods (1957)		Hourly Rate	Daily Volume
"4-2-1 Rule" for Maintenance Fluid Calculation			
First 10 kg	4 mL/kg/hour	4 × weight (kg)	100 mL/day
Second 10 kg	2 mL/kg/hour	2 × weight (kg)	50 mL/day
Each additional kg thereafter	1 mL/kg/hour	1 × weight (kg)	20 mL/day
Example Calculations			
5 kg infant	4 × 5 = 20 mL/hour	20 mL/hour	480 mL/day
15 kg child	(4 × 10) + (2 × 5) = 50 mL/hour	50 mL/hour	1200 mL/day
25 kg child	(4 × 10) + (2 × 10) + (1 × 5) = 65 mL/hour	65 mL/hour	1560 mL/day
Current Guidelines			
NICE (2020) and American Academy of Pediatrics (2018) recommend:			
Use isotonic solutions (e.g., 0.9% saline) rather than hypotonic solutions.			
Monitor serum sodium levels in children receiving IV fluids.			
Regular clinical reassessment to adjust fluid therapy as needed.			
Safety Considerations			
Hospital-acquired hyponatremia risks:			
SIADH (Syndrome of Inappropriate ADH secretion) common in hospitalized children.			
Hypotonic solutions may exacerbate water retention and hyponatremia.			
Symptoms include headache, nausea, seizures and, in severe cases, cerebral edema.			

Holliday-Segar method (1957) for calculating pediatric maintenance fluid requirements based on metabolic rate and body weight [137] [138]. The "4-2-1 rule" provides 4 ml/kg/hr for the first 10 kg, 2 ml/kg/hr for the next 10 kg, and 1 ml/kg/hr for each additional kilogram. Modern guidelines from NICE (2020) and AAP (2018) recommend isotonic rather than hypotonic solutions to prevent hospital-acquired hyponatremia [147]-[149]. This approach correlates fluid requirements with energy expenditure, recognizing that metabolic requirements per kilogram decrease with age and size.

rate and body weight [137]. Their "4-2-1 rule" (4 ml/kg/hr for the first 10 kg, 2 ml/kg/hr for the next 10 kg, and 1 ml/kg/hr for each additional kg) became the global standard for pediatric fluid management [138].

The Holliday-Segar method was based on careful studies of metabolic rate and insensible water losses in healthy children of different ages and sizes [139]. Their approach correlated fluid requirements with energy expenditure, recognizing that metabolic rate per kilogram body weight decreases with age and size. This method provided a simple, practical formula that could be applied globally, and became the foundation for pediatric fluid therapy protocols worldwide.

However, recent evidence suggesting the increased risk of hyponatremia with hypotonic maintenance solutions has led to revised guidelines recommending isotonic solutions for most hospitalized children, demonstrating how clinical practice evolves with new evidence [140].

The safety concerns about hypotonic solutions emerged from multiple case reports and systematic studies demonstrating hospital-acquired hyponatremia in

children receiving standard maintenance fluids [141]. The syndrome of inappropriate antidiuretic hormone secretion (SIADH), common in hospitalized children with various illnesses, increases water retention and leads to the risk of hyponatremia when combined with hypotonic fluid administration [142].

6.4. Specialized Pediatric Solutions

Daniel Darrow's work in the 1940s at Yale University emphasized the importance of potassium replacement in pediatric patients, leading to the development of Darrow's solution containing 35 mEq/L potassium—much higher than in adult solutions [143]. His recognition that children lose proportionally more potassium than adults during diarrheal illnesses revolutionized pediatric electrolyte management and reduced mortality from hypokalemic paralysis.

Darrow's clinical observations revealed that potassium depletion was a major cause of persistent ileus and respiratory failure in children with diarrheal diseases [144]. His systematic studies on potassium balance demonstrated that replacement requirements exceeded losses measured in stool and urine, leading to the recognition of transcellular potassium shifts during illness and recovery phases.

The Japanese approach to pediatric fluid therapy, developed by Takatsu and colleagues in the 1960s, involved numbered solutions (1 - 4) designed for sequential use depending on the patient's clinical status and treatment phase [145]. This system represents the early recognition that fluid requirements change during illness and recovery, anticipating modern goal-directed approaches to fluid management.

6.5. Modern Pediatric Guidelines and Evidence

Contemporary pediatric fluid management has been influenced by major clinical trials and systematic reviews that challenge traditional approaches [146]. The NICE guidelines (2015, updated 2020) recommend isotonic solutions for most hospitalized children, while the American Academy of Pediatrics (2018) provided similar recommendations based on accumulating evidence of hyponatremia risks [147] [148].

Recent studies have also questioned traditional approaches to fluid resuscitation in pediatric sepsis, with the FEAST trial demonstrating potential harm from fluid bolus therapy in African children with severe infection [149] [150]. These findings highlight the complexity of pediatric fluid management and the need for continued research to optimize treatment approaches in different clinical scenarios and geographic settings.

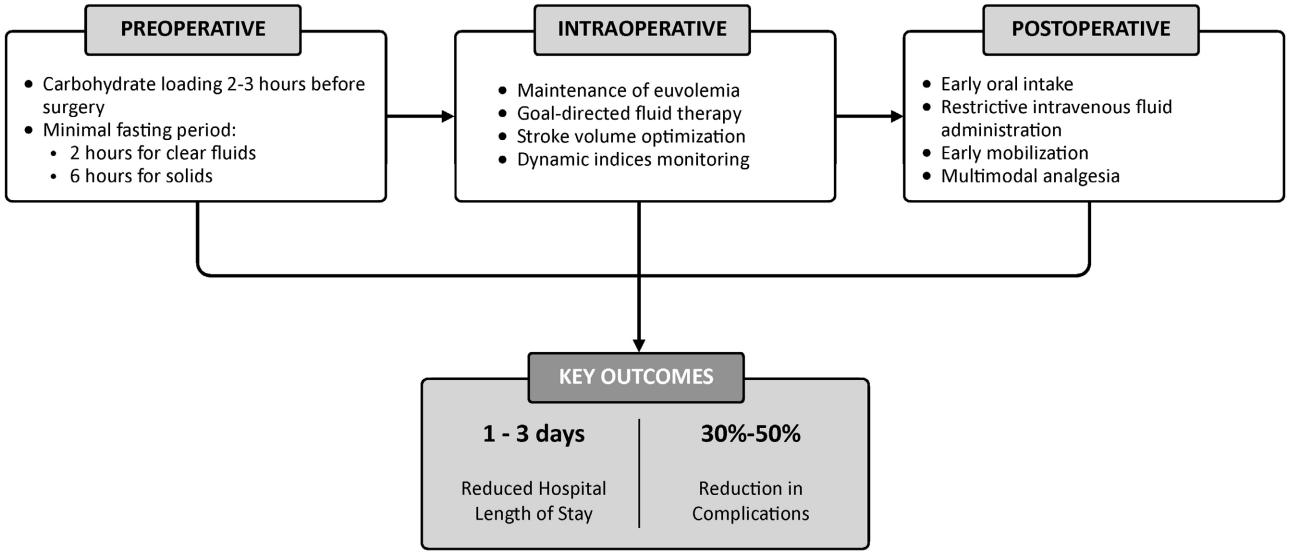
7. Modern Perioperative Fluid Management Including ERAS

Modern perioperative fluid management has evolved from intuition-based practices to evidence-driven protocols that have significantly impacted surgical outcomes, recovery times and healthcare costs. The transformation of perioperative fluid management from intuition-based practices to evidence-driven protocols represents one of the major advances in perioperative medicine of the past two

decades [151] [152]. This evolution has been driven by recognition that fluid management significantly impacts surgical outcomes, healthcare costs and patient satisfaction, leading to the development of sophisticated monitoring techniques and management algorithms.

7.1. Enhanced Recovery After Surgery (ERAS) Protocols (Figure 3)

Enhanced Recovery After Surgery (ERAS) protocols, pioneered by Henrik Kehlet in Denmark, represent a paradigm shift toward multimodal perioperative care designed to minimize surgical stress and accelerate recovery [153] [154]. Fluid management is a core component of ERAS, emphasizing several key principles.



Enhanced Recovery After Surgery (ERAS) fluid management principles, as established by Kehlet and the ERAS Society [153]-[156]. The protocol emphasizes preoperative carbohydrate loading 2 - 3 hours before surgery [154] [155], minimal preoperative fasting periods (2 hours for clear fluids, 6 hours for solids) [155], intraoperative maintenance of euvolemia using goal-directed fluid therapy based on dynamic indices [155] [156], and postoperative early oral intake with restrictive intravenous fluid administration [155] [156]. Implementation of the ERAS protocol reduces the duration of hospitalization by 1-3 days and the rate of postoperative complications by 30% - 50% [155] [156].

Figure 3. ERAS fluid management protocol.

The ERAS Society, founded in 2001, has published evidence-based guidelines for multiple surgical specialties, including colorectal, cardiac, orthopedic and gynecologic surgery [155] [156]. These guidelines are regularly updated based on emerging evidence and have been adopted worldwide, with demonstrated improvements in the duration of hospitalization, postoperative complications, and patient satisfaction. Implementation of ERAS protocols typically reduces the duration of hospitalization by 1 - 3 days, while reducing complications by 30% - 50% [157]. ERAS fluid management principles include avoiding preoperative fasting beyond 2 hours for clear fluids and 6 hours for solids, implementing carbohydrate loading 2 - 3 hours preoperatively to improve insulin sensitivity and reduce postoperative nausea, and maintaining intraoperative euvolemia, while avoiding both hypovolemia and fluid overload [158]. The concept of "zero fluid balance" aims

to prevent tissue edema while ensuring adequate organ perfusion.

Systematic reviews and meta-analyses have also consistently demonstrated that ERAS implementation reduces postoperative complications, duration of hospitalization and healthcare costs across multiple surgical specialties [159]. A 2019 Cochrane review of 17 randomized trials involving over 1800 patients found significant reductions in complications (RR 0.71, 95% CI 0.58 - 0.86) and duration of hospitalization (mean difference −2.28 days, 95% CI −3.09 to −1.46) with ERAS implementation [160].

However, it should also be cautioned that excessive fluid administration can lead to tissue edema, delayed wound healing, and prolonged recovery, while inadequate fluid replacement can cause organ hypoperfusion and dysfunction, requiring careful balance between restriction and adequacy.

7.2. Goal-Directed Fluid Therapy

Goal-directed fluid therapy (GDFT) uses hemodynamic monitoring to assess cardiac output, and fluid responsiveness to optimize fluid administration [161]. Parameters such as stroke volume variation, pulse pressure variation, and dynamic indices derived from arterial waveform analysis guide fluid and vasoactive drug administration.

GDFT protocols typically involve targeting specific hemodynamic parameters, such as stroke volume optimization, maintaining stroke volume variation at <13%, and achieving predetermined oxygen delivery targets [162]. Various monitoring systems have been developed, including esophageal Doppler (CardioQ), pulse contour analysis (FloTrac/Vigileo), and non-invasive cardiac output monitors (ClearSight), each with specific advantages and limitations [163].

Multiple randomized trials have demonstrated improved outcomes with GDFT, particularly in high-risk surgical patients [164]. The approach moves beyond traditional static parameters, such as central venous pressure, toward dynamic assessments of hemodynamic status and fluid responsiveness.

A 2016 systematic review of 38 randomized trials involving over 4000 patients demonstrated that GDFT reduces complications (OR 0.77, 95% CI 0.63 - 0.94), duration of hospitalization (mean difference −1.16 days), and may reduce mortality in high-risk surgical patients [165]. However, the benefits appear most pronounced in high-risk patients undergoing major surgery, with less clear evidence in routine surgical procedures [166].

7.3. Crystalloid vs. Colloid Debate (Table 2)

The choice between crystalloid and colloid solutions for fluid resuscitation in critically ill and surgical patients remains contentious despite decades of research. Large randomized trials, such as SAFE (2004), FEAST (2011) and CRISTAL (2013), have provided important insights, but have not definitively resolved the debate [150] [167] [168]. The SAFE trial found no difference in mortality between saline and albumin in ICU patients, while FEAST surprisingly demonstrated harm

Table 2. Comparison of crystalloid and colloid solutions.

Characteristics	Crystalloids	Colloids
Examples	Normal saline (0.9% NaCl) Lactated Ringer's solution Balanced solution (Plasma-Lyte)	Albumin (5%, 25%) Dextran (40, 70) Gelatins (Gelofusine) Hydroxyethyl starch (HES)
Duration of volume expansion	30 - 60 minutes *Rapid redistribution to interstitial space*	2 - 12 hours *HES: 4 - 6 hours; Albumin: 8 - 12 hours*
Cost	Low *~$1 - 4 per liter*	High *Albumin: ~$80 - 300 per unit* *HES: ~$50 - 90 per unit*
Risks	Hyperchloremic metabolic acidosis Tissue edema Electrolyte imbalance *Particularly with large volumes of normal saline*	Coagulation disorders Acute kidney injury (especially HES) Anaphylactic/anaphylactoid reactions Accumulation in tissues with repeated dosing
Clinical trial evidence	SMART trial (2018): Reduced kidney events with balanced crystalloids vs saline (14.3% vs 15.4%, p = 0.04)	SAFE trial (2004): No mortality difference between albumin and saline 6S, CHEST trial (2012): Increased kidney injury and mortality with HES in sepsis
Current recommendations	First-line fluid for most resuscitation scenarios Balanced solutions preferred over normal saline	Limited role in specific scenarios HES use restricted in many countries Albumin considered in select patients

Characteristics and clinical implications of crystalloid versus colloid solutions based on major clinical trials. Crystalloids include normal saline, lactated Ringer's solution and balanced solutions, such as Plasma-Lyte, providing short-duration volume expansion (30 - 60 minutes) at low cost, but with the risk of hyperchloremic acidosis and tissue edema [80]-[84] [167] [168]. Colloids, including albumin, dextran, gelatin and hydroxyethyl starch, provide longer duration volume expansion (2 - 12 hours), but at a higher cost and with risks of coagulation disorders, acute kidney injury (particularly with HES) and anaphylaxis. The SMART trial demonstrated reduced kidney injury with balanced crystalloids versus saline [169].

from fluid boluses in African children with severe infection [150] [167] [168].

More recent trials have focused on crystalloid composition rather than crystalloid versus colloid comparisons. The SMART trial (2018) demonstrated a reduction in major adverse kidney events within 30 days (14.3% vs 15.4%, p = 0.04) when balanced crystalloids were compared to saline in over 15,000 critically ill adults [169]. Similar findings in the SALT-ED trial in emergency department patients suggest that balanced crystalloids may have advantages over normal saline, although the effect sizes are modest [170].

Current evidence also increasingly favors balanced crystalloid solutions over normal saline due to the reduced risk of hyperchloremic acidosis and acute kidney injury [171]. The development of fourth-generation balanced solutions with physiological electrolyte compositions represents ongoing refinement of crystalloid therapy.

Modern balanced crystalloids include lactated Ringer's solution, Plasma-Lyte A, and newer formulations, such as Sterofundin and Jonosteril, that more closely approximate plasma electrolyte composition [172]. These solutions typically con-

tain 130 - 140 mEq/L sodium, 98 - 110 mEq/L chloride, and metabolizable anions (lactate, acetate, or gluconate) to provide appropriate strong ion differences and avoid the hyperchloremic metabolic acidosis associated with normal saline administration [173] [174] (**Table 3**).

Table 3. Major clinical trials in fluid therapy.

Trial (Year)	Patient Population	Interventions Compared	Primary Outcome	Key Findings
SAFE (2004)	ICU patients requiring fluid resuscitation (n = 6997)	4% Albumin vs. Normal saline	28-day all-cause mortality	No difference in mortality (Albumin: 20.9% vs. Saline: 21.1%)
FEAST (2011)	African children with severe infection and impaired perfusion (n = 3141)	Albumin bolus vs. Saline bolus vs. No bolus	48-hour mortality	Increased mortality with fluid boluses (Bolus: 10.5% vs. No bolus: 7.3%)
CRISTAL (2013)	ICU patients with hypovolemic shock (n = 2857)	Colloids (albumin, gelatins, dextrans, HES) vs. Crystalloids (saline, Ringer's)	28-day mortality	No difference in mortality (Colloids: 25.4% vs. Crystalloids: 27.0%)
SMART (2018)	Critically ill adults (n = 15,802)	Balanced crystalloids (LR, Plasma-Lyte) vs. Normal saline	Major adverse kidney events within 30 days	Reduced kidney events with balanced solutions (14.3% vs. 15.4%, p = 0.04)
BaSICS (2021)	Critically ill adults requiring fluid challenges (n = 10,520)	Balanced solution vs. Normal saline	90-day mortality	No mortality difference Confirmed safety of balanced solutions

Landmark randomized controlled trials that shaped modern fluid therapy practice. The SAFE trial (2004) found no mortality difference between albumin and saline in ICU patients [167]. The FEAST trial (2011) surprisingly demonstrated harm from fluid boluses in African children with severe infection [149]. CRISTAL (2013) showed no mortality difference between crystalloids and colloids [168]. The SMART trial (2018) demonstrated reduced major adverse kidney events with balanced crystalloids versus saline (14.3% vs 15.4%, p = 0.04) [169]. BaSICS (2021) confirmed the safety of balanced solutions without mortality benefits [171].

7.4. Individualized Fluid Management

Modern fluid management increasingly emphasizes individualized approaches based on patient-specific factors, including comorbidities, surgical procedure and real-time physiological monitoring [175]. Techniques such as transesophageal echocardiography, pulse wave analysis, and bioimpedance monitoring enable personalized fluid optimization.

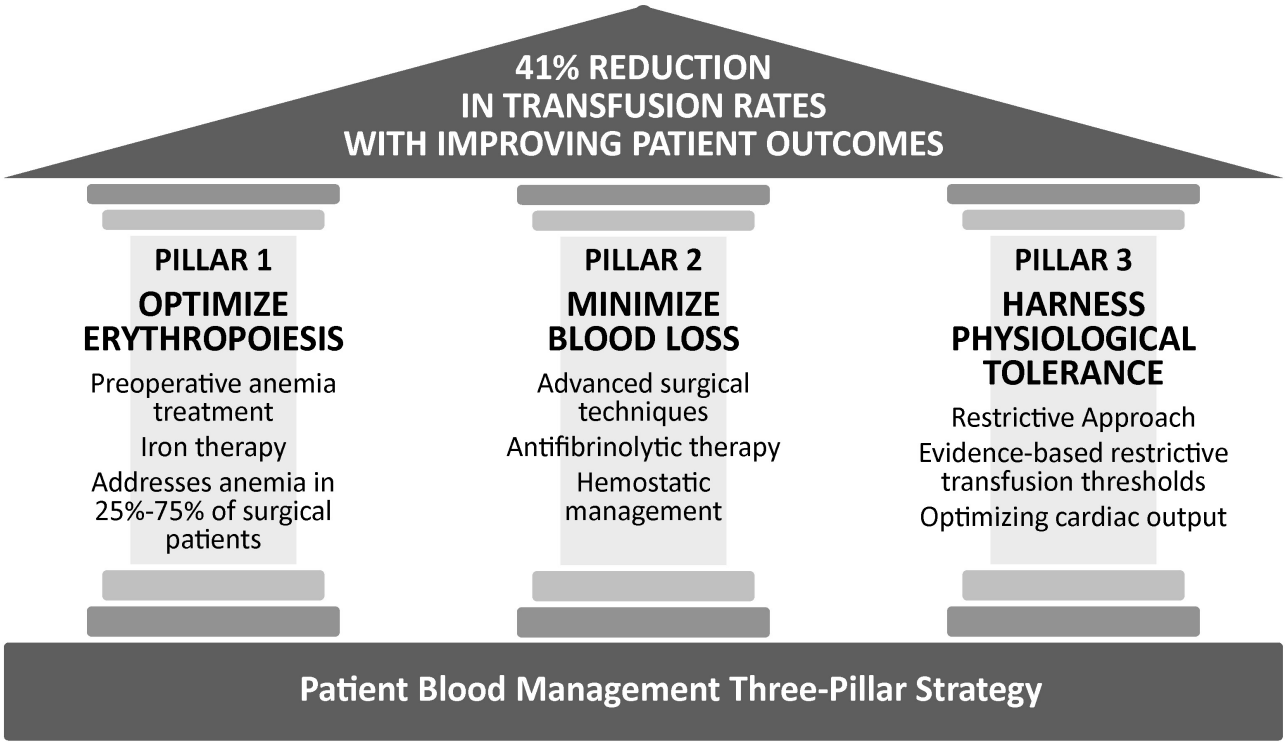
For example, patients with heart failure require restrictive fluid strategies with careful monitoring of central venous pressure and pulmonary artery wedge pressure to prevent pulmonary edema, while maintaining adequate preload for cardiac output optimization. Conversely, patients with chronic kidney disease may benefit from more liberal fluid administration to maintain renal perfusion and prevent contrast-induced nephropathy, though electrolyte balance requires meticulous attention due to impaired renal clearance.

Machine learning approaches are also being developed to predict fluid requirements and optimize management based on continuous monitoring data, electronic health records, and patient characteristics [176] [177]. Artificial intelligence systems can potentially integrate multiple data streams, including vital signs, la-

boratory values, surgical factors and patient comorbidities, to provide real-time recommendations for fluid management decisions.

8. Patient Blood Management and Modern Transfusion Strategies (Figure 4)

Patient Blood Management (PBM) represents a paradigm shift in transfusion medicine, evolving from traditional reactive approaches to proactive, evidence-based strategies that optimize patient outcomes while minimizing blood product utilization [178]. This comprehensive approach has gained international recognition and adoption, fundamentally changing how clinicians approach perioperative and critical care management. The integration of PBM principles with modern fluid management creates synergistic effects, where optimizing physiological tolerance to anemia through enhanced oxygen delivery and reduced consumption allows for more restrictive transfusion thresholds, thereby reducing the reliance on aggressive fluid resuscitation to maintain hemodynamic stability in anemic patients.



The three fundamental pillars of Patient Blood Management (PBM) as developed in Australia and endorsed by the World Health Organization [181]. **Pillar 1** focuses on optimizing erythropoiesis through preoperative anemia treatment with intravenous iron and erythropoiesis-stimulating agents, addressing anemia in 25% - 75% of surgical patients [189]-[191]. Systematic iron therapy increases hemoglobin by 1.5 - 2.5 g/dL within 2 - 4 weeks and reduces transfusion requirements [192]-[194]. **Pillar 2** emphasizes minimizing perioperative blood loss through meticulous surgical technique, tranexamic acid administration (reducing bleeding by 30% - 40%), and point-of-care viscoelastic testing [195] [196]. **Pillar 3** harnesses physiological tolerance to anemia through evidence-based restrictive transfusion thresholds (7 - 8 g/dL for stable patients) and optimization of oxygen delivery [197] [198]. Multimodal PBM implementation demonstrates 30% - 50% transfusion reduction, 20% - 30% complication reduction, and 1 - 2 day shorter hospital stays [199]-[201].

Figure 4. Three-pillar strategy of patient blood management.

PBM originated in Australia in the 1990s, driven by concerns about blood shortages, transfusion-related complications, and healthcare costs [179]. The Western Australia PBM initiative, launched in 2008 under the leadership of Axel Hofmann and Shannon Farmer, demonstrated significant reductions in red blood cell transfusion rates (41% reduction) and healthcare costs, while improving patient outcomes [180].

The Australian experience influenced its international adoption, with PBM programs implemented in Europe, North America and Asia. The World Health Organization endorsed PBM in 2010, recognizing it as essential for patient safety and healthcare sustainability [181]. Key professional organizations, including the Society for the Advancement of Blood Management (SABM) and the International Foundation for Patient Blood Management, have promoted evidence-based transfusion practices globally [182].

8.1. The Three-Pillar Strategy

PBM is built on three fundamental pillars that work synergistically to optimize patient outcomes while minimizing transfusion requirements [183]. This systematic approach addresses the entire perioperative period, from preoperative optimization through postoperative recovery.

8.1.1. Pillar 1: Optimize Erythropoiesis and Treat Anemia

Preoperative anemia represents one of the most significant modifiable risk factors in surgical patients, affecting 25% - 75% depending on surgical type, patient demographics, and underlying comorbidities [184]. The presence of even mild anemia (hemoglobin 10 - 12 g/dL) independently predicts increased morbidity, mortality, hospital length of stay, and transfusion requirements across diverse surgical populations [185]. Meta-analyses demonstrate a linear relationship between decreasing preoperative hemoglobin and adverse outcomes, with even hemoglobin levels of 12 - 13 g/dL showing elevated risk compared to normal values [185].

1) Pathophysiology and Etiology of Perioperative Anemia

Understanding anemia etiology guides appropriate treatment selection [186]. Iron deficiency constitutes the most common cause of preoperative anemia in surgical populations, accounting for 30% - 60% of cases [185] [186]. Absolute iron deficiency results from depleted total body iron stores (ferritin < 30 ng/mL), while functional iron deficiency occurs when adequate iron stores exist but cannot be mobilized for erythropoiesis due to hepcidin-mediated sequestration [187].

Hepcidin, a liver-produced hormone regulated by inflammation, represents the master regulator of iron homeostasis [187]. Inflammatory states—including malignancy, chronic infections, autoimmune disorders, and obesity—upregulate hepcidin synthesis, which then binds and degrades ferroportin (the sole cellular iron exporter) on duodenal enterocytes and macrophages. This blocks both dietary iron absorption and mobilization of stored iron, creating functional iron deficiency despite normal or elevated ferritin levels—the classical "anemia of chronic disease" [187].

Vitamin B12 and folate deficiencies contribute to macrocytic anemia in surgical patients, particularly in gastrointestinal surgery populations where malabsorption is common [188]. Recent studies reveal that 5% - 15% of preoperative anemic patients have B12 or folate deficiency, often coexisting with iron deficiency [188].

2) Iron Replacement Therapy

Iron replacement represents the cornerstone of preoperative anemia management for iron-deficient patients [189]. Route selection—oral versus intravenous—depends on time available before surgery, severity of deficiency, inflammatory status, and gastrointestinal tolerance.

Intravenous Iron Therapy: Intravenous iron preparations bypass hepcidin-mediated absorption blockade, delivering large iron doses directly into circulation for immediate incorporation into erythropoiesis [189]. Modern formulations—ferric carboxymaltose, iron isomaltoside, and low-molecular-weight iron dextran—allow administration of 500 - 1000 mg in single 15 - 30 minute infusions [189].

Multiple randomized trials demonstrate that preoperative IV iron significantly increases hemoglobin levels (mean increase 1.5 - 2.5 g/dL within 2 - 4 weeks) and reduces transfusion requirements [189]. The PREVENTT trial, while showing neutral primary outcomes, provided important insights about timing requirements (4 - 6 weeks optimal versus 10 - 14 days suboptimal) [190]. Recent meta-analyses of over 10,000 patients confirm IV iron reduces transfusion likelihood (RR 0.74, 95% CI 0.62 - 0.88) without increasing adverse events [191].

The PROVITA trial in cardiac surgery demonstrated that even ultra-short-term IV iron administration (2 - 7 days preoperatively) significantly reduced transfusion rates, establishing feasibility for urgent surgical scenarios [192].

3) Erythropoiesis-Stimulating Agents

ESAs—epoetin alfa, epoetin beta, darbepoetin alfa—directly stimulate red blood cell production and prove particularly valuable in inflammatory anemia where hepcidin limits iron availability, and in chronic kidney disease where endogenous erythropoietin production is impaired [193].

Cochrane systematic reviews demonstrate ESA efficacy in reducing perioperative transfusion rates when combined with iron supplementation [193]. ESAs are safe when hemoglobin targets do not exceed 13 g/dL, with recent evidence suggesting potential nephroprotective and cardioprotective effects independent of erythropoiesis [193].

4) Vitamin Supplementation and Comprehensive Management

Vitamin B12 (1000 mcg IM weekly or 1000 - 2000 mcg oral daily) and folate (1 - 5 mg daily) effectively correct deficiencies within 4 - 8 weeks [194]. Recent data emphasize testing all anemic surgical patients for vitamin deficiencies, as prevalence exceeds 15% in some populations and remains underdiagnosed [190].

5) Preoperative Anemia Clinics

Systematic preoperative anemia management requires organizational infrastructure supporting early identification (6-8 weeks preoperatively), comprehensive diagnostic evaluation, protocol-driven treatment, and reassessment [194].

Implementation of dedicated anemia clinics reduces transfusion rates by 20% - 50%, decreases length of stay by 1 - 2 days, and demonstrates cost savings of $1000 - 3000 per patient despite upfront investments [194].

8.1.2. Pillar 2: Minimize Perioperative Blood Loss

The second pillar addresses blood loss reduction through surgical technique optimization, pharmacological agents, and blood conservation technologies. Meticulous surgical hemostasis and minimally invasive approaches demonstrate 30% - 50% less blood loss than open procedures. Regional anesthesia reduces bleeding through sympathetic blockade and decreased venous pressure.

Tranexamic acid, an antifibrinolytic agent, reduces surgical blood loss by 30% - 40% when administered prophylactically (loading dose 10 - 15 mg/kg, then infusion 1 - 2 mg/kg/hour) [195]. Point-of-care viscoelastic testing (TEG®/ROTEM®) enables real-time coagulation assessment and goal-directed hemostatic therapy, reducing transfusion requirements by 30% - 50% [196].

Intraoperative cell salvage recovers and returns the patient's shed blood, proving cost-effective when blood loss exceeds 1000 mL [197]. Postoperative blood conservation includes minimizing phlebotomy through reduced laboratory testing frequency and smaller-volume collection tubes.

8.1.3. Pillar 3: Optimize Physiological Tolerance of Anemia

The third pillar recognizes that adequate tissue oxygenation depends on the entire oxygen delivery system. The body compensates for anemia through increased cardiac output, enhanced oxygen extraction, and regional blood flow redistribution [198].

Optimizing oxygen delivery involves supplemental oxygen administration and maintenance of adequate cardiac output through goal-directed fluid therapy. Reducing oxygen consumption through adequate analgesia, fever control, and infection prevention enhances anemia tolerance.

Restrictive transfusion strategies based on landmark trials establish safety of hemoglobin thresholds of 7 - 8 g/dL in stable patients, including those with cardiovascular disease [198] [199]. These evidence-based thresholds have reduced transfusion rates 30% - 50% without adverse outcomes. Single-unit transfusion strategies prevent unnecessary transfusions while achieving equivalent outcomes.

Postoperative anemia management includes intravenous iron to accelerate hemoglobin recovery, nutritional optimization, and continued adherence to restrictive transfusion thresholds [200]. Combined implementation of all three pillars creates synergistic effects, with multimodal PBM programs demonstrating 30% - 50% transfusion reduction, 20% - 30% complication reduction, and 1 - 2 day shorter hospital stays [201]-[203].

9. Artificial Oxygen Carriers: From Concept to Clinical Reality

The quest for artificial blood substitutes represents one of the most challenging endeavors in modern medicine, driven by fundamental limitations inherent in

conventional blood transfusion systems. The growing disparity between blood supply and demand, exacerbated by aging populations and declining donor participation, has created an urgent need for alternative oxygen-carrying solutions [204]. Beyond supply constraints, traditional blood transfusion faces multiple clinical challenges including ABO/Rh compatibility requirements, limited storage duration of 42 days for packed red blood cells, and persistent risks of pathogen transmission despite rigorous screening protocols [205]. These limitations become particularly critical in emergency situations, military conflicts, and remote medical settings where immediate blood availability can determine patient survival outcomes.

9.1. Historical Development of Artificial Oxygen Carriers

The scientific foundation for artificial oxygen carriers was established in 1966 when Clark and Gollan demonstrated the remarkable oxygen-dissolving capacity of perfluorocarbon (PFC) compounds [206]. Their groundbreaking experiments showed that laboratory mice could survive complete submersion in oxygenated perfluorocarbon solutions, breathing the liquid medium through their lungs. This discovery opened new possibilities for developing synthetic oxygen-carrying fluids that could potentially replace red blood cells in clinical applications.

The first commercial artificial blood product, Fluosol-DA-20, was developed by Green Cross Corporation of Japan and received FDA approval in 1989 [207]. This perfluorocarbon-based emulsion represented a milestone in blood substitute development, offering pathogen-free oxygen delivery with universal compatibility. However, clinical experience revealed significant limitations including low oxygen-carrying capacity (requiring high inspired oxygen concentrations), complement activation leading to pulmonary edema, and complex preparation requirements. These drawbacks ultimately led to its market withdrawal in 1994, highlighting the formidable challenges in artificial blood development [208].

Parallel development of hemoglobin-based oxygen carriers (HBOCs) during the 1980s and 1990s initially showed promise but encountered severe safety concerns. First-generation cell-free hemoglobin products, including PolyHeme, Hemopure, and Hemolink, demonstrated significant increases in myocardial infarction risk and mortality in clinical trials [209]. A comprehensive meta-analysis by Natanson and colleagues in 2008 revealed a 30% increase in death risk and threefold increase in myocardial infarction risk associated with these products, effectively halting their clinical development [210]. The mechanisms underlying these adverse effects were attributed to hemoglobin's intrinsic properties when released from the protective environment of red blood cells.

9.2. Two Major Approaches to Artificial Oxygen Carriers

9.2.1. Perfluorocarbon-Based Systems

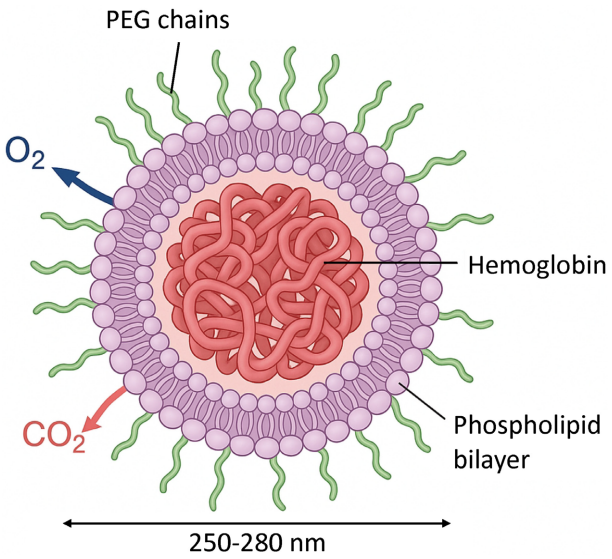
Perfluorocarbons possess unique physicochemical properties that make them attractive for oxygen delivery applications. These synthetic compounds demonstrate linear oxygen solubility relationships, allowing dissolution of up to 20 times

more oxygen than plasma at atmospheric pressure [211]. Unlike hemoglobin-based systems, PFCs do not chemically bind oxygen but rather dissolve it physically, creating a reservoir that releases oxygen in proportion to local tissue oxygen tension. Modern second-generation PFC emulsions have addressed many limitations of Fluosol-DA-20 through improved formulations with enhanced stability, reduced particle size, and minimal complement activation [212].

9.2.2. Hemoglobin-Based Oxygen Carriers

The fundamental challenge with cell-free hemoglobin lies in its inherent toxicity when removed from the red blood cell environment. Unencapsulated hemoglobin molecules readily extravasate through capillary walls, scavenge nitric oxide leading to vasoconstriction and hypertension, and undergo oxidative reactions producing methemoglobin and reactive oxygen species [213]. These mechanisms explain the cardiovascular toxicity observed with first-generation HBOCs and led to the development of encapsulation strategies to recreate the protective cellular environment.

Japanese Innovation: Hemoglobin Vesicles (HbV) (**Figure 5**).



Schematic cross-sectional representation of a hemoglobin vesicle (HbV) showing the innovative encapsulation design [214] [215] [217]. The vesicle consists of purified human hemoglobin encapsulated within a PEGylated phospholipid bilayer membrane with a diameter of 250 - 280 nanometers. Polyethylene glycol (PEG) chains extending from the outer surface provide stealth properties and prevent immune recognition. The lipid bilayer membrane maintains selective permeability, allowing bidirectional diffusion of oxygen (O_2) and carbon dioxide (CO_2) while containing hemoglobin molecules within the vesicle core.

Figure 5. Structural design and functional advantages of hemoglobin vesicles (HbV).

A revolutionary approach to hemoglobin-based oxygen carriers emerged from

the research laboratory of Professor Hiromi Sakai at Nara Medical University, Japan. Over three decades of dedicated research, Sakai and his team developed hemoglobin vesicles (HbV), representing a paradigm shift in artificial blood design [214]. These innovative nano-sized particles consist of purified human hemoglobin encapsulated within PEGylated phospholipid bilayer membranes, creating artificial red blood cells with diameters of 250 - 280 nanometers [215].

The unique structure of HbV addresses the fundamental problems of previous HBOC generations. The lipid bilayer membrane prevents hemoglobin extravasation while maintaining selective permeability for oxygen and carbon dioxide. This design significantly reduces nitric oxide scavenging, eliminates the hypertensive response characteristic of cell-free hemoglobin, and provides protection against oxidative damage [216]. Furthermore, HbV demonstrates remarkable stability with a shelf life of two years at room temperature and universal compatibility across all blood types, representing significant advantages over conventional blood products.

9.2.3. Clinical Development Progress

The clinical translation of HbV represents a methodical progression from laboratory concept to human application. Following extensive preclinical safety and efficacy studies in multiple animal models, Sakai's team conducted the first-in-human Phase 1 clinical trial from 2020 to 2022 [217]. This landmark study enrolled 12 healthy male volunteers across three dose-escalation cohorts receiving 10 mL, 50 mL, and 100 mL of HbV suspension respectively.

The Phase 1 results, published in Blood Advances in 2022, demonstrated encouraging safety profiles with no clinically significant blood pressure changes—a crucial distinction from previous HBOC failures [218]. The primary adverse events included mild infusion reactions typical of liposomal products and transient fever episodes, both manageable with standard premedication protocols. Pharmacokinetic analysis revealed a circulation half-life of approximately 8 hours, providing sufficient duration for emergency resuscitation until conventional blood products become available. Most importantly, the study confirmed the absence of hypertensive responses that had plagued earlier hemoglobin-based products.

9.2.4. Clinical Applications and Future Prospects

The successful Phase 1 trial has positioned HbV for expanded clinical development, with Phase 2 studies planned for 2025 targeting specific clinical scenarios where artificial oxygen carriers could provide maximum benefit [219]. These Phase 2 studies will focus on trauma patients with hemorrhagic shock, cardiac surgery patients with anticipated significant blood loss, and obstetric emergency cases where immediate blood availability is critical, representing clinical scenarios where HbV's universal compatibility and extended shelf life provide maximum therapeutic advantage. Primary applications include hemorrhagic shock resuscitation in trauma patients, where rapid volume replacement with oxygen-carrying capacity could improve survival outcomes compared to crystalloid or colloid solutions

alone.

The versatility of HbV extends beyond emergency medicine to specialized clinical contexts including disaster relief operations, military medicine, and remote healthcare delivery where blood banking infrastructure is unavailable. Additionally, the extended shelf life and universal compatibility make HbV particularly valuable for obstetric emergencies, where massive hemorrhage requires immediate intervention, and for organ preservation during transplantation procedures [220].

The development of artificial oxygen carriers represents the culmination of four centuries of progress in fluid therapy, from William Harvey's revolutionary description of blood circulation in 1628 to the pioneering intravenous saline therapy for cholera victims in the 1830s, through the establishment of modern transfusion medicine in the 20th century. Today, as we stand on the threshold of the artificial blood era, the work of Sakai and his colleagues embodies the convergence of historical knowledge, technological innovation, and clinical necessity.

The anticipated commercial availability of HbV by 2030 will mark a transformative milestone in medical history, potentially revolutionizing emergency medicine, trauma care, and surgical practice [221]. This achievement represents not merely a technological advancement but the fulfillment of a centuries-old medical aspiration to provide safe, effective, and universally compatible blood substitutes. As artificial oxygen carriers transition from experimental concepts to clinical reality, they embody the remarkable journey of fluid therapy from its humble origins in cholera treatment to the sophisticated life-saving interventions of modern medicine.

The story of artificial blood development exemplifies the iterative nature of medical progress, where each generation of researchers builds upon previous achievements while addressing fundamental challenges. From the early recognition of blood's vital role to the molecular engineering of hemoglobin vesicles, this journey reflects humanity's persistent quest to preserve and protect life through innovative medical solutions. The imminent clinical implementation of artificial oxygen carriers thus represents both a scientific triumph and a continuation of the humanitarian mission that has driven fluid therapy development throughout its remarkable 400-year evolution.

10. Conclusions

The historical evolution of fluid therapy represents a remarkable journey from ancient humoral theories to modern evidence-based medicine. From Christopher Wren's crude experiments with goose quills to today's sophisticated ERAS protocols and artificial intelligence-guided fluid management, each advance has built upon previous discoveries, while revealing new complexities and challenges.

The cholera epidemics of the 19th century demonstrated both the potential and limitations of fluid therapy, establishing principles that remain fundamental to modern resuscitation. Sydney Ringer's accidental discovery of electrolyte requirements revolutionized our understanding of cellular physiology, while the pediatric pioneers of the early 20th century established age-specific approaches that saved

countless lives.

Modern perioperative fluid management has evolved from the liberal fluid practices of the mid-20th century to today's precision medicine approaches. ERAS protocols and goal-directed fluid therapy represent the culmination of evidence-based practice, although debates continue about optimal fluid composition, administration timing and volume.

The quest for artificial blood substitutes illustrates both the promise and peril of medical innovation. Despite enormous investment and sophisticated technology, no product has successfully replicated blood's multiple functions, highlighting the complexity of physiological systems and the challenges of artificial blood replacement. However, promising developments, such as hemoglobin vesicles, continue to offer hope for future breakthroughs (**Table 4**).

Table 4. Classification of artificial blood substitutes.

Category	Mechanism	Advantages	Limitations
Hemoglobin-Based Oxygen Carriers (HBOCs) *PolyHb*, *DCLHb*, *Hemopure*	• Cell-free hemoglobin molecules • Cross-linked or polymerized to prevent rapid clearance • Directly bind and transport oxygen	• High oxygen-carrying capacity • Long shelf life (1 - 3 years) • No blood typing required • Reduced infection risk	• Vasoconstriction due to nitric oxide scavenging • Potential renal toxicity • Hypertension • Oxidative stress
Perfluorocarbon Emulsions (PFCs) *Fluosol*, *Oxygent*	• Synthetic compounds with high gas solubility • Dissolve oxygen physically rather than binding • Emulsified in water for intravascular use	• Dissolves large amounts of oxygen • Also transports CO_2 • Small particle size (<0.2 μm) • Completely synthetic (no biological contamination)	• Requires high inspired oxygen concentrations • Limited oxygen delivery at normal PaO_2 • Uptake by reticuloendothelial system • Flu-like symptoms
Hemoglobin Vesicles *Liposome-encapsulated Hb*, *HbV*	• Hemoglobin encapsulated in phospholipid vesicles • Mimics RBC structure and function • Isolates Hb from the sur rounding environment	• Reduced vasoactivity • Prevents nitric oxide scavenging • Maintains oxygen transport function • Cellular-scale oxygen delivery	• Complex manufacturing process • Limited stability • Potential immune response • High production costs
Stem Cell-Derived Red Blood Cells *iPSC-RBCs*, *CD34+ derived RBCs*	• Cultured from stem cells (iPSC, CD34+) • Differentiated through erythropoiesis pathway • Functionally identical to natural RBCs	• Potentially unlimited supply • Full biocompatibility • Normal oxygen carrying capacity • Customizable blood types	• Scalability challenges • Extremely high costs • Complex bioreactor requirements • Still in experimental phase

Current approaches to the development of artificial blood substitutes, with their mechanisms, advantages and limitations. Hemoglobin-based oxygen carriers (HBOCs), including polymerized hemoglobin (PolyHb), diaspirin cross-linked hemoglobin (DCLHb), and Hemopure provide high oxygen-carrying capacity, but cause vasoconstriction through nitric oxide scavenging [214]. Perfluorocarbon emulsions (PFCs), such as Fluosol and Oxygent, dissolve large amounts of oxygen, but require high inspired oxygen concentrations [212]. Hemoglobin vesicles represent promising encapsulation technology, reducing toxicity while maintaining oxygen transport function [214]. Stem cell-derived red blood cells offer a potential unlimited supply of red cells with full compatibility, but face scalability and cost challenges [221].

Patient Blood Management has caused a paradigm shift in transfusion medicine, demonstrating that proactive, evidence-based approaches can simultaneously improve patient outcomes, while reducing blood product utilization. This systematic approach exemplifies how modern medicine integrates multiple disciplines to optimize care.

Looking forward, fluid therapy will continue to evolve with advances in monitoring technology, personalized medicine, and artificial intelligence. Future directions may include real-time metabolomic monitoring (continuous assessment of cellular metabolic byproducts to guide fluid composition and timing), predictive algorithms for fluid requirements, and novel synthetic solutions designed for specific clinical scenarios.

The history of fluid therapy serves as a reminder that medical progress often comes through serendipitous discovery, careful observation and rigorous scientific testing. As we face new challenges in an aging population with complex comorbidities, the lessons learned from past successes and failures will continue to guide the development of safer and more effective fluid management strategies.

Author Declarations

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Conflicts of Interest

The author declares that there are no conflicts of interest related to any commercial entities, including those mentioned in this manuscript.

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Review Article

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Artificial Intelligence in Anesthesia, Critical Care, and Beyond: Current Applications, Future Prospects, and Limitations

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Abstract

The Artificial intelligence (AI) represents a paradigm shift in healthcare delivery, particularly in data-intensive, time-sensitive clinical specialties. Anesthesiology, intensive care medicine, and emergency medicine stand at the forefront of this technological transformation due to their reliance on continuous physiological monitoring, rapid decision-making, and complex data interpretation. Beyond acute care specialties, emerging applications extend to palliative care, pain management, and traditional East Asian medicine, demonstrating AI's versatility across diverse clinical contexts. This comprehensive narrative review synthesizes recent literature on AI applications across these specialties, providing a balanced assessment of current achievements, persistent limitations, and future research priorities. AI has demonstrated significant promise across multiple clinical domains, with applications including real-time anesthetic depth monitoring, predictive models for postoperative complications, ICU early warning systems, sepsis prediction algorithms, emergency department triage optimization, palliative care referral support, personalized pain management, and modernization of traditional medicine practices. Despite these advances, significant limitations persist, including lack of prospective validation in diverse populations, challenges in model interpretability, heterogeneity in data quality, and ongoing concerns regarding algorithmic bias and ethical implications. AI technology is positioned to augment rather than replace clinical expertise, offering enhanced precision, efficiency, and personalized patient care. However, successful implementation requires addressing fundamental challenges in model validation, regulatory approval, and clinical integration. Future progress depends critically on the development of explainable AI models, robust external validation, establishment of comprehensive regulatory frameworks, and thoughtful integration strategies that preserve essential human judgment, empathy, and the therapeutic relationship.

Keywords: Artificial intelligence; Machine learning; Hybrid AI; Monte Carlo simulation; Neural networks; Anesthesia; Intensive care; Emergency medicine; Palliative care; Pain management; Traditional Chinese medicine; Clinical decision support; Predictive analytics; Large language models; Deep learning; Healthcare automation

Introduction

Historical context and evolution of AI in medicine

The integration of artificial intelligence (AI) into healthcare represents one of the most transformative and rapidly evolving trends in modern medicine. The journey began in the 1970s with knowledge-driven systems such as MYCIN,

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an expert system developed at Stanford University that used rule-based reasoning to diagnose bacterial infections and recommend antibiotics. While MYCIN demonstrated expert-level performance, its reliance on manually encoded rules limited scalability and adaptability.

Contemporary medical AI has evolved into primarily data-driven approaches, characterized by exponential advances in computational capacity, unprecedented data availability, and sophisticated machine learning (ML) techniques that fundamentally reshape clinical practice across diverse medical disciplines. The convergence of several key factors has created an optimal environment for AI adoption: the widespread implementation of electronic health records (EHRs), the proliferation of continuous monitoring devices, advances in cloud computing infrastructure, and the development of increasingly sophisticated algorithms capable of processing complex, multimodal healthcare data.

Three paradigms of modern medical AI

Contemporary AI applications in healthcare can be categorized into three complementary paradigms, each addressing different aspects of clinical decision-making:

Knowledge-driven AI systems, exemplified by MYCIN and early expert systems, rely on explicit rule-based reasoning encoded by domain experts. While largely superseded by data-driven approaches, these systems established foundational principles for explainability and clinical integration that remain relevant today.

Data-driven AI encompasses machine learning, neural networks, deep learning, and large language models (LLMs) such as ChatGPT and Gemini. These systems learn patterns directly from data without explicit programming. Machine learning algorithms excel at risk stratification and outcome prediction using structured clinical data. Deep learning, particularly convolutional neural networks (CNNs), has revolutionized medical image interpretation, achieving expert-level performance in radiology, pathology, and ultrasound analysis. Large language models, the most recent advancement, demonstrate remarkable capabilities in natural language understanding, clinical documentation, and patient communication, though they require careful validation in medical contexts.

Probabilistic methods, including Monte Carlo simulations and Bayesian approaches, quantify uncertainty in predictions—a critical capability for clinical decision-making. These methods can model variability in vascular resistance, circulating blood volume, and intervention effects (e.g., vasopressor or fluid administration), enabling clinicians to understand prediction stability and risk distributions under different clinical scenarios.

Modern medical AI increasingly adopts a hybrid approach, integrating data-driven predictions with probabilistic uncertainty quantification and domain knowledge constraints. This synthesis addresses limitations of individual paradigms while preserving interpretability and clinical relevance.

Technical foundations: neural networks and activation functions

Understanding the technical foundations of deep learning is essential for clinical implementation. Neural networks consist of interconnected layers of artificial neurons, each performing weighted summation of inputs followed by nonlinear transformation through an activation function. The hierarchical structure of deep networks—comprising input layers, multiple hidden layers, and output layers—enables automatic feature extraction and representation learning from raw data.

Activation functions introduce essential nonlinearity that allows neural networks to model complex patterns. Historical approaches used sigmoid or hyperbolic tangent (tanh) functions, which map inputs to bounded ranges (0-1 for sigmoid, -1 to 1 for tanh). However, these functions suffer from vanishing gradient problems in deep networks. Contemporary architectures predominantly employ Rectified Linear Unit (ReLU) functions and their variants (Leaky ReLU, Parametric ReLU), which output the input directly if positive and zero (or a small negative value) otherwise. ReLU functions facilitate deeper network training, accelerate convergence, and have become the de facto standard in medical image analysis and signal processing applications. Recent theoretical work has revealed universal scaling laws governing signal propagation in deep networks with ReLU activation, providing principled guidance for architecture design.

In this review, "artificial intelligence (AI)" is used as an umbrella term encompassing three methodological categories: knowledge-driven systems (e.g., the historical MYCIN system from the 1970s which utilized rule-based reasoning), data-driven approaches (e.g., machine learning [ML], deep learning [DL], and large language models [LLMs]), and probabilistic methods (e.g., Monte Carlo simulation). The hierarchical relationship is defined such that DL is a subset of neural networks (NN), which is a subset of ML, which in turn falls under AI (DL $\subset$ NN $\subset$ ML $\subset$ AI). While contemporary medical AI predominantly relies on data-driven models, probabilistic methods serve a critical complementary role by quantifying uncertainty, facilitating the development of "Hybrid AI" frameworks essential for robust clinical decision-making.

Understanding the technical foundations of these systems is essential for clinicians. Neural networks, the backbone of modern DL, consist of input, hidden, and output layers where information processing mimics synaptic transmission.

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The activation functions within these nodes, such as the Rectified Linear Unit (ReLU) or Leaky ReLU, determine the output signal. Notably, the sigmoid activation function historically parallels the oxyhemoglobin dissociation curve—a relationship fundamental to the pulse oximetry principle (PaO_2 vs. SpO_2)—illustrating the mathematical continuity between physiological modeling and modern AI architectures.

The application of AI is particularly pertinent and promising in clinical specialties that are inherently data-rich, time-critical, and decision-intensive. Anesthesiology, intensive care medicine, and emergency medicine exemplify these characteristics, making them natural pioneers in AI integration. These specialties routinely generate vast amounts of high-frequency physiological data, require rapid decision-making under conditions of uncertainty, and benefit significantly from predictive analytics and automated monitoring systems. The unique characteristics of these specialties—including continuous patient monitoring, complex pharmacological interventions, and the need for immediate response to physiological changes—create an ideal environment for AI-driven clinical decision support.

Historically, anesthesiology was among the first medical specialties to embrace technological innovation, from the introduction of pulse oximetry and capnography to the development of sophisticated monitoring systems and drug delivery devices. This tradition of technological adoption has naturally extended to AI applications, with early implementations focusing on anesthetic depth monitoring, automated drug delivery, and perioperative risk prediction. Similarly, intensive care medicine, with its reliance on continuous monitoring and data- driven decision-making, has emerged as a fertile ground for AI applications ranging from early warning systems to predictive models for clinical deterioration.

Over the past decade, AI applications have expanded beyond acute care specialties into areas traditionally considered less amenable to technological intervention. Palliative medicine, pain management, and even traditional East Asian medicine are increasingly incorporating AI-driven approaches to enhance clinical care, optimize treatment selection, and improve patient outcomes. This expansion reflects both the maturation of AI technology and growing recognition of its potential to address complex clinical challenges across the entire spectrum of healthcare delivery.

The COVID-19 pandemic has served as a significant catalyst for AI adoption in healthcare, highlighting the critical need for predictive analytics, resource optimization, remote monitoring capabilities, and automated decision support systems. The pandemic demonstrated both the potential of AI to address large-scale healthcare challenges and the importance of robust, validated systems that can perform reliably under extreme conditions. Lessons learned during this period have informed current approaches to AI development and implementation, emphasizing the need for rigorous validation, ethical considerations, and careful integration with existing clinical workflows.

AI in Anesthesia and Perioperative Medicine

Anesthesiology is unusually well-suited to AI because it generates continuous, high-frequency physiologic waveforms, device parameters, imaging, and interventions recorded at exact times within a tightly controlled environment. These data streams enable three practical capabilities: bedside prediction and early warning, perioperative risk stratification that informs preparation and surveillance, and automation through closed-loop control of hypnosis, analgesia, and ventilation/oxygenation. In clinical use, the most effective systems pair predictions with clear action pathways or machine-executable targets, emphasize transparency and calibration, and ensure clinicians can take control instantly whenever needed. Evidence to date shows consistent improvements in process quality (e.g., time in target, fewer manual adjustments, better image acquisition) with mixed but growing signals for patient-centered outcomes (Figure 1).

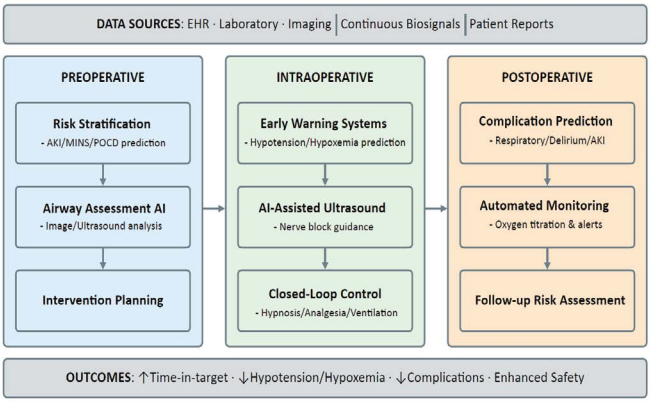

Figure 1: Integrated AI Workflow in Perioperative Anesthesia Care.

Prediction and early warning at the bedside

Intraoperative hypotension (IOH) is common and consistently linked to postoperative organ injury. Large perioperative cohorts show graded risk with both severity and duration of low mean arterial pressure (MAP). Even brief exposures below approximately 55 mmHg are associated with myocardial injury and acute kidney injury (AKI), while time spent below 60-65 mmHg also correlates with harm, supporting proactive avoidance of these ranges [1,2]. These relationships persist after risk adjustment across surgical populations, motivating bedside systems that forecast imminent IOH events, typically defined as "MAP < 65 mmHg for > 1 min in the next 5-15 min", to shift care from reactive rescue to anticipatory management.

A prominent approach is the Hypotension Prediction Index (HPI), a machine-learning (ML) model trained on high-fidelity arterial waveforms that captures subtle beat-to-beat features reflecting emerging failure of preload, afterload, contractility compensation, and produces a 0-100 risk score [3]. Prospective evidence suggests that prediction must be coupled to action. In a randomized clinical trial, integrating an HPI-based early-warning workflow with a structured hemodynamic diagnostic/treatment algorithm significantly reduced intraoperative hypotension compared to standard care, demonstrating process improvement while underscoring the need for multicenter trials powered to evaluate patient-centered outcomes [4].

Prediction is no longer only about blood pressure. Real-time ML models trained on perioperative data can warn of intraoperative hypoxemia minutes before it happens. Some systems also provide brief, case-specific explanations, such as low tidal volume or rising oxygen needs, which help clinicians understand and respond to the alert. In testing, these explanations improved the anticipation and prevention of desaturation [5]. Beyond the OR, continuous oximetry and capnography in the PACU and on surgical wards provide early warning of opioid-related respiratory depression. The multicenter PRODIGY risk prediction model uses five simple bedside variables (age, sex, opioid-naïve status, sleep-disordered breathing, heart failure) to flag high-risk patients. It has been validated against clinical and resource outcomes [6].

Important limitations remain. Model performance can decline when models are transferred to new hospitals, devices, or patient groups; recent reviews recommend multicenter validation and ongoing monitoring after deployment [7]. The standard event definition, MAP < 65 mmHg for more than 1 minute, is convenient but imperfect. Relative drops or patient-specific targets may better reflect perfusion risk and should be studied [1,2]. Most trials improve process measures (e.g., time in hypotension) rather than hard outcomes such as AKI or myocardial injury, which need larger, carefully controlled studies [2,4,7]. Finally, many waveform-based tools require an arterial line, which limits use; broader impact will likely depend on noninvasive signals or hybrid approaches [7].

Machine learning in perioperative risk stratification

Machine learning models are increasingly used to convert preoperative demographics, comorbidity profiles, laboratory data, and intraoperative signals into individualized risk estimates for major postoperative complications. Recent systematic reviews in perioperative medicine conclude that discrimination is often promising. Still, external validation, calibration reporting, and impact evaluation remain inconsistent, underscoring the need for methodologically rigorous development and validation pipelines [8].

Acute kidney injury illustrates both potential and pitfalls. Large noncardiac surgical cohorts have yielded interpretable machine learning models that achieve AUCs around 0.83-0.85 using preoperative and intraoperative features, with only modest performance loss when restricted to preoperative variables. This pattern is helpful for early counseling and optimization [9]. Calibration curves and feature attribution (e.g., age, preoperative serum creatinine, surgical duration) facilitate clinical interpretability, but multicenter external validation and clinical utility testing are required before routine adoption.

For myocardial injury after non-cardiac surgery, explainable multicenter models have outperformed traditional scores in development and internal validation; however, their performance typically drops on external datasets, highlighting the importance of transportability assessments and threshold selection tailored to local prevalence [10].

Neurocognitive outcomes are also an active area. Prospective and real-world evaluations of delirium risk models demonstrate acceptable discrimination and operational feasibility in surgical inpatients. Live clinical deployment has been associated with increased detection and changes in sedative/antipsychotic use; nevertheless, the benefits of these outcomes require further study [11].

Beyond model performance, implementation matters. A randomized clinical trial in anesthesiology investigated whether presenting clinicians with machine learning predictions improved their own risk estimates for 30-day mortality and acute kidney injury. Assistance did not significantly improve AUC for clinician predictions, emphasizing that risk models should be embedded within action pathways (e.g., prompts for troponin/creatinine surveillance, hemodynamic, or nephroprotective bundles) rather than presented in isolation [12].

Deep learning for difficult airway assessment

Deep learning (DL) systems for airway assessment aim to reduce unanticipated difficulty by converting routine preoperative data, facial photographs, ultrasound measurements, and imaging into quantitative risk estimates that complement bedside tests [13,14]. DL models trained on facial images can flag patients at risk for a poor laryngoscopic view or difficult intubation, in some cohorts, outperforming classic scores. A recent study shows these tools can run on smartphone photographs taken at the bedside, which lowers the barrier to use in the preoperative clinics [15]. Models that show which visual features drove the prediction (e.g., highlighting limited mouth opening, neck contour, or jawline cues) can help clinicians plan devices and backup strategies, rather than simply providing a "difficult/not difficult" label [16].

Beyond photographs, ultrasound adds soft-tissue

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information that simple inspection misses [17]. Prospective work shows that combining ultrasound measurements (e.g., skin-to-epiglottic distance, tongue thickness, thyromental metrics) with standard clinical tests improves discrimination for difficult laryngoscopy compared with either alone [18,19]. In small single-center studies, composite ultrasound-clinical models have reported AUCs around 0.75-0.85 with high negative predictive values (93-99%) [18,19]. Tongue thickness alone shows more variable performance (AUC 0.92 for predicting difficult laryngoscopy, 0.69 for difficult intubation; negative predictive values 76% for difficult intubation) [20].

Imaging-based approaches extend this idea. A large study trained a DL model on lateral cervical radiographs and predicted Cormack-Lehane grade 3 or 4 views with high internal performance [21]. Radiomics work has combined clinical measurements with 3D CT features to estimate the risk of difficult mask ventilation in oral and maxillofacial surgery populations [22]. Three-dimensional facial scans have also been used to model facial geometry associated with mask seal and ventilation difficulties in prospective cohorts [23].

CNN-based image segmentation for tracheal intubation

Recent advances in convolutional neural networks (CNNs) and image segmentation have enabled the development of AI-assisted systems for airway management. Tracheal intubation fundamentally relies on the rapid visual identification of laryngeal structures, including the epiglottis, vocal cords, arytenoids, and the glottic opening. From a computer vision perspective, this task can be formulated as a semantic or instance segmentation problem, in which anatomically relevant regions are identified at the pixel level.

Fully convolutional networks (FCNs) and their derivatives, such as U-Net [24] and SegNet architectures [25], have demonstrated strong performance in medical image segmentation tasks due to their ability to preserve spatial resolution while extracting hierarchical features. These architectures are particularly suitable for real-time analysis of laryngoscopic images and video streams, as they enable dense prediction without reliance on fully connected layers. In airway management, FCN-based models can be trained to segment the glottic opening and surrounding soft tissues, thereby providing objective, real-time visualization of airway anatomy during intubation attempts.

Instance segmentation techniques, such as Mask R-CNN [26], may offer additional advantages in difficult airway scenarios, where edema, tumors, secretions, or anatomical variants obscure the laryngeal view. By separating individual anatomical structures within the same class, instance-level models can support airway identification even under suboptimal visualization conditions. Such approaches align with the concept of human-in-the-loop AI, in which the system augments rather than replaces clinical judgment [27].

Important caveats remain. Most studies are single-center and use different reference standards for "difficulty," predicting a difficult laryngoscopic view (e.g., Cormack-Lehane 3-4), a difficult intubation (defined as failed or requiring multiple attempts), or difficult mask ventilation. Therefore, performance may not be consistent across different populations, devices, or teams [13,14,21]. Recent reviews recommend larger, multicenter, prospective studies with external validation, reporting of calibration and fairness across subgroups, and trials that test whether model-guided preparation reduces hypoxemia, failed first attempts, or the need for escalation to a surgical airway [14]. Until such evidence accumulates, these tools are best used as decision aids that complement a thorough airway examination and plan [17].

Deep learning-assisted ultrasound for peripheral nerve blocks

Deep learning-assisted ultrasound systems for peripheral nerve blocks utilize computer vision to highlight nerves, vessels, and relevant fascial planes on live scans, aiming to simplify view acquisition and interpretation for clinicians. In an external validation across nine block regions, an assistive overlay correctly identified target structures in most cases and was judged likely to reduce the risk of adverse events or block failure [28]. In a randomized study involving non-expert anesthetists, assistance increased the rate of acquiring an acceptable block view. It improved the correct identification of sono-anatomy compared to standard scanning [29]. A subsequent randomized crossover study suggested these benefits were still present two months after training, indicating potential support for skill retention beyond the immediate teaching period [30]. Recent scoping reviews map a rapidly growing literature and conclude that computer vision assistance can standardize scanning and accelerate learning, while emphasizing the need for robust prospective trials that link assistance to patient-centered outcomes such as block success and complications [31-33].

On the algorithmic side, multiple groups report the use of deep-learning models for nerve detection and segmentation in common block regions. Studies have demonstrated automatic localization of the interscalene brachial plexus on ultrasound [34,35] and femoral nerve segmentation with good agreement to expert annotations [36]. An evaluation compared AI-based nerve segmentation across the brachial plexus, femoral, and sciatic regions, highlighting both the promise of these tools and the need for standardized benchmarks and clinical endpoints [37]. Limitations across the literature include single-center designs, heterogeneity in probes and machines, small datasets, and a focus on process measures (acceptable

view, time to view, trainee confidence) rather than patient outcomes; generalizability and post-deployment monitoring remain priorities for future work [31-33,37].

Machine learning-assisted closed-loop control in anesthesia

Contemporary "autonomous" anesthesia is best understood as a form of supervised autonomy. Clinicians set goals and safety limits, and the software adjusts drug delivery to keep EEG-derived depth of anesthesia and nociception surrogates within target ranges [38]. Design principles emphasize robust feedback signals, conservative control rules, explicit limits and alarms, and the ability for the clinician to take over immediately [39]. Evidence syntheses of intravenous closed-loop systems suggest tighter time in target and small efficiency gains, while underlining variable bias, heterogeneity, and the need for outcome-powered trials [40].

Hypnosis–closed-loop TIVA: Randomized trials comparing BIS-guided closed-loop propofol with manual control show more time spent with BIS values of 40-60 and fewer overshoots during induction and maintenance [41]. A multicenter trial of a Bayesian controller similarly achieved better hypnosis control than manual titration [42]. Pediatric data indicate feasibility and smoother depth control in preschool children without added adverse events [43]. Early reports of dual-drug loops (propofol and remifentanil) demonstrate technical feasibility, but larger trials are needed to illustrate patient-centered benefits [44]. Overall, closed-loop TIVA improves process metrics and may reduce drug use or recovery times, yet generalizability across monitors/patient groups remains a key gap [40].

Analgesia–nociception-guided titration: ML-supported nociception monitors (e.g., Nociception Level: NOL, Analgesia Nociception Index: ANI) convert multi-signal physiology into a real-time pain surrogate, guiding intraoperative opioid dosing [45,46]. A pooled analysis of two RCTs found lower PACU pain and fewer cases of severe pain with NOL-guided fentanyl vs standard care [46]. A meta-analysis reported reduced postoperative pain and opioid consumption with NOL guidance. However, effects on postoperative nausea and vomiting and length of stay were not significant, and study results varied widely [45]. A network meta-analysis across five nociception monitors suggested monitor-guided strategies can improve perioperative analgesic use and early pain endpoints, while stressing the need for standardized protocols and outcome trials [47]. For ANI, a systematic review and meta-analysis in patients under sedation or general anesthesia reported moderate diagnostic accuracy and lower opioid use with ANI-guided care, again with considerable variation between studies [48].

Ventilation and oxygenation automation: Closed-loop ventilatory controllers adjust respiratory rate, tidal volume/pressure support, FIO_2, and sometimes PEEP to keep end-tidal CO_2 and SpO_2 within targets while limiting undue pressures/volumes. In perioperative and immediate postoperative settings, these systems have reduced the need for manual adjustments and kept patients closer to the intended gas-exchange and "lung-protective" ranges compared with clinician-set modes, without generating new safety signals [49,50]. In a randomized trial following cardiac surgery, fully automated ventilation increased the time spent in lung-protective settings, reduced severe hypoxemia, and accelerated the return to spontaneous breathing compared to conventional ventilation [51]. In an ICU randomized trial, closed-loop ventilation required fewer manual interventions and achieved more time with optimal SpO_2 and tidal volume than conventional modes over 48 hours [50]. Automated oxygen titration is maturing in parallel. In patients with acute hypoxemic respiratory failure receiving high-flow nasal oxygen, a randomized crossover trial demonstrated that closed-loop FIO_2 control increased time spent within the individualized SpO_2 range and reduced bedside workload compared to manual titration [52]. A meta-analysis reported substantially more time within prescribed SpO_2 targets and signals for less hypoxemia and lower workload with closed-loop oxygen control [53].

AI in Critical and Intensive Care Medicine

The intensive care unit (ICU) represents an optimal environment for AI applications, characterized by continuous collection of high-dimensional physiological, laboratory, and imaging data from critically ill patients who require immediate intervention for life-threatening conditions. The complexity of critical care decision-making, combined with the volume and velocity of data generation, creates unique opportunities for AI-driven clinical support systems to enhance patient care and outcomes.

Early warning systems and sepsis prediction

Biesheuvel et al. [7] outlined a comprehensive framework for AI integration in acute and intensive care, highlighting three primary domains of application: forecasting clinical deterioration, predicting sepsis onset, and optimizing resource allocation [7]. Their analysis emphasized the potential for ML systems to process vast amounts of continuously generated data to identify subtle patterns indicative of impending clinical deterioration, often hours before traditional monitoring approaches would detect changes. These early warning systems represent a paradigm shift from reactive to proactive critical care management.

Mușat et al. [54] conducted systematic reviews of machine learning (ML) in sepsis, covering both deterioration and outcome predictions [54]. They consistently reported encouraging discrimination but emphasized the heterogeneity

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of sepsis definitions, time windows, predictors, and validation strategies. Recent years have seen a shift from retrospective model development to implementation research. Adams et al. [55] reported a multisite prospective study examining associations between the deployment of an ML-based sepsis early warning system (TREWS) and improved process/outcome measures [55]. While demonstrating feasibility and some positive signals, the study also highlighted open questions about generalizability, alert fatigue, and causal attribution in real-world deployments. These findings underscore the critical importance of careful implementation strategies and ongoing monitoring when transitioning AI tools from development to clinical practice.

Diagnostic applications and risk stratification

The work by Yoon et al. [56] provided an extensive review of AI applications in critical care diagnostics, with particular emphasis on neuroimaging for traumatic brain injury and risk stratification for multi-organ failure [56]. Their analysis highlighted the superior performance of deep learning models in interpreting complex imaging studies, including computed tomography scans for intracranial hemorrhage detection and chest radiographs for pneumonia identification. These DL-driven diagnostic tools can provide rapid, accurate interpretations that support clinical decision-making, particularly in settings where immediate specialist consultation may not be available.

ARDS-focused systematic reviews by Tran et al. [57] and Yang et al. [58] have reported that ML supports diagnosis, risk stratification, and mortality prediction [57,58]. Performance depends strongly on dataset scale, feature availability, and external validation. These studies demonstrate AI's potential to identify patients at risk for developing ARDS before clinical criteria are fully met, enabling earlier intervention and potentially improved outcomes. However, the heterogeneity of ARDS definitions, variable timing of predictions, and differences in patient populations across studies limit generalizability and highlight the need for standardized approaches.

Mechanical ventilation and respiratory support

Regarding mechanical ventilation, comprehensive reviews by Ahmed et al. [59] and Jiang et al. [60] have described ML applications in ventilator management, weaning prediction, and detection of patient–ventilator asynchrony [59,60]. These efforts are clinically aligned with reducing the duration of ventilation and associated complications. ML-driven weaning prediction models analyze multiple physiological parameters, ventilator settings, and patient characteristics to identify optimal timing for extubation attempts, potentially reducing the risks of both premature and delayed extubation. Patient-ventilator asynchrony detection algorithms can identify subtle mismatches between patient effort and ventilator delivery that may escape clinical observation, enabling timely adjustments that improve comfort and potentially reduce ventilator-induced lung injury. However, these applications remain limited by heterogeneous labels, varying definitions of successful weaning, and bedside integration barriers.

Workflow optimization and clinical decision support

Saqib et al. [61] expanded the scope of AI applications in critical illness, providing a comprehensive assessment of impacts on workflow efficiency, patient monitoring, and safety outcomes [61]. Their review demonstrated that AI implementation in critical care settings can significantly reduce alarm fatigue through intelligent filtering of physiological alerts, improve medication dosing accuracy through predictive pharmacokinetic models, and enhance communication between healthcare team members through automated documentation and clinical summaries. These workflow enhancements have the potential to reduce cognitive burden on clinicians, allowing more time for direct patient care and complex decision-making.

The nursing perspective on AI in critical care, as examined by Porcellato et al. [62], revealed important insights into the practical implementation challenges and opportunities [62]. Their systematic review emphasized AI's potential to optimize nursing workload distribution, enhance patient risk monitoring, and support clinical decision-making at the bedside. The integration of AI tools into nursing workflows requires careful consideration of user interface design, alert management, and the preservation of critical thinking skills among healthcare providers. Successful implementation depends on engaging nurses early in the design process and ensuring that AI systems complement rather than complicate existing workflows.

Large language models in critical care

The emergence of large language models (LLMs), a class of deep learning-based generative AI, introduces entirely new possibilities for AI application in intensive care settings [63]. These sophisticated natural language processing systems can automate clinical documentation, provide decision support through analysis of medical literature, facilitate patient and family communication, and support medical education through interactive learning platforms. However, the implementation of LLMs in critical care requires careful validation to ensure accuracy, reliability, and appropriate integration with existing workflows. Concerns about hallucinations, outdated information, and liability must be addressed before widespread clinical adoption.

Current barriers and future directions

Despite these promising applications, substantial barriers to routine ICU-scale deployment persist. Prospective validation in diverse patient populations remains limited, with most studies conducted in single centers or specific

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patient subgroups. Transportability across different ICU environments, with varying patient populations, staffing models, and technical infrastructure, represents a significant challenge. Model interpretability remains critical for clinical acceptance, as intensivists require understanding of why a particular prediction or recommendation was generated. Governance frameworks that define roles, responsibilities, and liability for AI-assisted decisions are still evolving. Moving forward, AI should be deployed as a supervised clinical tool that augments expertise within regulatory and ethical frameworks that preserve human judgment, clinical autonomy, and the irreplaceable value of experienced intensivists in managing complex, critically ill patients.

AI in Emergency Medicine

Emergency departments (EDs) generate large volumes of clinical data, yet many high-stakes decisions must be made within minutes. In major trauma, acute coronary syndromes, and acute ischemic stroke, small delays can translate into irreversible organ injury and worse long-term function. The field's familiar shorthand—"golden hour," "time is brain," "time is myocardium"—reflects a system that is highly sensitive to technologies capable of removing avoidable latency between arrival, diagnostic clarification, and definitive treatment.

However, ED presentations are frequently undifferentiated, and diagnostic uncertainty is often greatest at the point where time pressure is most intense. In this setting, false-positive outputs risk increasing cognitive load, contributing to alert fatigue, and prompting unnecessary escalation or intervention. False-negative outputs can be more consequential still, because they may suppress urgency when it is most needed and delay time-critical care. ED-facing AI therefore needs to be assessed as a clinical intervention embedded in work: who receives the output, what thresholds trigger action, what safeguards exist, and how responsibility is assigned when recommendations are followed—or ignored.

Recent reviews have underscored both the breadth of development and the fragility of real-world translation. Farrokhi et al. [64] catalogued AI applications spanning prehospital care, emergency radiology, triage and patient classification, diagnostic and interventional support, trauma and pediatric emergency care, and outcome prediction, while emphasizing that most published work remains retrospective and that prospective trials are required to establish true clinical value [64]. Amiot et al. [65] similarly reviewed recent advances in AI and emergency medicine, balancing opportunities and challenges—illustrating how AI holds promise for improving emergency care while emphasizing the need for careful attention to explainability, bias, privacy, and validation across diverse settings [65]. Taken together, these syntheses point to a practical lesson for emergency care: workflow design often determines whether an algorithm improves timeliness without compromising safety.

A useful way to keep this problem clinically grounded is to organize ED AI by system function—that is, where in the acute pathway a tool intervenes and which delays it is meant to remove. Here, ED AI can be framed as three complementary functions: (1) front-end prioritization, (2) diagnostic acceleration, and (3) operational optimization. This structure aligns with how emergency care fails under strain: mis-prioritization at the front door, bottlenecks in high-throughput diagnostics, and throughput collapse during crowding. It also keeps attention on actionable effects—earlier recognition, earlier escalation, earlier definitive care—rather than prediction as an end in itself.

Front-end prioritization

Front-end prioritization concerns decisions closest to entry into emergency care: triage, initial clinician assessment, and (in some systems) prehospital screening. The unit of action is the individual patient. The clinical aim is to support consistent choices about who must be seen first, who can safely wait, and which time-sensitive pathways should begin before diagnostic certainty is established. Inputs are typically limited to data available at triage— vital signs, age, chief complaint, brief text, and proxies for comorbidity—because any requirement for delayed testing defeats the purpose.

Two influential studies illustrate how routinely collected triage data can support meaningful early risk stratification. Raita et al. [66], using adult ED data from the National Hospital and Ambulatory Medical Care Survey (NHAMCS, 2007–2015), trained several machine-learning models using triage-available predictors (demographics, vital signs, chief complaints, comorbidities) and compared them with a conventional approach based on Emergency Severity Index (ESI) level [66]. They evaluated outcomes that map directly to early prioritization—critical care (ICU admission or in-hospital death) and hospitalization (admission or transfer)—and reported better discrimination with machine learning than the ESI-based reference model (e.g., AUC 0.86 vs 0.74 for critical care in the deep neural network model). The implication is not that triage should be automated, but that clinically useful signals exist in early data and can help identify high-risk patients who may be embedded within apparently lower-acuity strata.

Levin et al. [67] developed an electronic triage tool ("e-triage") based on a random forest model that predicts the need for critical care, an emergency procedure, and inpatient hospitalization in parallel, then translates predicted risk into triage-level designations [67]. In a multisite retrospective study of 172,726 ED visits, e-triage showed AUC values ranging from 0.73 to 0.92 and was reported to improve identification of acute outcomes relative to ESI, particularly

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within ESI level 3—a large, heterogeneous group in many ED. When matched to the ESI distribution, e-triage identified more than 10% of ESI level 3 patients as needing up-triage; those up-triaged patients had higher rates of critical care or emergency procedure (6.2% vs 1.7%) and hospitalization (45.4% vs 18.9%). This addresses a common operational failure mode: when workload rises, heterogeneity within "middle acuity" categories can obscure time-critical illness unless reassessment is frequent and systematic.

A central question, however, is whether front-end tools change timelines and outcomes rather than only improving retrospective discrimination. A concrete example comes from a multisite quality improvement study by Hinson et al. [68] evaluating an AI-informed, outcomes-driven triage decision support system for adults presenting with chest pain [68]. At arrival, TriageGO estimates probabilities for critical care, emergency procedures, and hospital admission from variables including demographics, arrival mode, vital signs, chief complaints, and active medical problems, then recommends an acuity level. Implementation across three EDs was staggered between 2021 and 2023, and the tool replaced ESI at those sites. After adjustment, length of stay for hospitalized patients decreased (by 76.4 minutes), and time to emergency cardiovascular procedures decreased (by 205.4 minutes; cardiac catheterization by 243.2 minutes), without observed changes in 30-day mortality or 72-hour ED returns requiring hospitalization or emergency procedures. Even allowing for the limitations inherent to quality improvement designs, this study is valuable because it evaluates a triage algorithm using endpoints that matter to ED systems: time-to-procedure, throughput, and proximate safety signals.

Across these examples, the operational lesson is consistent. Front-end prioritization tools are most defensible when they do not simply add alerts, but instead tighten the mapping between early data and predetermined actions (earlier reassessment, earlier senior review, earlier pathway activation) while monitoring both over-intervention and missed deterioration.

Diagnostic acceleration

Diagnostic acceleration targets time loss in high-throughput diagnostic steps where queues, interpretation delays, and communication friction become rate-limiting. In many ED pathways, the bottleneck is not ordering or acquiring a test, but the interval from data availability to interpretation, notification, and mobilization of the team capable of definitive treatment. Imaging-driven workflows are a natural focus because time-critical conditions often require CT or CT angiography, and because rapid benefit depends on converting findings into coordinated action.

Acute ischemic stroke due to large vessel occlusion (LVO) has become a leading implementation target because the workflow has discrete, measurable milestones and clear time dependence. Martinez-Gutierrez et al. [69] conducted a cluster randomised stepped-wedge clinical trial across four comprehensive stroke centers (January 2021 to February 2022) assessing automated CT angiogram interpretation coupled with secure group messaging [69]. The intervention produced real-time alerts to clinicians and radiologists within minutes of CT completion. Among included patients treated with thrombectomy, implementation was associated with a reduction in door-to-groin time by 11.2 minutes (95% CI −18.22 to −4.2) and a reduction in time from CT initiation to endovascular therapy start by 9.8 minutes (95% CI −16.9 to −2.6), with no differences in IV thrombolysis times or hospital length of stay. The mechanism is clinically intelligible: earlier notification advances team mobilization and compresses communication delays that often sit between imaging and procedure.

This example also clarifies what "diagnostic AI" must include to matter in emergency care. Detection alone is insufficient if outputs are not routed to the responsible team, if thresholds are poorly calibrated to local prevalence, or if the tool disrupts the radiology–ED interface. Reviews focused on emergency imaging highlight both the promise of rapid interpretation support and the persistent implementation challenges—bias, privacy, and the need for extensive validation across institutions and patient groups. For diagnostic acceleration, therefore, the key evaluation endpoints are not limited to sensitivity or AUC, but include time-to-notification, time-to-team activation, time-to-definitive intervention, and the downstream consequences of false alarms (avoidable mobilization) and misses (avoidable delay).

Operational optimization

Operational optimization addresses system-level delays driven by congestion, crowding, and downstream capacity constraints. Even when diagnoses are recognized promptly and pathways are activated appropriately, definitive care can be delayed by boarding, bed shortages, imaging queues, and staffing mismatches. Operational AI tools therefore focus on forecasting and resource allocation: predicting near-term arrivals and acuity mix, anticipating bottlenecks, estimating admission likelihood early enough to trigger bed management, and supporting staffing or space adjustments intended to stabilize flow.

Here, the evidence base is expanding, but also uneven. Farimani et al. [70] systematically reviewed models predicting ED length of stay and identified substantial heterogeneity, with common shortcomings in reporting and methodological quality [70]. Among included studies, only a minority externally validated models, and several recurrent issues were noted—predictor selection practices, sample size considerations, reproducibility, handling of missing data,

and problematic dichotomization of continuous variables. These limitations matter because operational predictions are highly sensitive to local practice patterns (testing thresholds, admission policies, staffing), and transport poorly across institutions without careful recalibration and monitoring.

Demand forecasting faces similar challenges. Blanco et al. [71] reviewed AI-based models for hospital ED demand forecasting (2019–2025) and found that machine learning and deep learning methods often outperform classical time series approaches, particularly when external variables—weather, air quality, and calendar effects—are incorporated [71]. Yet the same review noted limited external validation and relatively infrequent use of interpretability methods, both of which constrain confident deployment. The consequence is that operational tools must be treated as part of governance and planning, not simply as technical add-ons: forecasts need explicit decision hooks (e.g., staffing triggers, surge bed activation thresholds) and a process for auditing whether actions actually reduce waiting, boarding, or time-to-critical intervention.

Across all three functions, one requirement is constant: ED AI must be integrated into real work with clear accountability. Farrokhi et al. [65] emphasized that much of the field remains retrospective and that prospective trials are essential to establish value in emergency settings [65]. Function-based framing can help design those evaluations. Front-end prioritization should be studied using under-triage, time-to-senior review, time-to-pathway activation, and safety outcomes that capture over-intervention as well as missed deterioration. Diagnostic acceleration should be evaluated with pathway-relevant time endpoints (scan-to-notification, door-to-procedure) and measures of workflow burden (false alerts, unnecessary mobilization). Operational optimization should be judged on avoidable waiting and maintenance of access for time-critical patients under strain, rather than on predictive accuracy alone.

Finally, implementation requires continuous surveillance: performance drift monitoring, auditing of alerts and actions, and periodic recalibration as case mix, staffing, and processes change. Without these controls, ED AI is vulnerable to distribution shift and to subtle harm through misplaced confidence. Under appropriate governance, however, AI can contribute to the ED's core objective: timely definitive care delivered safely in an environment defined by uncertainty and constraint.

AI in Palliative Care

Palliative care, traditionally characterized by nuanced clinical judgment, empathetic communication, and individualized approaches to complex psychosocial needs, represents an emerging frontier for machine learning application. While the integration of technology in this humanistic specialty requires careful consideration of ethical implications and preservation of the therapeutic relationship, machine learning tools are beginning to demonstrate significant potential in supporting clinicians and improving patient outcomes.

Prognostic modeling and identification of needs

Wilson et al. [72] conducted a landmark randomized clinical trial examining the effect of a machine learning-based decision support tool on palliative care referral patterns in hospitalized patients [72]. Their study demonstrated that the ML-driven system, which analyzed multiple data points including diagnosis, prognosis, functional status, symptoms, and healthcare utilization patterns, resulted in a statistically significant increase in appropriate referrals, earlier intervention, and improved patient and family satisfaction. This proactive approach addresses the longstanding challenge of delayed palliative care referrals, ensuring that patients receive symptom management and goal-concordant care earlier in their disease trajectory.

Quantitative comparison of machine learning models with traditional prognostic indices

Traditional prognostic tools in palliative care, such as the Palliative Prognostic Index (PPI) and Palliative Performance Scale (PPS), have demonstrated moderate discriminative ability for survival prediction. Stone et al. [73] reported that for 3-week survival prediction, PPS alone achieved an area under the receiver operating characteristic curve (AUROC) of approximately 0.71, while a simplified PPI incorporating PPS components achieved an AUROC of 0.87 [73]. For 6-week survival prediction, PPS demonstrated an AUROC of approximately 0.69, compared to 0.73 for simplified PPI. While these tools provide valuable clinical guidance, their reliance on single-time-point assessments limits their ability to capture disease trajectory dynamics.

Machine learning approaches that integrate longitudinal data demonstrate superior prognostic accuracy. Huang et al. [74] developed models incorporating actigraphy data (objective physical activity monitoring) alongside traditional clinical variables [74]. In their prospective validation, baseline Karnofsky Performance Status (KPS) achieved an AUROC of 0.833, while PPI demonstrated an AUROC of 0.615. Actigraphy data alone substantially improved discrimination to 0.893, and the combination of actigraphy with clinical variables achieved an AUROC of 0.924. This substantial improvement reflects machine learning's capacity to model temporal dynamics and complex nonlinear interactions that static indices cannot capture. Such enhanced accuracy enables earlier and more confident advance care planning discussions, ensuring that interventions align with patients' values and goals. However, the communication of ML-generated prognostic information requires sensitivity and

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skill, ensuring that predictions are presented as ranges with appropriate uncertainty quantification and used to empower rather than distress patients.

Symptom management and communication support

The bibliometric analysis conducted by Pan et al. [75] revealed emerging research hotspots and trends in machine learning applications for palliative care [75]. Key areas of development include symptom assessment and management systems that continuously monitor patient-reported symptoms and recommend personalized interventions. Deep learning algorithms analyzing voice biomarkers or facial expressions can detect pain or distress in patients unable to communicate verbally, enabling more effective symptom control.

Depression and psychological distress detection

Depression represents one of the most prevalent and undertreated symptoms in palliative care populations, yet physical frailty, fatigue, and disease burden may limit patients' ability to articulate emotional suffering. Deep learning-based analysis of facial expressions, gaze behavior, head movements, and Facial Action Coding System (FACS) features has emerged as a promising approach for detecting and monitoring depressive states.

Studies using video-recorded clinical interviews have demonstrated that deep learning models trained on facial and behavioral features can discriminate between depressed and non-depressed individuals with high accuracy. Facial expression analysis using long short-term memory (LSTM) neural networks has achieved classification accuracy of approximately 91.7% and F1-scores of 88.9% in detecting depressive states [76]. Multimodal approaches integrating facial analysis with voice biomarkers and linguistic patterns show even greater potential, with some systems demonstrating sensitivity and specificity exceeding 80% for major depressive disorder detection [77]. Patient Health Questionnaire (PHQ) score prediction using machine learning has achieved mean absolute errors of approximately 3.7 points, enabling continuous monitoring without repeated questionnaire administration [78].

Clinical implementation of these technologies requires careful consideration of contextual factors that may affect model performance, including cultural differences in emotional expression, effects of sedation or delirium, and fatigue-related changes in facial appearance. These systems should complement rather than replace clinical assessment, serving as screening tools that prompt comprehensive evaluation when concerning patterns are detected.

Large language models in palliative care communication

Large language models represent a distinct application domain, offering support for clinical communication and patient education. These systems can help clinicians prepare for difficult conversations by generating empathetic language frameworks for breaking bad news, simulating patient interactions for communication skills training, and creating personalized educational materials that explain complex medical concepts in accessible language tailored to individual health literacy levels. Furthermore, AI-driven bereavement support platforms can provide personalized resources and follow-up for grieving families, extending the continuum of care beyond the patient's death.

Ethical considerations and future outlook

The implementation of machine learning and AI technologies in palliative care requires rigorous attention to ethical considerations, including patient autonomy, data privacy protection, algorithmic transparency, cultural sensitivity in emotional expression interpretation, and the preservation of human connection in end-of-life care. There is a risk that reliance on algorithmic predictions could inadvertently lead to the "medicalization" of dying, introduce bias in resource allocation decisions, or create pressure for prognostic certainty that is incompatible with the inherent uncertainty of end-of-life trajectories.

Success depends on designing systems that augment rather than replace human judgment and empathy, ensuring that technology enhances rather than diminishes the therapeutic relationship between patients, families, and healthcare providers. Machine learning models should be presented as decision support tools that provide additional information to inform clinical judgment, not as definitive answers that dictate care decisions. Future research must focus on prospective validation in diverse cultural contexts, assessment of impact on patient-reported outcomes and quality of life, and ensuring alignment with the core values of palliative medicine: relieving suffering, honoring patient autonomy, and supporting dignity throughout the dying process.

AI in Pain Management

The management of chronic pain remains one of the most complex challenges in contemporary medicine, requiring integration of biological, psychological, and social dimensions. AI offers an increasingly powerful means of addressing this complexity by analyzing multimodal data, revealing hidden patterns, and generating individualized predictions that extend beyond the scope of conventional clinical reasoning. Recent advances in machine learning, deep learning, and natural language processing have positioned AI as a transformative tool in pain medicine, capable of enhancing assessment accuracy, guiding treatment decisions, and improving long-term outcomes.

Zhang et al. [79] conducted a comprehensive scoping review encompassing thirty studies that explored AI-based

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interventions for pain assessment and management [79]. Their analysis demonstrated that algorithms using facial recognition, thermography, data mining, and natural language processing could identify pain with remarkable precision, even in non-verbal or cognitively impaired patients. Deep learning approaches analyzing facial expressions achieved diagnostic accuracies exceeding 90%, while text-based classifiers reliably detected pain documentation within electronic health records. Other models integrated imaging and clinical data to predict postoperative or chronic pain trajectories, such as the development of persistent pain following breast surgery or microvascular decompression. Mobile-health applications that applied adaptive algorithms to deliver behavioral feedback improved self-management and functional outcomes among individuals with chronic back pain.

Complementary evidence is provided by Lo Bianco et al. [80], who examined the educational and communicative potential of generative AI in chronic opioid therapy [80]. In their cross-model assessment, large language models such as GPT-4 produced highly reliable and comprehensible responses to common patient inquiries about long-term opioid use, including addiction risk, tapering, and management of adverse effects. The study underscored that AI can serve as a valuable adjunct to patient education by offering accessible, empathetic, and evidence-based explanations. However, it also cautioned that technical accuracy and contextual nuance diminish when AI systems address complex pharmacological or individualized topics, reinforcing the necessity of clinical oversight and ongoing model refinement.

Synthesizing evidence from both studies, AI currently contributes to six interrelated domains of pain management: chronic pain phenotyping; personalized treatment recommendation; opioid risk assessment; real-time pain monitoring; predictive modeling of treatment response; and integrated care coordination. Despite encouraging results, implementation remains limited by the subjective nature of pain reporting, heterogeneity of datasets, and ethical concerns about privacy, transparency, and algorithmic bias. Most current models are trained on small, homogeneous samples, restricting generalizability.

AI in Traditional and East Asian Medicine

The convergence of artificial intelligence (AI) and traditional East Asian medicine (TEAM) represents a remarkable synthesis of empirical wisdom and computational innovation. By translating the qualitative insights of traditional practices into quantifiable, data-driven frameworks, AI provides new means to modernize diagnostic systems, validate pharmacological mechanisms, and design personalized interventions that bridge ancient and modern paradigms (Figure 2).

Li et al. [81] demonstrated how AI has transformed multi-

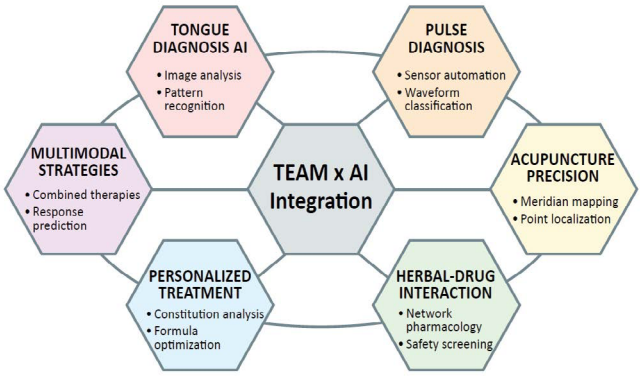

Figure 2: AI Applica7ons in Tradi7onal and East Asian Medicine.

metabolite–multi-target modeling in herbal pharmacology [81]. Traditional Chinese Medicine (TCM) relies on the synergistic interaction of multiple active compounds, yet such complexity historically limited mechanistic elucidation. Through multi-omics integration, deep learning, and cross-modal data fusion, AI now enables predictive modeling of compound–target networks, identification of synergistic bioactive components, and simulation of pharmacokinetic trajectories. These approaches surpass traditional reductionist methods, offering a systems-level understanding of polypharmacology while preserving TCM's holistic framework.

Zhou et al. [82] expanded this technological foundation to industrial modernization of the TCM sector [82]. They emphasized AI's role in standardization, quality assurance, and manufacturing optimization, addressing long-standing issues such as variability in raw materials and lack of reproducible extraction standards. Machine learning and computer vision tools enable automated quality grading, adulterant detection, and real-time process control, thereby aligning TCM production with international pharmaceutical norms.

The application of AI to acupuncture represents another frontier where computational precision meets clinical heritage. Wang et al. [83] described AI-directed acupuncture, in which data-mining algorithms such as the Apriori association rule reveal effective acupoint combinations for complex diseases, transforming empirical prescriptions into statistically validated treatment patterns [83]. Computer-vision systems record and analyze needle manipulation techniques, preserving expert craftsmanship and enhancing reproducibility in education. Furthermore, machine-learning models predicting treatment response can guide patient selection and optimize therapy parameters. Complementing these mechanistic and clinical perspectives, Zhou et al. [82] conducted a bibliometric analysis quantifying the global evolution of AI-acupuncture research, identifying exponential growth and dominant methodologies like deep learning [82].

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Song et al. [84] assessed AI empowering TCM through extensive bibliometric analysis spanning 2004-2023, revealing exponential research growth particularly after 2019, with the United States and China as leading contributors and Harvard University as the most prolific institution [84]. Machine learning and deep learning emerged as dominant methodologies, reflecting the field's transition from traditional knowledge-driven to data-intensive computational approaches. Key application domains include AI-integrated TCM databases (TCMBank, ETCM v2.0, BATMAN-TCM 2.0) enabling target discovery and herb-drug interaction screening; ensemble learning and AlphaFold-based structure prediction for TCM compound activity; constitutional analysis and personalized diagnosis; pulse diagnosis automation; tongue diagnosis using computer vision; and meridian mapping with acupoint localization. Challenges include data heterogeneity, inconsistent curation standards, limited model interpretability, and the need for cross-disciplinary collaboration to align computational outputs with TEAM principles.

The integration of AI into TEAM holds particular relevance for anesthesiology and perioperative care. Traditional herbal formulations used in East Asian populations may interact with anesthetic agents, influence coagulation status, or affect perioperative hemodynamics. AI-driven herb-drug interaction databases can alert clinicians to potential risks during preoperative assessment. Additionally, AI-enhanced constitutional analysis and pulse diagnosis may complement Western risk stratification by capturing patient-specific vulnerabilities not readily apparent through conventional assessment. Pain management represents another intersection, where acupuncture guided by AI-derived acupoint selection algorithms could offer adjunctive analgesia in the perioperative period, potentially reducing opioid requirements. However, clinical integration requires rigorous validation of these tools in diverse populations and healthcare settings, ensuring that they augment rather than complicate existing perioperative care pathways.

Current Limitations and Challenges

Despite the promising applications of AI across anesthesia, critical care, emergency medicine, palliative care, pain management, and traditional medicine, significant limitations constrain widespread clinical implementation. These challenges span technical, methodological, regulatory, and ethical domains, requiring coordinated efforts across multiple stakeholders to address (Figure 3).

Lack of prospective validation and external validation

The majority of AI models in medical literature are developed and validated using retrospective data from single institutions. While retrospective studies can demonstrate proof-of-concept and identify promising approaches, they are inherently limited by selection bias, missing data, and the inability to assess real-world clinical impact. External validation—testing models on data from different hospitals, patient populations, and healthcare systems—remains uncommon, yet it is essential for demonstrating generalizability. Models that perform excellently in development cohorts often show significant performance degradation when applied to external datasets due to differences in patient demographics, disease severity, clinical workflows, and data collection practices. Prospective validation studies, particularly randomized controlled trials that compare AI-assisted care with standard practice, are necessary to establish clinical utility and cost-effectiveness before widespread adoption.

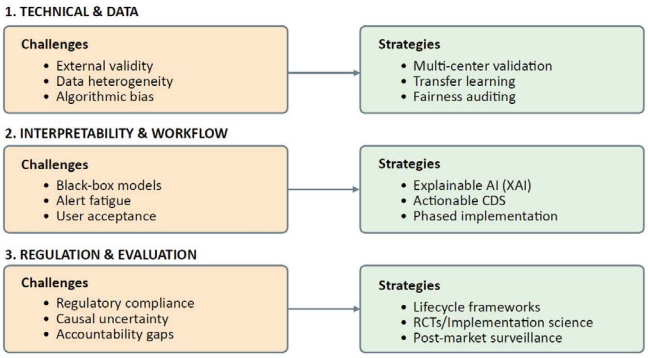

Figure 3: Challenges and Solu7ons for Clinical AI Implementation.

Model interpretability and explainability

Many high-performing AI models, particularly deep neural networks, function as "black boxes" that provide predictions without transparent explanations of their reasoning. While techniques such as attention mechanisms, saliency maps, and SHAP (SHapley Additive exPlanations) values offer some insight into model decision-making, they often fall short of the level of explanation required for clinical acceptance and regulatory approval. Clinicians need to understand not only what a model predicts but why it made that prediction, particularly when recommendations diverge from clinical judgment or when outcomes are adverse. Explainable AI (XAI) remains an active research area, with ongoing efforts to develop models that balance predictive performance with interpretability.

Data quality and availability

AI model performance is fundamentally dependent on the quality, completeness, and representativeness of training data. Electronic health records, the primary data source for many medical AI applications, contain numerous quality issues including missing values, inconsistent coding practices, temporal misalignment, and documentation variability across providers. Laboratory values may be missing-not-at-random,

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introducing bias when models impute or exclude these cases. Physiological waveforms from monitoring devices are susceptible to artifact, sensor malfunction, and calibration drift. Furthermore, available datasets often underrepresent certain demographic groups, socioeconomic strata, and geographic regions, raising concerns about algorithmic bias and health equity. The development of large, diverse, high-quality datasets with standardized formats and annotation remains a critical priority.

Algorithmic bias and health equity

AI models can perpetuate and amplify existing healthcare disparities if training data reflect historical biases in access to care, diagnostic practices, or treatment decisions. For example, models trained predominantly on data from academic medical centers may perform poorly in community hospitals or resource-limited settings. Race-based corrections in clinical algorithms have been criticized for reinforcing inequities; AI models that learn from such data may inadvertently incorporate these biases. Ensuring fairness requires deliberate attention to dataset composition, evaluation of model performance across demographic subgroups, and ongoing monitoring after deployment to detect and mitigate disparate impacts. The development of fairness-aware ML algorithms that explicitly optimize for equitable performance across protected groups represents an important research direction.

Regulatory and approval pathways

AI-based medical devices are regulated as Software as a Medical Device (SaMD) by agencies such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA). However, regulatory frameworks designed for traditional medical devices may not adequately address the unique characteristics of AI systems, including their ability to learn and evolve over time, their dependence on data infrastructure, and their potential for performance drift. The FDA has proposed a framework for regulating adaptive AI, but implementation details remain under development. Clear regulatory pathways that balance innovation with patient safety, define requirements for validation and post-market surveillance, and establish standards for algorithm transparency are essential for responsible AI deployment.

Clinical integration and workflow challenges

Successful AI implementation requires more than technical performance; it demands thoughtful integration into clinical workflows that enhances rather than disrupts care delivery. Poorly designed interfaces, excessive alerts, and lack of integration with electronic health record systems can lead to alert fatigue and user frustration, ultimately causing clinicians to ignore or override AI recommendations. The "human-in-the-loop" principle, ensuring that AI serves as a decision support tool rather than an autonomous agent, is critical for maintaining clinical judgment and accountability. Implementation science research examining barriers and facilitators of AI adoption, user experience design, and change management strategies will be essential for translating promising technologies into routine clinical practice.

Future Directions and Research Priorities (Figure 4)

Advancing AI applications in healthcare requires coordinated efforts across multiple domains. Key research priorities include:

Development of explainable AI models

Future AI systems must provide transparent, interpretable explanations for their predictions and recommendations. Research should focus on developing inherently interpretable model architectures, improving post-hoc explanation techniques, and establishing standards for what constitutes adequate explanation in clinical contexts. Hybrid approaches that combine interpretable models with deep learning components may offer optimal trade-offs between performance and explainability.

Prospective validation and implementation research

Randomized controlled trials comparing AI-assisted care with standard practice are essential for demonstrating clinical utility. Beyond efficacy trials, implementation science research examining real-world adoption barriers, user acceptance, workflow integration, and long-term sustainability will inform successful deployment strategies. Pragmatic trial designs that allow for model updates and adaptation during the study period may better reflect real-world conditions than traditional RCT designs.

Regulatory and Ethical Considerations

The deployment of AI in healthcare raises complex regulatory and ethical questions that must be addressed through thoughtful policy development, stakeholder engagement, and ongoing dialogue.

Regulatory frameworks for adaptive AI

Traditional regulatory pathways assume that medical devices remain static after approval. AI systems that continuously learn and adapt challenge this assumption, requiring new frameworks that allow for iterative improvement while maintaining safety and efficacy standards. The FDA's proposed approach for predetermined change control plans (PCCPs) represents one model, allowing manufacturers to specify in advance how algorithms may be modified and under what conditions re-review is required. However, implementation details, including thresholds for acceptable performance drift and requirements for post-market surveillance, remain under development.

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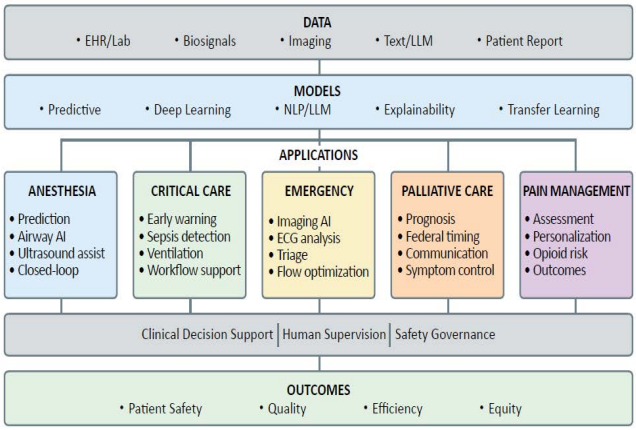

Figure 4: Hierarchical Framework of AI Integration Across Medical Specialties.

Liability and accountability

When AI systems contribute to medical decisions, questions of liability arise: Who is responsible when an AI-assisted decision results in patient harm—the clinician who relied on the recommendation, the institution that deployed the system, or the developer who created the algorithm? Legal frameworks must evolve to address these questions while preserving incentives for innovation and ensuring that patients have recourse in cases of injury. The concept of "AI as a medical device" provides one framework, but additional clarity is needed regarding the standard of care for AI-assisted decision-making.

Data privacy and security

AI systems require large datasets for training and validation, raising concerns about patient privacy and data security. While regulations such as HIPAA in the United States and GDPR in Europe provide frameworks for protecting health information, the use of data for AI development—particularly when data is shared across institutions or with commercial entities—requires careful attention to consent, de-identification, and data governance. Federated learning and differential privacy techniques offer promising approaches to enable collaborative model development while protecting individual privacy.

Informed consent and patient autonomy

Patients have the right to know when AI systems are involved in their care and to understand how these systems may influence clinical decisions. Informed consent processes should disclose AI involvement, explain its role in decision-making, and ensure that patients can opt out if they choose. The level of detail required for adequate disclosure—ranging from general notification of AI use to detailed explanations of specific algorithms—remains an area of active ethical debate.

Equity and access

As AI technologies become integral to high-quality care, ensuring equitable access becomes an ethical imperative. AI systems that require expensive infrastructure, specialized training, or proprietary data may exacerbate existing disparities between well-resourced and under-resourced healthcare settings. Policy interventions, including open-source models, infrastructure support for safety-net hospitals, and training programs for diverse healthcare workforces, will be necessary to prevent AI from widening the equity gap.

Clinical Implementation Strategies

Successful translation of AI from research to clinical practice requires deliberate implementation strategies that address technical, organizational, and human factors.

Stakeholder engagement

Early and ongoing engagement with clinicians, nurses, patients, administrators, and IT personnel is essential for understanding needs, addressing concerns, and building support for AI adoption. Co-design approaches that involve end-users throughout the development process can ensure that systems align with clinical workflows and address real-world needs.

Pilot testing and iterative refinement

Deploying AI systems initially in controlled pilot settings allows for identification and resolution of technical issues, workflow disruptions, and usability problems before widespread rollout. Iterative refinement based on user feedback and performance monitoring can improve system design and increase user acceptance.

Training and education

Clinicians require training not only in how to use AI systems but also in understanding their capabilities and limitations, interpreting predictions, and maintaining critical thinking skills. Medical education curricula should incorporate AI literacy, including basic concepts in machine learning, interpretation of algorithmic outputs, and ethical considerations in AI-assisted decision-making.

Continuous monitoring and quality improvement

Post-deployment monitoring is essential for detecting performance drift, identifying unintended consequences, and ensuring ongoing safety and effectiveness. Quality improvement frameworks should incorporate AI performance metrics, user satisfaction assessments, and patient outcome measures. Mechanisms for rapid response when problems are detected—including the ability to temporarily disable systems while issues are addressed—should be established before deployment.

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Conclusion

Artificial intelligence represents a transformative technology with significant potential to enhance healthcare delivery across anesthesiology, critical care, emergency medicine, palliative care, pain management, and traditional medicine. Current applications demonstrate AI's capacity to process vast amounts of data, identify subtle patterns, predict clinical outcomes, and support complex decision-making. From real-time intraoperative monitoring to personalized pain management and modernization of traditional medical practices, AI is expanding the boundaries of what is clinically possible.

However, realizing this potential requires addressing fundamental challenges in validation, interpretability, data quality, algorithmic bias, and clinical integration. The path forward demands rigorous prospective studies that demonstrate not only technical performance but also meaningful improvements in patient outcomes. Regulatory frameworks must evolve to accommodate the unique characteristics of AI systems while maintaining high standards for safety and efficacy. Ethical considerations—including equity, privacy, consent, and accountability—must be integrated into every stage of AI development and deployment.

Most importantly, the successful integration of AI into healthcare depends on maintaining the essential human elements of medicine: clinical judgment, empathy, compassion, critical thinking, and the therapeutic relationship between patients and providers. AI should augment rather than replace these irreplaceable human capabilities, serving as a tool that enhances clinicians' ability to provide personalized, evidence-based, compassionate care. The future of AI in medicine lies not in autonomous systems that operate independently of human oversight but in thoughtfully designed collaborative frameworks that combine the pattern recognition and computational power of AI with the wisdom, ethical judgment, and human connection that define excellent clinical care.

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Online Access to Selected Publications

Book-1

目を閉じるその瞬間に―麻酔科医の真実とその物語．山蔭道明編著，蒼木　怜著．中西印刷(株)，札幌 2025（Kindle Direct Publishing）（written in Japanese） 1

Book-2

こだわる神経ブロック「頭頸部・体幹」．山蔭道明監修，澤田敦史・村木真美編．総合医学社，東京．2026（written in Japanese） 2

Book-3

いまさら聞けない麻酔科の疑問108（第2版）．山蔭道明監修，平田直之・枝長充隆編．文光堂，東京．2026（written in Japanese） 3

Book-4

必携：麻酔科初期研修マニュアル（改訂第4版）．山蔭道明監修，吉川裕介編．中外医学社，東京．2026（written in Japanese） 4

Book-5

体温管理：初心者からベテランまで（仮題）．山蔭道明監修，立花俊祐編．中外医学社，東京．2026（written in Japanese） 5

Review-1

酒井　渉，茶木友浩，小笠原裕樹，名和由布子，枝長充隆，山蔭道明：新生児心臓血管手術におけつ血液粘弾性検査を用いた輸血戦略．Cardiovasc Anesth 2025; 29(1): 13-9.（written in Japanese） 6

Review-2

Yamakage M: The evolution and global impact of pulse oximetry: from innovation to standard of care - a comprehensive review for anesthesiologists and critical care physicians. Anesth Crit Care 2025; 7(4): 122-32. 7

Review-3

Yamakage M: Remimazolam: Five years of clinical experience since its first-in-world approval in Japan. Open J Anesthesiol 2025; 15(12): 273-93. 8

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Review-4
Yamakage M: Role of anesthesiologists in disaster medicine: lessons from Japan and future perspectives. Open J Anesthesiol 2025; 15(12): 294-316.

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Review-5
Yamakage M: Historical evolution of fluid therapy and contemporary challenges: from intravenous injection to artificial blood. Open J Anesthesiol 2025; 15(12): 326-69.

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Review-6
Edanaga M, Sato T, Yamakage M: The current status and future perspectives of transfusion products in Japan. J Anesth, published online

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Review-7
Yamakage M: Sustainable anesthesiology: evidence-based strategies for environmental stewardship in preoperative care. J Anesth, published online

12

Review-8
Yamakage M, et al: Artificial intelligence in anesthesia, critical care, and beyond: current applications, future prospects, and limitations. Anesth Crit Care, published online

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Our department will celebrate its 70th anniversary in 2027.
In conjunction with this milestone, we will host the 30th Annual Meeting of the Japanese Society for Medical Gas, which is planned to be held concurrently.
We sincerely look forward to welcoming you again on this special occasion.