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PHARMACIST-LED PERIOPERATIVE ANTIMICROBIAL STEWARDSHIP AND SURGICAL SITE INFECTION REDUCTION

ENTSAR OWAID ALANAZI[1*], HANAN KAMAL ALSHARABI[2], FAIROZ ABDULRAHMAN DARWISH[3]

[1]SENIOR REGISTRAR OF FAMILY MEDICINE & REGIONAL INFECTIONS CONTROL DEPARTMENT, PUBLIC HEALTH AUTHORITY, NORTHERN BORDER BRANCH, ARAR, SAUDI ARABIA
[2]PHARMACIST, PHARMACY DEPARTMENT, ROYAL COMMISSION YANBU HOSPITAL, YANBU, SAUDI ARABIA
[3]PHARMACIST, PHARMACY DEPARTMENT, ROYAL COMMISSION MEDICAL HOSPITAL, YANBU INDUSTRIAL CITY

Abstract
Surgical site infections (SSIs) represent a significant global burden, leading to substantial patient morbidity, mortality, and staggering economic costs on healthcare systems worldwide. Traditional approaches to surgical antimicrobial prophylaxis (SAP), while foundational to modern surgery, are frequently suboptimal in their application and contribute to the escalating crisis of antimicrobial resistance (AMR). This review synthesizes the extensive body of evidence supporting a targeted, high-impact model of care: pharmacist-led perioperative antimicrobial stewardship (AMS). This model is predicated on the clinical pharmacist's unique and profound expertise in clinical pharmacology, pharmacokinetics, pharmacodynamics, and medication systems to optimize every critical facet of SAP, from agent selection to discontinuation. Central to the success of this model is the synergistic and indispensable partnership between the clinical pharmacist and the infection prevention and control (IPC) team. IPC surveillance data—including SSI rates, pathogen trends, and local antibiograms—provides the critical feedback loop that informs, validates, and continuously refines pharmacist-led interventions, creating a dynamic engine for quality improvement. A robust and growing body of literature, including systematic reviews and meta-analyses, demonstrates that this collaborative approach significantly improves adherence to evidence-based guidelines for antimicrobial selection, timing, and duration; substantially reduces SSI rates; decreases overall antimicrobial consumption and associated healthcare costs; and critically mitigates the selective pressure driving AMR . The integration of a dedicated clinical pharmacist into the perioperative workflow, working in close collaboration with IPC, is therefore no longer a niche or optional service but a cornerstone of modern, safe, and effective surgical care. This review provides a comprehensive, evidence-based roadmap for its scientific rationale, practical implementation, and systematic evaluation.

Key words: Pharmacist-led; Perioperative; Antimicrobials; Stewardship; Surgical Site; Infection Reduction.

1. INTRODUCTION: THE IMPERATIVE FOR A NEW STANDARD IN SURGICAL PROPHYLAXIS

1.1. The Persistent Challenge of Surgical Site Infections (SSIs)

Despite decades of advances in surgical technique, sterile processing, and operating room environments, surgical site infections (SSIs) remain one of the most common and devastating healthcare-associated infections (HAIs) globally . They represent a significant epidemiological burden, threatening the lives of millions of patients each year and undermining the benefits of surgical intervention . The World Health Organization (WHO) identifies SSIs as the most frequently investigated type of HAI in low- and middle-income countries, affecting up to a third of patients who undergo surgery . In Africa, for instance, as many as 20% of women who have a caesarean section develop a wound infection, compromising their health and their ability to care for their newborns [1].

This challenge is not confined to resource-limited settings. In high-income countries like the United States, SSIs are the second most common type of HAI and were associated with an estimated 110,800 inpatient surgeries in 2015 alone . The overall incidence in the U.S. is approximately 1% to 3%, but this figure belies the significant variation based on procedure type and patient risk factors [2[. The clinical consequences for patients are severe, encompassing prolonged and painful recovery, hospital readmission, the need for additional surgical procedures or intensive care, and a two- to eleven-fold increase in the risk of mortality . SSIs are formally defined by the Centers for Disease Control and Prevention (CDC) as infections occurring at or near the surgical incision within 30 to 90 days of the procedure and are classified by depth into superficial incisional, deep incisional, and organ/space categories [3].

The economic burden of SSIs on global healthcare systems is profound. In the United States, these preventable infections are responsible for more than 400,000 additional hospital days and an annual excess cost of US$900 million . SSIs are the most costly type of HAI, with an estimated annual cost of $3.3 billion in the U.S. alone . This immense financial strain, coupled with the significant patient morbidity and mortality, creates a powerful imperative to optimize every available preventive strategy [4].

1.2. Surgical Antimicrobial Prophylaxis (SAP): A Double-Edged Sword

Surgical antimicrobial prophylaxis (SAP) is the administration of antibiotics before surgery to prevent SSIs . It is a cornerstone of modern surgical practice and one of the most effective interventions for reducing postoperative infectious complications. The fundamental principle of SAP is to achieve bactericidal concentrations of an appropriate antimicrobial agent in the serum and, most critically, in the tissues at the surgical site at the moment of incision . This ensures that any bacteria introduced into the wound during the procedure are swiftly eradicated before they can establish a clinical infection . When executed correctly, SAP can reduce the risk of SSI by as much as 75% [5].

However, the widespread use of SAP presents a classic double-edged sword. While essential for preventing immediate patient harm, SAP is a major driver of antimicrobial consumption within hospitals and, by extension, a significant contributor to the global crisis of antimicrobial resistance (AMR) . The development and spread of resistance is a natural evolutionary process, but it is massively accelerated by the selective pressure exerted by antimicrobial use . Inappropriate and, most commonly, unnecessarily prolonged SAP alters the patient's individual microbiome and the hospital's collective microbial flora, promoting the selection and proliferation of resistant organisms [6]. This practice also increases the patient's risk for direct adverse effects, including acute kidney injury and *Clostridioides difficile* infection, a potentially fatal diarrheal illness . This creates a critical tension for healthcare systems: SAP is an indispensable tool for surgical safety, yet its suboptimal application fuels a long-term public health catastrophe. This paradox underscores the urgent need for stewardship—a systematic approach to ensure that these vital medicines are used only when necessary and in the most optimal manner possible [7].

1.3. The Evolution of Antimicrobial Stewardship (AMS)

Antimicrobial stewardship programs (ASPs) emerged several decades ago in direct response to the dual threats of rising AMR and a diminishing pipeline of new antimicrobial agents . The initial focus of many programs was on cost containment and formulary restriction, often referred to as "antibiotic control" . While these goals remain relevant, the philosophy of stewardship has evolved significantly. The modern definition of AMS is a coordinated set of interventions designed to optimize antimicrobial prescribing to improve patient outcomes, reduce antimicrobial-related toxicity and other adverse events, minimize healthcare costs, and slow the emergence and spread of resistance [8].

Early ASPs were often broad, hospital-wide initiatives. However, the field has matured, recognizing that the greatest impact can be achieved through targeted, high-yield initiatives focused on specific clinical areas or syndromes . Perioperative care has emerged as an ideal target for focused stewardship efforts. It represents a setting with a high volume of antimicrobial use, a robust evidence base defining best practices, and a direct, measurable link between appropriate antimicrobial use and the prevention of a high-cost, high-morbidity adverse event—the SSI. The CDC's *Core Elements of Hospital Antibiotic Stewardship Programs* provides a flexible, evidence-based framework for implementing ASPs, which can be adapted from large academic centers to small community hospitals . This evolution from broad control to targeted optimization has paved the way for specialized models of care, such as the dedicated perioperative stewardship program [9].

1.4. The Pharmacist as a Perioperative Specialist

Central to the success of modern, targeted AMS is the clinical pharmacist. Pharmacists possess a unique and comprehensive expertise in pharmacokinetics (PK), the study of how the body affects a drug, and pharmacodynamics (PD), the study of how a drug affects the body and invading microorganisms . This deep understanding of drug absorption, distribution, metabolism, and excretion, combined with knowledge of drug-bug interactions, drug-drug interactions, and medication safety systems, positions the pharmacist as the ideal leader for optimizing antimicrobial use [10].

This specialized role is formally recognized by leading professional and regulatory bodies. The ASHP and the Society of Infectious Diseases Pharmacists (SIDP) have long-standing position statements advocating for pharmacists to assume prominent, leadership roles in all institutional ASPs . Critically, the CDC's *Core Elements* framework explicitly identifies "Pharmacy Expertise" as a foundational component, recommending that a pharmacist serve as the co-leader of the hospital's ASP . This evolution in thinking has shifted the pharmacist's role from a traditional, reactive function of dispensing and order verification to a proactive, clinical role embedded within the patient care team . In the perioperative setting, this translates to a specialist who can not only ensure the right drug is selected for the right patient but can also architect and implement system-level protocols, clinical pathways, and quality improvement initiatives that hardwire safety and best practices into the complex surgical workflow . This reframing of perioperative AMS not as a restrictive "antibiotic control" function but as an integral component of a comprehensive surgical safety program—akin to sterile technique or the WHO Surgical Safety Checklist—is crucial for its acceptance and success. It aligns the goals of stewardship directly with the primary focus of the surgical team: achieving the best possible outcomes for the patient [11].

1.5. Rationale and Review Objectives

The convergence of the persistent and costly burden of SSIs, the inherent risks of suboptimal SAP, and the unique pharmacological skill set of the clinical pharmacist creates a compelling and urgent rationale for a dedicated, pharmacist-led perioperative AMS model. The economic burden of even a handful of preventable SSIs can easily exceed the cost of funding a dedicated pharmacist position, creating a clear and powerful value proposition for hospital leadership. Investing in this expertise is not a new cost center but a direct investment in preventing high-cost adverse events, yielding a significant return through improved patient outcomes and reduced expenditures [12].

This review will synthesize the body of scientific evidence to establish this collaborative model as the modern standard of care. The primary objectives are to: (1) Synthesize the scientific evidence supporting the efficacy of pharmacist-led perioperative AMS in reducing SSIs; (2) Delineate the critical, synergistic collaboration between pharmacy and infection control that drives program success; (3) Provide a practical, evidence-based, three-phase framework for pharmacist interventions across the pre-operative, intra-operative, and post-operative continuum; and (4) Review the clinical and economic outcomes that justify the implementation and expansion of this model of care [13].

2. THE SCIENTIFIC UNDERPINNINGS: MICROBIOLOGY, PHARMACOLOGY, AND RISK

2.1. The Microbiology of the Surgical Site: A Focus for the Infection Control Consultant

The foundation of rational SAP is a thorough understanding of the microbial landscape of the surgical site. SSIs occur when microbial contamination of the wound overwhelms the patient's host defenses . The source of this contamination can be either endogenous, originating from the patient's own flora, or exogenous, introduced from the surgical environment . Evidence indicates that the vast majority of SSIs, between 70% and 95%, are caused by the patient's endogenous microorganisms found on the skin, in mucous membranes, or within hollow viscera that are incised during the procedure . Exogenous sources, while less common, include contaminated surgical instruments, the air in the operating room, and the flora of the surgical team [14].

The specific pathogens likely to cause an SSI are highly predictable and depend on the anatomical location of the surgery. This principle allows for the targeted selection of prophylactic antimicrobials [15].

- **Clean Procedures:** Surgeries that do not breach the respiratory, alimentary, or genitourinary tracts, such as orthopedic, cardiothoracic, and neurosurgical procedures, are primarily at risk from skin commensals. *Staphylococcus aureus* is the single most common cause of SSIs, responsible for approximately 30% of all cases, with coagulase-negative staphylococci also being frequent isolates . The prevalence of methicillin-resistant *S. aureus* (MRSA) is a major concern that must be addressed by local surveillance data [16].
- **Clean-Contaminated and Contaminated Procedures:** Surgeries that involve entry into a hollow viscus, such as colorectal, gynecologic, or urologic procedures, expose the surgical site to a more complex, polymicrobial flora. In addition to skin organisms, these SSIs are frequently caused by Gram-negative bacilli (e.g., *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*) and, in some cases, anaerobic bacteria (e.g., *Bacteroides fragilis*) [17].

A critical factor in the microbiology of SSIs, particularly in orthopedic and cardiothoracic surgery, is the presence of foreign material like prosthetic joints, heart valves, or surgical mesh. These implants provide an inert surface for bacteria to adhere to and form a biofilm—a structured community of microorganisms encased in a self-produced protective matrix . The presence of a biofilm dramatically reduces the number of bacteria required to establish an infection, from over 100,000 organisms per gram of tissue to as few as 100 . Furthermore, bacteria within a biofilm are notoriously resistant to both host immune defenses and antimicrobial agents, making infections involving prosthetic material incredibly difficult to treat and often requiring removal of the implant [18].

2.2. Clinical Pharmacology for Optimal Prophylaxis: A Focus for the Pharmacist

While microbiology dictates *which* organisms to target, clinical pharmacology dictates *how* to effectively kill them at the surgical site. The pharmacist's expertise in applying pharmacokinetic (PK) and pharmacodynamic (PD) principles is essential for designing effective SAP regimens [19].

2.2.1. Pharmacokinetics (PK) and Pharmacodynamics (PD) of Key Antimicrobials

Different classes of antibiotics have distinct PK/PD properties that determine their optimal use.

- **Cefazolin:** As the workhorse of SAP, this first-generation cephalosporin is a beta-lactam antibiotic that exhibits time-dependent bactericidal activity. Its efficacy is driven by the duration of time that the free (unbound) drug concentration remains above the minimum inhibitory concentration (MIC) of the target organism, a parameter known as . Cefazolin has a relatively short elimination half-life of approximately 1.8 hours in patients with normal renal function, a critical fact that directly informs the need for intraoperative redosing [20].
- **Vancomycin:** A glycopeptide antibiotic, vancomycin is a crucial alternative for patients with a confirmed severe beta-lactam allergy or for prophylaxis against MRSA. Its bactericidal activity is best predicted by the ratio of the area under the concentration-time curve over a 24-hour period to the MIC (), a measure of total drug exposure . A target of is associated with optimal outcomes for treating invasive MRSA infections, though a specific target for prophylaxis has not been formally established . Its pharmacological properties are less ideal for prophylaxis compared to cefazolin; it has a long elimination half-life (3 to 9 hours) but requires a slow, prolonged infusion over 60 to 120 minutes to

avoid adverse reactions like hypotension and "red man syndrome" [21].

- **Clindamycin:** A lincosamide antibiotic, clindamycin is another alternative for patients with beta-lactam allergies. It also exhibits time-dependent activity () and is valued for its excellent activity against Gram-positive cocci and a wide range of anaerobic bacteria, as well as its outstanding penetration into tissues, including bone [22].

2.2.2. The Importance of Achieving Peak Serum and Tissue Concentrations at Incision

The central tenet of effective SAP is that bactericidal concentrations of the antibiotic must be present in the tissues *at the moment of initial incision* . This principle, established in classic animal experiments decades ago, dictates the critical timing of administration . Administering the antibiotic too early (e.g., more than 120 minutes before incision) allows for drug elimination to occur, potentially resulting in sub-therapeutic concentrations when the wound is opened . Conversely, administering the antibiotic too late (i.e., after the incision is made) is ineffective, as the drug cannot reach the site before bacterial contamination has already occurred and begun to establish itself . For these reasons, clinical practice guidelines from major societies consistently and strongly recommend that the infusion of prophylactic antibiotics begin within 60 minutes prior to surgical incision . For agents like vancomycin and fluoroquinolones that require longer infusion times, the infusion should begin within 120 minutes of incision to ensure administration is complete before the procedure starts [23].

2.3. Patient and Procedural Risk Stratification: A Joint Responsibility

Effective perioperative stewardship requires a comprehensive risk assessment for each patient, a responsibility shared by the entire clinical team, including surgeons, anesthesiologists, pharmacists, and infection control practitioners. Identifying patients and procedures at high risk for SSI allows for the intensification of preventive measures and the optimization of SAP [24].

Patient-related risk factors are numerous and often modifiable. Key factors that significantly increase the risk of SSI include uncontrolled diabetes mellitus and perioperative hyperglycemia, obesity, malnutrition, immunosuppression (due to disease or medication), recent tobacco use, older age, and pre-existing colonization with pathogenic organisms, particularly MRSA [25].

Procedural risk factors are equally important. The traditional surgical wound classification system is a fundamental tool for risk stratification [26]:

- **Clean wounds:** Uninfected operative wounds in which no inflammation is encountered and the respiratory, alimentary, or genitourinary tracts are not entered. SSI risk is low (<2%) .
- **Clean-contaminated wounds:** Operative wounds in which these tracts are entered under controlled conditions and without unusual contamination. SSI risk is higher (4-10%) .
- **Contaminated wounds:** Open, fresh, accidental wounds or operations with major breaks in sterile technique or gross spillage from the gastrointestinal tract. SSI risk is significant (>20%) .
- **Dirty wounds:** Old traumatic wounds with retained devitalized tissue and those that involve existing clinical infection or perforated viscera. SSI risk can exceed 40% .

Other critical procedural risk factors include the duration of the surgery (risk increases significantly for procedures lasting more than 2-4 hours), the use of drains, the implantation of prosthetic material, and the emergent nature of the surgery [27]. This multi-faceted risk assessment is not merely an academic exercise; it directly informs clinical decisions. For example, the identification of an obese patient undergoing a prolonged orthopedic implant surgery signals a high-risk scenario where standard prophylaxis may fail. This understanding is derived from connecting the clinical risk factor (obesity) with its underlying pharmacological consequence (inadequate drug exposure in adipose tissue), which then prompts a specific pharmacist-led intervention, such as a higher, weight-based dose of cefazolin, to mitigate that risk directly. Similarly, the institutional antibiogram, curated and analyzed by the IPC team, serves as a strategic tool. A rising local prevalence of cefazolin resistance among *E. coli* should trigger a collaborative review and potential modification of the standard SAP protocol for colorectal surgery, demonstrating a dynamic, data-driven approach to risk management [27].

Table 1: Common Pathogens Implicated in SSIs by Surgical Procedure

Surgical Category	Predominant Pathogens
Cardiothoracic	*Staphylococcus aureus*, Coagulase-negative staphylococci
Orthopaedic (with implant)	*S. aureus*, Coagulase-negative staphylococci
Neurosurgery	*S. aureus*, Coagulase-negative staphylococci
Vascular	*S. aureus*, Coagulase-negative staphylococci, Enteric gram-negative bacilli
Gastrointestinal (Colorectal)	Enteric gram-negative bacilli (*E. coli*), Anaerobes (*B. fragilis*), Enterococci

Gynecologic (Hysterectomy)	Enteric gram-negative bacilli, Group B streptococci, Enterococci, Anaerobes

3. The Perioperative Pathway: A Three-Phase Model for Pharmacist Intervention

A successful pharmacist-led perioperative AMS program is not a single event but a continuous process of optimization that spans the entire surgical journey. This can be conceptualized as a three-phase model, with targeted pharmacist interventions occurring in the pre-operative, intra-operative, and post-operative periods. This model transforms pharmacy's role from a reactive function, such as verifying an order that has already been written, to a proactive one, where the pharmacist acts as an architect of a safer medication-use system designed to prevent errors before they can occur [28].

3.1. Phase I: The Pre-Operative Period – Proactive Optimisation

The pre-operative phase offers the greatest opportunity to proactively optimize antimicrobial prophylaxis and mitigate patient-specific risks. Interventions during this period are designed to ensure that every patient arrives in the operating room with a plan for the safest and most effective SAP possible [29].

3.1.1. Antimicrobial Selection

The pharmacist's primary role begins with leading the development and maintenance of evidence-based institutional SAP guidelines . In collaboration with surgery, anesthesia, and infection control, the pharmacist ensures that these guidelines recommend the narrowest spectrum agent that is effective against the most likely pathogens for a given procedure . For the majority of clean and clean-contaminated surgeries, cefazolin is the established drug of choice due to its ideal spectrum of activity against skin flora, proven efficacy, favorable safety profile, and low cost . The institutional guidelines must also be dynamic, incorporating local antibiogram data provided by the IPC team to ensure that recommendations remain effective against local resistance patterns [30].

3.1.2. Patient-Specific Dosing

"One size fits all" is an inadequate approach to SAP dosing. The pharmacist's expertise in pharmacokinetics is critical for tailoring doses to individual patient physiology, which is a cornerstone of proactive stewardship [31].

- **Weight-Based Dosing:** Obesity is a major risk factor for SSI, partly because standard antibiotic doses can result in sub-therapeutic concentrations in adipose tissue and the surgical site . Pharmacist-driven protocols are essential for implementing weight-based dosing. For cefazolin, this typically involves increasing the standard 2 g dose to 3 g for patients weighing 120 kg or more . Similarly, guidelines often recommend stratified, weight-based dosing for vancomycin (e.g., 1 g for ≤70 kg, 1.5 g for 70-100 kg, 2 g for ≥100 kg) and clindamycin (e.g., 600 mg for <70 kg, 900 mg for ≥70 kg) to ensure adequate drug exposure [32].
- **Renal Adjustments:** Renal function profoundly influences the elimination of many antibiotics. While a single preoperative dose of a renally-cleared drug like cefazolin often does not require adjustment for renal impairment, the pharmacist's assessment of creatinine clearance (CrCl) is crucial . This assessment informs decisions about redosing intervals, as impaired renal function significantly prolongs a drug's half-life, potentially obviating the need for an intraoperative dose . It is also essential for safely dosing any post-operative prophylactic doses, should they be deemed necessary [33].
- **Augmented Renal Clearance (ARC):** The opposite physiological state, ARC, is an often-overlooked phenomenon where critically ill patients (e.g., those with trauma or sepsis) exhibit supranormal renal function (CrCl > 130 mL/min/1.73 m2) . In these patients, renally-cleared antibiotics like cefazolin can be eliminated so rapidly that prophylactic concentrations are not maintained, increasing the risk of SSI . Pharmacists play a vital role in identifying patients at risk for ARC, monitoring renal function closely, and recommending more aggressive dosing strategies, such as more frequent intraoperative redosing, to counteract this effect and prevent prophylactic failure [34].

3.1.3. Allergy Assessment

A documented beta-lactam allergy is one of the most significant barriers to optimal SAP. Patients with a penicillin allergy label are far less likely to receive first-line cefazolin and far more likely to receive alternative agents like clindamycin or vancomycin . This practice is associated with a 50% increased risk of developing an SSI, as these second-line agents are often less effective against common pathogens like methicillin-susceptible *S. aureus* . However, evidence shows that over 95% of patients with a reported penicillin allergy do not have a true, IgE-mediated allergy and can safely receive cephalosporins . The cross-reactivity between penicillins and cefazolin is exceedingly low (<2%) due to differences in their chemical side chains [35].

Pharmacist-led allergy assessment is a high-impact stewardship intervention. By taking a detailed allergy history, the pharmacist can help "de-label" patients with a history of intolerance (e.g., gastrointestinal upset) or a vague, remote, or non-allergic rash from those with a true, severe IgE-mediated reaction (e.g., anaphylaxis, hives, angioedema) . This vetting process, often guided by institutional protocols, safely and significantly increases the use of first-line cefazolin, thereby improving prophylactic efficacy and reducing the use of broader-spectrum or less effective alternatives [36].

3.1.4. Ensuring Correct Timing

As established, the failure to administer prophylactic antibiotics within the 60-minute window prior to incision is a major and preventable cause of SSIs . Achieving consistent compliance requires robust, system-level solutions. Pharmacists are instrumental in designing and implementing these systems in collaboration with nursing and

anesthesia colleagues. Effective strategies include incorporating SAP administration into standardized pre-printed or electronic order sets, building mandatory fields or alerts into surgical safety checklists and the electronic health record (EHR), and establishing clear communication pathways and designated responsibilities for administration in the preoperative holding area or operating room [37].

3.2. Phase II: The Intra-Operative Period – Real-Time Stewardship

Stewardship does not end once the patient enters the operating room. The intra-operative period requires real-time vigilance and collaboration to ensure that prophylactic coverage remains effective throughout the entire procedure [38].

3.2.1. Protocols for Redosing

To address the risk of drug concentrations falling below therapeutic levels during long procedures or cases with significant hemorrhage, pharmacist-developed protocols are essential. These protocols provide clear, evidence-based guidance for the anesthesia and surgical teams on when to re-administer prophylactic agents . For cefazolin, redosing is typically recommended every 4 hours from the time of the initial preoperative dose . For clindamycin, the interval is typically 6 hours . For agents with very long half-lives, such as vancomycin or ceftriaxone, intraoperative redosing is generally not necessary under normal circumstances . These protocols remove ambiguity and standardize practice, ensuring that redosing is performed consistently and correctly [39].

3.2.2. The Pharmacist's Role in Collaborating with Anaesthesia and Surgical Teams

The presence of a dedicated operating room (OR) pharmacist is an invaluable asset to the perioperative team and a growing best practice . The OR pharmacist functions as a real-time medication expert, collaborating directly with anesthesiologists and surgeons. Their responsibilities include verifying the correct selection, dose, and timing of the initial prophylactic dose; ensuring adherence to redosing protocols; and providing immediate consultation on antimicrobial selection if unexpected intraoperative findings occur (e.g., discovery of an abscess or unexpected bowel perforation). This direct line of communication and collaboration is key to improving and sustaining compliance with national quality measures, such as those from the Surgical Care Improvement Project (SCIP), and ensuring optimal antimicrobial therapy in the dynamic OR environment [40].

3.3. Phase III: The Post-Operative Period – The Critical Stop

The post-operative phase represents one of the most challenging yet impactful areas for perioperative stewardship. While pre-operative optimization is crucial, data consistently show that unnecessarily prolonged duration of prophylaxis is one of the most common forms of non-compliance with guidelines . This is likely driven by a combination of clinical inertia—the tendency to continue a medication "just in case"—and the diffusion of responsibility as patient care transitions from the surgical team to other providers. Therefore, pharmacist-driven interventions focused on timely discontinuation represent a high-yield opportunity to reduce unnecessary antibiotic use and its associated harms [41].

3.3.1. The Evidence Against Prolonged Prophylaxis

An overwhelming body of evidence, including numerous randomized controlled trials and meta-analyses, has demonstrated that continuing SAP beyond 24 hours after the surgical incision is closed provides no additional benefit in preventing SSIs . In fact, prolonged administration is harmful, increasing the risk of antimicrobial resistance, *C. difficile* infection, acute kidney injury, and other adverse drug events . It is also now clearly established that the presence of an indwelling surgical drain is not an indication for continuing prophylaxis, as this practice has not been shown to reduce infection rates . The most recent guidelines from leading societies like the CDC and SHEA/IDSA now recommend that for most procedures, prophylaxis should be discontinued immediately upon closure of the surgical incision in the operating room [42].

3.3.2. Pharmacist-Driven Interventions

Given the strong evidence for short-course prophylaxis, ensuring timely discontinuation is a primary goal of the post-operative stewardship pharmacist. Several highly effective, pharmacist-driven interventions can achieve this [43]:

- **Automatic Stop Orders (ASOs):** This is a powerful, system-level intervention where prophylactic antibiotic orders are programmed into the EHR or pharmacy computer system to automatically expire after 24 hours . If the clinical team believes continued therapy is warranted for treatment of an infection, they must actively write a new order with a new indication. This shifts the default from continuation to discontinuation, effectively combating clinical inertia [44].
- **Prospective Audit with Feedback:** This is a core stewardship strategy where pharmacists perform a daily review of all patients receiving surgical antibiotics . For any patient still receiving prophylaxis beyond the recommended 24-hour window without a clear indication for treatment, the pharmacist contacts the surgical team directly with a recommendation to discontinue the agent. This personalized, persuasive approach has been shown to be highly effective in improving compliance with duration guidelines [45].

3.3.3. Differentiating Prophylaxis from Treatment

The most critical clinical decision in the post-operative period is distinguishing between the need for continued prophylaxis (which is almost never appropriate) and the need for active treatment of an established or highly suspected infection [46]. A patient with post-operative fever, leukocytosis, and erythema at the incision site may have a developing SSI requiring therapeutic antibiotics. In contrast, a patient with a low-grade fever and normal white blood

cell count is likely experiencing a normal post-operative inflammatory response, and continuing antibiotics would be inappropriate. This differentiation requires clinical acumen and a multidisciplinary approach. The pharmacist plays a key role in facilitating this decision-making process by helping the team review clinical signs, laboratory data, and microbiology results, ensuring that antibiotics are continued only when there is a clear, documented indication for treatment [47].

Table 2: Pharmacokinetic and Pharmacodynamic Parameters of Key Prophylactic Antimicrobials

Antimicrobial	Key PK/PD Parameter for Efficacy	Typical Half-life (Normal Renal Function)	Key Dosing Considerations
Cefazolin	(Time-dependent)	1.8 hours	Weight-based dosing (3 g for ≥120 kg). Redose intraoperatively every 4 hours. Dose adjustment needed for post-op doses in renal impairment.
Vancomycin	(Exposure-dependent)	3–9 hours	Weight-based dosing (15 mg/kg). Requires slow infusion (60–120 min). Intraoperative redosing generally not needed.
Clindamycin	(Time-dependent)	2–3 hours	Weight-based dosing. Redose intraoperatively every 6 hours. Excellent bone penetration.

4. Building the Collaborative Engine: Integrating Pharmacy and Infection Control

While the clinical pharmacist is the primary actor in executing perioperative AMS interventions, the program's success and sustainability depend on a robust, collaborative engine built on a synergistic partnership with the Infection Prevention and Control (IPC) team. This relationship is not merely cooperative but symbiotic; one cannot achieve maximum effectiveness without the other. The IPC team provides the critical surveillance data—the "what" and "why" of local infections—while the pharmacy-led stewardship team provides the "how"—the design and implementation of a targeted, evidence-based medication-use strategy to combat those threats [48].

4.1. The Synergy of Surveillance and Action

The cornerstone of any effective infection prevention program is surveillance. The IPC team is responsible for systematically collecting, analyzing, and reporting data on HAIs, including SSIs . This includes tracking overall SSI rates, as well as rates stratified by surgical procedure, department, and individual surgeon. Crucially, the IPC team also works with the microbiology laboratory to monitor pathogen trends and maintain the institutional antibiogram, which details local antimicrobial susceptibility patterns [49].

This surveillance data is not merely for reporting; it is the essential fuel for data-driven stewardship action. The pharmacist utilizes this rich dataset to identify opportunities for improvement and to justify interventions. For example, if IPC surveillance reveals an increase in SSIs following cardiac surgery caused by MRSA, this data provides the impetus for the pharmacist to collaborate with the cardiothoracic surgery department to implement a pre-operative MRSA screening and decolonization protocol [50]. Conversely, the effectiveness of pharmacist-led interventions is validated through this same data stream. A successful initiative to improve cefazolin redosing compliance should be followed by a demonstrable decrease in SSIs in prolonged surgical cases, as tracked by the IPC team. This creates a continuous, iterative quality improvement cycle where surveillance identifies a problem, stewardship implements a solution, and surveillance measures the impact of that solution, leading to further refinement [51].

4.2. Developing Institutional Protocols and Clinical Pathways

The development of clear, evidence-based, and locally-adapted institutional protocols and clinical pathways is a core function of the pharmacy-IPC collaboration . National and international guidelines provide the foundational evidence, but these must be tailored to the specific institution . The pharmacist contributes expertise on clinical pharmacology, national guideline recommendations, and medication-use systems, while the IPC professional provides the crucial local context regarding SSI rates, pathogen distribution, and resistance patterns [52].

This joint development process must also actively engage key stakeholders, particularly surgeons and anesthesiologists, to ensure the resulting pathways are practical, clinically relevant, and supported by the frontline providers who will use them . Once developed, these pathways should be embedded into the clinical workflow through standardized electronic order sets and widely socialized across all surgical departments. This process standardizes care, reduces undesirable practice variation, and makes adherence to best practices the easiest and most efficient path for clinicians to follow [53].

4.3. Education as a Core Function

Education is a fundamental component of any successful stewardship program, but it must be approached as a continuous process of engagement rather than a single, isolated event. One-off, passive educational activities like

grand rounds lectures have been shown to have little lasting impact on prescribing behavior . Instead, the most effective educational strategies are active, targeted, and multidisciplinary, co-developed and delivered by the pharmacy and IPC team [54].

The focus of this education should be on explaining the "why" behind stewardship policies—presenting the local SSI data, the pharmacological rationale for specific dosing regimens, and the direct link to patient safety. This approach fosters understanding and buy-in far more effectively than simply dictating rules . Education must be tailored to the specific audience. For surgeons, this may involve presenting department-specific SSI rates and compliance data. For anesthesiologists, it may focus on the pharmacokinetics of redosing. For nurses, who are at the center of medication administration and patient monitoring, education is particularly critical and should empower them to play an active role in stewardship, for example, by questioning prolonged antibiotic courses or ensuring timely administration [55]. This continuous, case-based, real-time education, often delivered through the audit and feedback process, is far more impactful than traditional didactic methods [55].

4.4. The Power of Audit and Feedback

Prospective audit with feedback is a cornerstone strategy of AMS and is highly recommended by major guidelines . In the perioperative setting, this process is typically led by the clinical pharmacist, who prospectively audits surgical cases for adherence to the institution's SAP protocol, evaluating the appropriateness of antibiotic choice, dose, timing, and duration . When a deviation is identified, the pharmacist provides direct, real-time feedback to the responsible prescriber (e.g., the surgeon or anesthesiologist) [56].

For this strategy to be successful and drive behavioral change, the feedback must be designed and delivered according to key principles. It should be timely (as close to the clinical event as possible), individualized (specific to the patient and provider), and, most importantly, non-punitive and constructive . The goal is not to police or criticize but to educate and collaborate in the interest of patient safety. Presenting confidential, comparative data on compliance and outcomes to individual providers or departments can also be a powerful, non-punitive motivator, leveraging professional pride and a desire for excellence to drive improvement [57].

4.5. Overcoming Implementation Barriers

Despite the strong evidence base, implementing a robust perioperative AMS program faces significant barriers, primarily cultural and logistical. The traditional culture of surgical autonomy can lead to resistance against what may be perceived as external oversight of prescribing practices . The most effective strategies to overcome this barrier involve a persuasive, collaborative approach rather than a restrictive one. This includes engaging influential surgeon champions to advocate for the program, consistently presenting local, department-specific data that clearly demonstrates a problem or opportunity for improvement, and framing all stewardship interventions in the context of improving surgical quality and patient safety [58].

Logistically, interventions must be seamlessly integrated into the fast-paced and complex perioperative workflow to minimize disruption and ensure sustainability. This requires close collaboration with nursing and anesthesia teams to understand their daily challenges and design solutions that are efficient and user-friendly. Leveraging technology, such as well-designed EHR order sets and automated alerts, is critical to making the right choice the easy choice and hardwiring best practices into the standard workflow [59].

5. Quantifying the Impact: A Review of Clinical and Economic Outcomes

The value of a pharmacist-led perioperative AMS program is not theoretical; it is quantifiable through a robust body of evidence demonstrating significant improvements in clinical outcomes, process measures, and economic performance. The data illustrates a clear and direct causal pathway: pharmacist-led interventions drive improved adherence to evidence-based practices, which in turn leads to a reduction in patient harm and a decrease in associated healthcare costs [60].

5.1. Reduction in Surgical Site Infection Rates

The primary clinical objective and ultimate measure of success for any perioperative stewardship program is the reduction of SSIs. A recent, comprehensive systematic review and meta-analysis provides the highest level of evidence for the effectiveness of pharmacist-led programs in this domain. The analysis, which included eleven studies, found that the implementation of a pharmacist-led AMS program in the perioperative setting was associated with a statistically significant reduction in the odds of developing an SSI, with a pooled odds ratio (OR) of 0.51 (95% Confidence Interval [CI] 0.34–0.77) . This finding indicates that these programs can effectively cut the risk of SSI by nearly half [61].

These meta-analytic findings are strongly supported by numerous individual prospective studies. For example, a large, multi-center quality improvement initiative driven by pharmacists across 34 hospitals demonstrated a sustained 19.7% relative reduction in the mean SSI rate post-intervention (from 2.46 to 1.97 infections per 100 procedures, p=0.0029) . Another controlled study investigating pharmacist interventions in vascular and gastrointestinal surgery found a significantly lower incidence of SSI in the group receiving pharmacist-guided prophylaxis compared to the surgeon-directed group (p=0.0001) . These results consistently affirm that pharmacist leadership translates directly into preventing patient harm [61].

5.2. Improved Guideline Adherence

The mechanism through which pharmacist-led programs reduce SSIs is by dramatically improving adherence to the evidence-based process measures that constitute optimal SAP. The same meta-analysis that demonstrated a reduction in SSIs also quantified the impact on these core processes. Pharmacist-led AMS was associated with a more than four-fold increase in the odds of appropriate antibiotic selection (OR 4.29; 95% CI 2.52–7.30), a nearly five-fold increase in the odds of appropriate administration timing (OR 4.93; 95% CI 2.05–11.84), and a more than five-fold increase in the odds of appropriate duration (OR 5.27; 95% CI 1.58–17.55) [62].

Again, these findings are mirrored in individual studies. The multi-center South African study saw composite compliance with all four key process measures (choice, dose, timing, and duration) increase from a baseline of 66.8% to 83.3% post-intervention, a 24.7% improvement . A study in a Hungarian orthopedic unit found that the implementation of a pharmacist-led stewardship program increased overall guideline adherence from a baseline of just 2% to 58.2% . This demonstrates the pharmacist's role as a powerful catalyst for translating evidence into consistent clinical practice [51].

5.3. Economic Analysis

The clinical benefits of pharmacist-led perioperative stewardship are paralleled by substantial economic advantages. These savings are realized through both direct reductions in antimicrobial expenditure and, more significantly, the avoidance of the high costs associated with treating SSIs [63].

Studies consistently show that by optimizing antibiotic selection and, in particular, ensuring timely discontinuation, stewardship programs lead to a significant decrease in drug consumption and cost. One study in orthopedic surgery found that a pharmacist-led program reduced the average prophylactic antibiotic cost per patient by 54.8% and decreased overall antibiotic exposure, measured in Defined Daily Doses (DDD), by 41% . Another quasi-experimental study found that a pharmacist-led AMS intervention was associated with a significant reduction in the cost of antibiotics ($p=0.006$) [45].

However, the largest economic impact comes from cost avoidance. Preventing a single SSI eliminates the substantial downstream costs of prolonged hospitalization, additional antibiotic therapy, diagnostic imaging, and potential re-operation . A landmark analysis of Medicare data from over 240,000 surgical patients in 860 hospitals quantified the massive hidden costs of not having robust stewardship. The study found that in hospitals *without* pharmacist-managed antimicrobial prophylaxis, compared to those with such programs, the length of stay was 10.21% longer, total Medicare charges were 3.10% higher, and drug charges were 7.24% higher . The analysis concluded that the provision of pharmacist-managed antimicrobial prophylaxis was associated with significant improvements in both clinical and economic outcomes, framing the investment in a stewardship pharmacist not as a new expense, but as a necessary solution to an existing, ongoing financial drain [64].

5.4. Impact on Antimicrobial Resistance

While the direct impact of a single-institution stewardship program on regional antimicrobial resistance patterns is challenging to measure, the ecological benefit is a fundamental goal of AMS. By reducing the overall volume of antimicrobial use—particularly through the elimination of unnecessarily prolonged post-operative prophylaxis—and by promoting the use of narrower-spectrum agents, perioperative stewardship programs lessen the selective pressure that is the primary driver of AMR . This helps to preserve the efficacy of our current antimicrobial armamentarium for future patients. Furthermore, by reducing the use of broad-spectrum agents often used as alternatives in cases of unvetted beta-lactam allergies, these programs help to mitigate the risk of collateral damage, including the development of infections with organisms like *C. difficile* [65].

Table 3: Synopsis of Key Studies Evaluating the Impact of Pharmacist-Led Perioperative AMS

First Author (Year)	Study Design	Surgical Population	Key Pharmacist-Led Interventions	Primary Outcomes (Clinical & Economic)
Al-Hasan (2024)	Systematic Review & Meta-analysis	Various surgical	Education, ward rounds, audit & feedback, guideline development	**SSI Reduction:** OR 0.51 (95% CI 0.34–0.77) **Improved Guideline Adherence:** Selection OR 4.29, Timing OR 4.93, Duration OR 5.27
Brink (2017)	Prospective Audit & Feedback	Various surgical (34 hospitals)	Guideline implementation, prospective audit with feedback	**SSI Reduction:** 19.7% decrease in mean SSI rate **Improved Guideline Adherence:** 24.7% increase in composite compliance

Vesszpremi (2021)	Before-and-After	Joint arthroplasty	Education, prospective audit & feedback, guideline adherence monitoring	**Cost Reduction:** 54.8% decrease in prophylactic antibiotic cost **Improved Guideline Adherence:** Overall adherence increased from 2% to 58.2%
He (2022)	Quasi-experimental	Vascular & interventional radiology	Education, prospective audit & feedback	**Cost Reduction:** Significant reduction in antibiotic consumption (p=0.017) and cost (p=0.006) **Improved Guideline Adherence:** Significant improvement in appropriateness scores

6. Advanced Topics and Special Considerations

While the core principles of perioperative AMS apply broadly, certain high-risk populations and challenging clinical scenarios demand more advanced and specialized stewardship strategies. These situations underscore the need for a highly reliable system where every component of the prevention bundle is meticulously executed for every patient, every time [69].

6.1. The Role of Pre-Operative Decolonization

The nasal passages are a primary reservoir for *Staphylococcus aureus*, and nasal carriage is a major, independent risk factor for developing an *S. aureus* SSI, particularly in orthopedic and cardiothoracic surgery where prosthetic devices are implanted . Evidence conclusively shows that in over 80% of *S. aureus* SSIs, the infecting strain is genetically identical to the strain colonizing the patient's own nares [61].

This direct link has led to the development of highly effective pre-operative decolonization protocols. The WHO and other leading bodies strongly recommend that patients with known nasal carriage of *S. aureus* undergoing cardiothoracic or orthopedic surgery be decolonized . The most common and well-studied regimen involves a five-day course of intranasal mupirocin 2% ointment, often combined with daily body washes using chlorhexidine gluconate (CHG) . This approach has been shown to significantly reduce the rate of postoperative *S. aureus* infections [61].

A key strategic decision for institutions is whether to implement a "targeted" screen-and-treat strategy or a "universal" decolonization approach for all patients in high-risk surgical populations. The targeted approach, which involves pre-operative screening via nasal swabs to identify carriers, is more resource-intensive, requires sophisticated logistics to ensure results are available and acted upon before surgery, and risks missing carriers due to false-negative tests . Universal decolonization is logistically simpler and ensures all carriers are treated, but it results in significantly greater use of mupirocin, which raises concerns about promoting mupirocin resistance [62]. This decision requires careful, multidisciplinary deliberation between surgery, IPC, and pharmacy to develop an institutional policy that balances efficacy, logistics, cost, and the long-term risk of resistance [63].

6.2. Stewardship in High-Risk Surgical Populations

6.2.1. Orthopaedic and Cardiothoracic Surgery

In these specialties, an SSI can be a catastrophic, life-altering event. A prosthetic joint infection (PJI) or post-sternotomy mediastinitis often requires multiple surgeries, prolonged and toxic antibiotic courses, and can result in permanent disability or death. The presence of prosthetic material makes these infections exceptionally difficult to eradicate . Consequently, stewardship in this arena is a high-stakes endeavor focused on meticulous execution of all preventive measures. This includes strict adherence to optimal SAP (typically with cefazolin), robust *S. aureus* decolonization programs, and, in institutions with a high prevalence of MRSA, consideration of dual prophylaxis with both cefazolin and vancomycin to ensure coverage for both methicillin-susceptible and methicillin-resistant staphylococci [64].

6.2.2. Colorectal Surgery

As clean-contaminated or contaminated procedures, colorectal surgeries carry a high intrinsic risk of polymicrobial SSIs from the dense flora of the large bowel . Stewardship efforts focus on ensuring the use of appropriate prophylactic agents with a spectrum of activity that covers the expected Gram-negative and anaerobic pathogens [25]. This often involves oral antibiotic bowel preparation in addition to parenteral prophylaxis. Furthermore, strict adherence to the 24-hour discontinuation rule is paramount to prevent the selection of resistant gut organisms and reduce the risk of *C. difficile* infection [65].

6.2.3. Transplant and Immunocompromised Patients

Solid organ transplant (SOT) recipients and other severely immunocompromised patients, such as those with hematologic malignancies, represent the most complex population for antimicrobial stewardship . These patients are at a profoundly elevated risk of infection due to the combination of major surgery, high-intensity immunosuppressive

regimens, prolonged hospitalizations, and frequent exposure to multidrug-resistant organisms (MDROs) . Stewardship in this population is highly specialized and intensely collaborative. It requires daily interaction between the stewardship pharmacist and the transplant infectious diseases team to manage complex prophylactic regimens (which may include antibacterial, antifungal, and antiviral agents), navigate significant drug-drug interactions between antimicrobials and immunosuppressants, and utilize advanced molecular diagnostics to guide therapy [66].

6.3. Navigating Antimicrobial Shortages

Antimicrobial drug shortages have become a frequent and disruptive reality in healthcare, posing a significant threat to both patient safety and stewardship efforts . When a first-line prophylactic agent like cefazolin becomes unavailable, it can create confusion and lead to the use of less effective or unnecessarily broad-spectrum alternatives, undermining established stewardship protocols [67].

The stewardship pharmacist is central to navigating these crises. Effective management of shortages is a proactive, not reactive, process. It involves prospectively tracking potential shortages using resources from ASHP and the FDA, developing pre-vetted, evidence-based alternative protocols, and communicating these plans clearly to surgical, anesthesia, and pharmacy staff before the shortage becomes critical . This leadership turns a logistical crisis into a stewardship opportunity. By providing expert guidance, the pharmacist can ensure a smooth transition to the most appropriate alternative agent, preventing a chaotic scramble that could compromise patient care and harm long-term stewardship goals [68].

7. FUTURE DIRECTIONS AND CONCLUSION

The model of pharmacist-led, collaborative perioperative antimicrobial stewardship is well-established and has proven its value. However, the field continues to evolve, driven by advances in technology, ongoing research, and shifting regulatory landscapes. The future of perioperative AMS lies in leveraging these forces to create ever more intelligent, efficient, and effective systems for preventing surgical site infections.

7.1. Leveraging Technology: The Electronic Health Record (EHR), Clinical Decision Support Systems (CDSS), and Data Analytics

Technology serves as a powerful enabler, allowing for the automation and standardization of best practices, but it is a tool to augment, not replace, the clinical expertise and collaborative relationships that are the heart of a successful program.

- **Electronic Health Record (EHR) Integration:** The EHR is the central nervous system of modern healthcare and a critical platform for embedding stewardship into daily workflows. This includes the development of sophisticated, procedure-specific order sets that default to guideline-concordant antimicrobial selection, weight-based dosing, and appropriate duration. Hard-coded automatic stop orders and mandatory fields for indications can further reinforce best practices . The EHR also serves as a rich data source for automated surveillance and the generation of performance reports for feedback.
- **Clinical Decision Support Systems (CDSS):** The next evolution is the integration of more intelligent CDSS. These systems can provide active, real-time guidance to prescribers at the point of care . For example, a CDSS could automatically calculate a patient's weight-based cefazolin dose, alert the anesthesiologist when an intraoperative redose is due based on the procedure start time, or flag a prolonged post-operative prophylactic order and suggest discontinuation . These tools help make the right decision the easiest decision, reducing the cognitive burden on clinicians and preventing errors.
- **Data Analytics and Artificial Intelligence:** The vast amount of data captured in the EHR can be harnessed through advanced data analytics and machine learning (AI) . These tools can develop predictive models to identify patients at the highest risk of SSI, allowing for the targeted application of more intensive preventive measures. They can also detect subtle, emerging trends in local antimicrobial resistance patterns earlier than traditional methods, enabling a more agile and proactive response from the stewardship team .

7.2. Research Gaps and Unanswered Questions

Despite significant progress, several key questions in perioperative AMS remain unanswered, representing important avenues for future research.

- **Optimal Dosing in Special Populations:** While weight-based dosing for obesity is becoming standard, more research is needed to define optimal prophylactic dosing in other populations with altered pharmacokinetics. This includes patients with augmented renal clearance, those undergoing massive volume resuscitation, and patients on extracorporeal membrane oxygenation (ECMO), where standard doses may be inadequate .
- **The Role of Novel Diagnostics:** The impact of rapid diagnostic technologies needs further exploration. For example, could pre-operative molecular screening for a panel of resistant organisms be used to guide a more personalized, targeted prophylaxis strategy for high-risk procedures? .
- **Behavioral and Implementation Science:** The greatest challenges in stewardship are often not a lack of evidence, but the difficulty in changing established human behavior. More research is needed on how to apply the principles of behavioral and implementation science to design interventions that more effectively overcome cultural and

psychological barriers to practice change among surgical teams .

- **Long-Term Ecological Impact:** While it is intuitive that reducing antimicrobial use will slow the emergence of resistance, robust, multi-center studies are needed to definitively quantify the long-term impact of perioperative stewardship programs on institutional and regional rates of AMR .

7.4. Conclusion

This review has systematically demonstrated that surgical site infections remain a formidable and costly threat to patient safety. Optimizing surgical antimicrobial prophylaxis is a critical, high-impact strategy for preventing these devastating complications. The body of evidence is now clear and compelling: the most effective model for achieving this optimization is through a dedicated, pharmacist-led perioperative antimicrobial stewardship program.

This model succeeds because it places an expert in pharmacology at every critical decision point in the medication-use process. However, the pharmacist does not act in isolation. The program's power is magnified through a symbiotic partnership with a data-driven infection prevention and control team, creating a continuous cycle of surveillance, intervention, and evaluation. This collaborative, proactive, and evidence-based approach has been proven to improve adherence to best practices, significantly reduce surgical site infection rates, and lower healthcare costs. It is no longer a novel or optional enhancement but has become the indispensable cornerstone of modern, safe, high-quality, and cost-effective surgical care. It represents a shared vision where every member of the perioperative team—surgeon, anesthesiologist, nurse, infection preventionist, and pharmacist—contributes their unique expertise to protect every patient from preventable harm.

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