Global Alliance for
Infections in Surgery

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worldwide | antimicrobial | resistance | national | international | network | group

GLOBAL INFECTION PREVENTION AND MANAGEMENT IN HEALTHCARE

VOLUME 3

Sepsis and infections in surgery

Editors: Massimo Sartelli, Federico Coccolini, Fausto Catena and Leonardo Pagani

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GLOBAL INFECTION PREVENTION AND MANAGEMENT IN HEALTHCARE

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Editors

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Global collaboration to achieve better outcomes in healthcare

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Introduction

The importance of antibiotic resistance, its consequences, and the need for tailored treatment of surgical infections cannot be overemphasized. This is a global problem that needs global attention and global strategies to be effectively mitigated.
In this chapter, I will describe, using examples from my experience dealing with other important clinical issues, how professional organizations participating in coalitions can help mobilize large groups of people and develop effective communication, discussion, and education about critical problems.

The importance of leadership and collaboration

Any global initiative must be inclusive. They should involve individuals, professional organizations, and large institutions such as universities, hospital networks, and foundations. Unfortunately, most initiatives in global surgery are limited in scope or reach, as they have been based on individual efforts, eventually sponsored by a professional society, with deliverables that include educational materials and a few scientific publications, usually, review articles or opinion pieces. Although the deliverables, as stated, may increase awareness about an important problem, they do not “move the needle” globally because they lack the power to change policy at the local level and lack specificity in the development of plans tailored to different regions. Although noble, this approach is not sustainable, begging the question of how to make these important initiatives sustainable, permanent, and self-sufficient.
In the best-seller book “Good to Great,” published in 2001, Jim Collins and a group of researchers explored what good companies do to become great, turning long-term weaknesses into outstanding sustainable results. Applying specific research methods, they found 11 companies that successfully made the “good-to-great” transition and sustained their successes. Analyzing those companies, the authors described two elements consistently found in “good-to-great” companies. They all had Level-5 leaders, and the selection of people occurred before the team and the company defined their goals. Level 5 leaders are not high-profile individuals with big egos or personalities who want to be on the cover of newspapers or TV all the time. These unique individuals combine two main characteristics: personal humility and intense professional will. They understand that important initiatives need solid plans to function, including a well-defined succession plan

for leadership. Additionally, they are not usually deterred by difficulties and have an unwavering resolve and determination to succeed.

All those “good-to-great” companies went through a buildup phase followed by a breakthrough phase. They persisted in their efforts until the turning point was reached. The researchers found specific behavioral patterns in the leaders of those companies as well as in the people who worked for them. The three identified patterns were: 1) Disciplined people, 2) Disciplined thought, and 3) Disciplined action.

With the right people on board, good-to-great companies started their pathway to greatness by confronting their current reality, trying to understand the current scenario, and developing strategies and tactics to achieve their ultimate goals. At all levels, the “right people” could be heard and engaged in dialogue and debate without shying away from conflict until conflict was resolved. Giving a voice to people increased their commitment to their goals and made it possible for the team to stay focused on a single organizing idea. Anything that did not relate to the unifying idea became irrelevant and non-essential. With disciplined people and disciplined thought, the team is ready for the final phase, which involves action. This is when the build-up phase of a sustainable project ends and the breakthrough phase starts.

Giving people a chance to freely and openly express what they can do best and articulate strategies on how they could be most effective creates a framework allowing the main focus areas of a project to emerge. Once this is accomplished, well-designed strategies and tactics in a multipronged approach will create momentum, after which there is no return, and the project has a significantly high chance of succeeding and becoming sustainable.

Using the “Good-to-Great” framework to develop and mature a surgical specialty: acute care surgery

The development of Acute Care Surgery (ACS) as a concept of a new surgical specialty started in the United States in 2003, when David B. Hoyt, MD, delivered his presidential address to the American Association for the Surgery of Trauma (AAST). The idea of creating the new specialty of Acute Care Surgery was based on the principle that the public deserved excellent emergency general surgery care, similar to what was already delivered in trauma surgery and surgical critical care. Combining those three domains and developing a clinical practice model of care delivery that was already being used in trauma care, with surgeons being available in-house, 24 hours a day, seven days/week, and 365 days/year, would improve the delivery of high-quality and timely care for time-sensitive diseases. By having a group of outstanding leaders, the AAST promulgated and disseminated this new concept, adopted by many institutions in the United States and abroad over the next two decades. A few years after the “launching” of this new surgical specialty, it became apparent that the training paradigm at the time in trauma and surgical critical care (fellowship) had to change and include EGS. Again, by assembling the right people and the right ideas, a new ACS fellowship, which includes the current surgical critical care fellowship and expands into structured trauma and EGS training (a 2-year program), was created. Similarly to the good-to-great companies, the build-up phase was completed, and the breakthrough phase had started. In parallel to the creation of the fellowship, robust research showed that the ACS clinical care model was effective in providing timely surgical care for several acute diseases, outcomes were better than the traditional model, and cost of care and resource utilization decreased.

In 2017, the AAST leadership felt that the ACS project would only be completed if it had three additional components: 1) a robust EGS quality improvement process, so progress would be based on continuous improvement and critical analysis of clinical data, b) a set of EGS standards to guide the development and

practice of new ACS programs in hospitals across the country, similar to what has required from trauma centers in the last four decades, and c) a national EGS data repository to allow comparisons between institutions on several outcome measures after consistent risk-adjustment of the data. These three elements formed the base for a national EGS verification program. The AAST contacted the American College of Surgeons and collaborated to develop the standards and the national EGS registry. Using the above framework for a period of five years, we selected the right people, discussed the relevant ideas, developed the EGS standards, and in 2022, launched the American College of Surgeons-AAST Emergency General Surgery Verification Program and the national EGS-National Surgical Quality Improvement Program database. Currently, 11 EGS programs have been verified, and many more are on the list to be site-visited in 2025.

Creation of the World Coalition for Trauma Care

In 2007, the World Health Assembly (WHA) approved resolution 60.22, which called for the adoption of measures to strengthen trauma and emergency care systems worldwide, and the Global Alliance for the Care of the Injured (GACI) was created. In 2010, the World Health Organization mobilized a few international professional organizations to join GACI to carry on the above-described mandate. Most of the work was unfunded, and no infrastructure was made available to the working groups. The requests of professional organizations and working groups were impossible to complete in a timely fashion, and there were no mechanisms to disseminate the results globally. Many issues that were hindering trauma care and trauma systems development in low- and middle-income countries were identified at the time. The biggest problems were inconsistency in knowledge, care delivery, systems development (pre-hospital, trauma centers, rehabilitation, and injury prevention), trauma registries applicable globally, and quality improvement processes also used globally. Educational offerings, books, and checklists may solve some of these issues. However, others require real resources and investment toward dissemination, implementation, and training.

At the same time, a group of trauma surgeons realized that the trauma world had not come together to discuss these issues. We felt that without a broad discussion, where a diverse group of trauma providers care was heard, it would be impossible to disseminate knowledge and achieve the goals of the WHA resolution 60.22.

In 2012, using the good-to-great framework, we decided that we could contribute to improving knowledge, education, and dissemination of new concepts and create a forum to discuss these issues regularly. The initiative was independent of the WHO. This time, instead of selecting people, we first invited several international trauma professional organizations to sit at the table. The professional organizations then identified and assigned two of their officers to be part of the leadership group of a potential world coalition. Instead of predetermining an agenda, we opted for bringing people together in a scientific and highly educational conference, the 1st World Trauma Congress (WTC), where we pitched our ideas to the leadership members of 17 professional organizations and the 3,500 attendees of the congress, held in Rio de Janeiro. At that time, with unanimous approval, the World Coalition for Trauma Care (WCTC) was created, and it was decided that the WTC would be a recurrent global forum for discussion and dissemination of knowledge and strategies toward trauma systems development, injury prevention, and clinical care delivery. Fast-forward 12 years, we just completed the 7th WTC in Las Vegas, USA, and the WCTC is stronger than ever, now being composed of 37 professional organizations, with some of them having continental reach, such as the European Society of Trauma and Emergency Surgery and the Panamerican Trauma Society.

Why have we not started with people and decided to choose professional organizations? The decision was simple: professional organizations are composed of people: officers, committee chairs, committee members,

and members-at-large of the organization. They would be better positioned to disseminate information about new knowledge, therapies, tool kits for trauma center setup and systems development to their members, etc. The WTC is held every two years, with the annual meeting of one of the professional organizations part of the WCTC. Meetings in Brazil, Germany, India, the United States, and Japan have occurred in the last 12 years. A few years ago, the WCTC was invited to be a GACI member of the WHO.

It takes a village…

Tackling global problems requires strong leadership, incredible will, and collective hard work. Sometimes, the best strategy is to choose people first, but sometimes, choosing larger organizations of people is a better option. This is not limited to specialty professional organizations. It can also include hospitals, universities, other coalitions, and foundations.

Funding will always be an issue when dissemination starts; therefore, relying on the outreach of those organizations is a key element to achieving success.

The Global Alliance for Infections in Surgery (GAIS), led by Prof. Massimo Sartelli, is geared toward incredible success in the fight against surgical infections globally. We hope that some of the good-to-great strategies for sustainable success described in this brief chapter will help the GAIS achieve greatness.

Competing interests

The author has no financial and non-financial competing interests to declare.

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Chapter 96

The silent burden of sepsis: a global health emergency

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Introduction

Sepsis is a term first used in Greek literature more than 2,500 years ago to signify decay and decomposition. As our understanding of infection has evolved through the years, so too has the definition of sepsis, with the first worldwide consensus definition developed as recently as 1991 and continually revised. Today, sepsis is formally defined as life-threatening organ dysfunction caused by dysregulated host response to infection. On a global scale, sepsis impacts up to 50 million people each year and is a major threat to global population health. This chapter aims to define the global burden of sepsis, discuss contributing factors, and promote and inspire community initiatives so that we may all work together to address this ever-evolving public health challenge.

The global sepsis burden

Sepsis is a leading contributor to morbidity, mortality, and disability worldwide. By one estimate, sepsis is responsible for approximately 8 million deaths per year and contributes to 25-30% of hospital mortality. Even these estimates may not fully capture the true scope of the burden of sepsis as data from low- and middle-income countries - where 87% of the world's population resides - is severely underrepresented in the current literature. Management and treatment of sepsis also poses an extensive cost to hospital systems at an estimated rate of greater than 32,000 USD per patient in high-income countries.

In May 2017, the World Health Organization formally recognized sepsis as a global health emergency and implemented a resolution aimed at improving the prevention, diagnosis, and clinical management of sepsis. The key pillars of this resolution include: 1) establishing defined guidelines in the management and prevention

of sepsis, 2) developing strategies and tools to reduce morbidity and mortality from sepsis, 3) promoting collaboration at the international level to enhance sepsis treatment and prevention, and 4) highlighting the public health impacts of sepsis and estimating the global burden of sepsis.

Global causes of sepsis

Diarrheal diseases were found to be the most common cause of sepsis worldwide followed by lower respiratory infections and maternal disorders. In terms of mortality, lower respiratory tract infections caused the greatest number of deaths. However, in children less than 5, deaths were mostly attributed to neonatal disorders, lower respiratory tract infections, and diarrheal infections. Prevention of infections before they progress to sepsis, including providing access to clean water, diligence to hand hygiene, and timely and appropriate uptake of age and condition-specific vaccinations are crucial interventions. In war-torn areas, entities such as cholera can cause profound dehydration for which access to fluids and rehydration as well as supportive care are important for survival. Furthermore, war and regional strife can lead to disruptions in vaccination campaigns, so, global cooperation, trust, and dedicated resources may be needed to prevent vaccine-preventable diseases such as polio, influenza and more.

Sepsis in high-income *vs.* low- and middle-income countries

The vast majority of the existing data on sepsis is from high-income countries. A 2020 review on sepsis was based on 51 studies and revealed an overall mortality of 26.7% and an ICU-treated sepsis mortality of 42 percent. The data, however, had disparities due to a lack of robust data from low- and middle-income countries. Significant disparities exist in global sepsis cases. According to a World Health Organization report on the global burden of sepsis, 85% of sepsis cases and deaths occurred in low- or middle-income countries, especially in sub-Saharan Africa and South East Asia.

Though the greatest burden of sepsis is in low- and middle-income countries, the degree of morbidity and mortality due to sepsis is unknown due to a myriad of reasons. The majority of the data on sepsis is from studies in high-income countries. Some of the barriers which exist that preclude accurate sepsis data collection in low-income countries include a lack of criteria-defining sepsis, lack of access to healthcare, and the need to build a robust healthcare workforce which can sustain the demand of sepsis patients.

Lack of immunizations, which increases the risk for communicable diseases, is another risk factor for sepsis and contributes to the higher rates of sepsis mortality. Childhood immunization rates have been declining, impacted by the COVID-19 pandemic. Barriers to immunization such as lack of access to healthcare, displacement due to wars, lack of awareness and misinformation and disinformation have been attributed to the rising rates of vaccine hesitancy globally.

Neonatal and maternal sepsis

Globally, there is an incidence of 3 million cases of sepsis in neonates and 1.2 million cases in children. The characterization of sepsis differs between adults *versus* neonates; in neonates, greater emphasis is placed on the identification of a pathogen that invades the bloodstream resulting in serious health conditions and

neonatal death. Neonatal sepsis is temporally delineated into early-onset sepsis and late-onset sepsis. Early-onset sepsis is defined as sepsis within 72 hours after birth and is commonly associated with prenatal and intrapartum infection; late-onset sepsis refers to sepsis 72 hours after birth and is typically a hospital or community-acquired infection. Research for a time- and cost-effective biomarker to accurately diagnose sepsis in neonates is still underway.

One in ten maternal deaths globally is due to sepsis, and there is an estimated global prevalence of maternal sepsis of 4.4% among live births. Assessment of the global burden of maternal sepsis is challenging due to inconsistencies in the definition. Measures to define sepsis in non-pregnant adults are not accurate when applied to pregnant adults; current components of SIRS (systemic inflammatory response syndrome) criteria, for example, often overlap with normal physiologic parameters in pregnancy and are not appropriate for diagnosis. The World Health Organization defines maternal sepsis as "a life-threatening condition defined as organ dysfunction resulting from infection during pregnancy, childbirth, post-abortion, or postpartum period", opting for a more clinically based *versus* laboratory-based diagnosis.

Infection prevention

According to Sepsis Alliance, Infection Prevention is Sepsis Prevention™, the devastating effects of sepsis – including organ dysfunction, post-sepsis sequelae such as physical and cognitive aftereffects, and mortality – make it paramount to prevent infections from ever occurring in the first place. According to the World Health Organization, the prevention strategies are multi-layered[1]. To prevent sepsis in newborns, mothers are recommended to breastfeed instead of bottle-feed. While hand washing lies at the foundation of infection prevention, whether this is done effectively and consistently needs to be monitored and human behaviors need to improve. Over the course of mankind, one of the greatest triumphs has been the development of vaccinations which have helped to prevent infections; one of the tragedies has been when there is a lack of access to life-saving vaccinations or vaccine hesitancies, which have led to unnecessary tragic deaths. Ensuring food safety is also important to prevent death from food-borne illnesses which can lead to sepsis. Part of infection prevention is also educating about the signs and symptoms of infection and prompt referral to clinicians to diagnose and treat infections.

Global antimicrobial resistance

Once bacterial causes of sepsis are suspected in a patient, empiric treatment with broad-spectrum antibiotics may be started. If not treated as quickly as possible with the right antibiotics, sepsis can be deadly. However, prescribers are often challenged with making the tough decision to withhold treatment until a source is identified but risks the potential harm of clinical decompensation. The alternative would be to treat empirically with antibiotics which in retrospect might demonstrate antimicrobial resistance in cultures, subsequently exposing patients to adverse antibiotic side effects and potentially further contributing to the development of antimicrobial resistance. Antibiotic treatment can lead to deleterious side effects such as reducing the number of homeostatic bacteria present in the gut as well as alterations in the type of bacteria present, leading to consequent infections such as *Clostridioides difficile*. Antimicrobial resistance is a global threat to public health. In 2019 alone, antimicrobial resistance was directly responsible for 1.27 million global deaths.

Climate change and impact on sepsis globally

Increases in global temperature due to climate change can create conditions that are favorable for the spread of infections. Climate variations can cause disruptions in the life cycles of certain pathogens and/or their animal hosts that can promote disease outbreaks. Alterations in weather patterns such as precipitation, humidity, and temperature can contribute to the survival and transmission of pathogens. Increased frequency and severity of natural disasters such as hurricanes, typhoons, droughts, and wildfires can cause disruption of healthcare services and promote crowding as people congregate in emergency shelters which would promote the spread of infection. Vector and pathogen adaptation and evolution in response to the shifting climate can result in increased incidence of disease.

Access to diagnostics in sepsis

In developed countries, access to rapid diagnostics may be more readily available than in developing countries. Though access to healthcare may be more widely available in a developed country such as the United States, health disparities still exist in abundance. There are areas in the United States which lack large healthcare systems with multispecialty access such as infectious diseases and infectious disease pharmacists. Barriers to accessing health such as distance, lack of transportation, inability to find childcare, or eldercare can inhibit timely diagnosis of sepsis. However, even within the United States, not every acute care system may have access to polymerase chain reaction (PCR) blood culture diagnostics results. In sepsis, a part of survival is not only ensuring that antibiotics are given on a timely basis, but that the most appropriate ones are given. Blood cultures are an important tool and are often included in sepsis workup; however, the time to finalization can take 24 hours for a gram stain if it is positive then another 24 hours for a species, and then another 24 hours after that for sensitivity results. While there are many rapid diagnostics from whole blood, this is not as commonly used as a rapid PCR once the gram stain is positive. Some diagnostics can identify the species and determine whether it is a bacteria or yeast; others provide the detection or absence of resistance genes. If a resistant gene is detected and if this is appropriately addressed, then patients can receive antibiotics faster, and decreased time to appropriate antibiotics can help improve survival.

Artificial intelligence in sepsis

Given the high rates of mortality associated with sepsis, prompt and early diagnosis as well as treatment are crucial. Physicians typically utilize diagnostic criteria such as SIRS (systemic inflammatory response syndrome) or qSOFA (quick Sepsis Related Organ Failure Assessment) to aid in diagnosis of sepsis. However, given the rapid advancements in Artificial Intelligence (AI) programs across all domains, there may be utility in integrating this into medical record systems to allow for faster and more accurate screening. Artificial intelligence programs can be integrated into Electronic Medical Record (EMR) systems to help better detect whether a patient has sepsis at the time of sepsis as well as their likelihood of developing sepsis in the coming days and hours. In 2021, a Singapore-based hospital system implemented an AI algorithm (SERA) to detect sepsis and to predict the risk of sepsis in patients at the time of consultation as well as in the next 4, 6, 12, 24, and 48 hours. This AI program was found to predict sepsis in patients at a much higher rate of accuracy than physician prediction. The utilization of technological advancements such as AI has the potential to improve the rapid

recognition of sepsis and prompt initiation of antibiotics. More research is needed to improve accuracy and complement clinical workup for sepsis.

Equity in sepsis

Current approaches to combating sepsis place great emphasis on efforts at the individual level. The authors would be remiss to neglect addressing the social determinants of health that promote and perpetuate disparities in sepsis diagnosis, treatment, and management in certain populations. There are several factors that influence this disparity such as race, gender, ethnicity, language, and socioeconomic status. Additionally, the current studies on sepsis do not capture all subgroups equally, with most studies performed in high-income countries even though the majority of the worldwide sepsis burden impacts the lowest-income countries. Marginalized communities face undue disadvantages such as chronic stress, decreased access to healthcare and education, and poor living conditions that place them at greater risk of chronic disease that in turn predisposes them to contracting severe infections. Even when properly diagnosed and treated for these diseases, they often do not have the support system to cope with the aftereffects of the disease and can end up with recurrent infections and/or chronic disabilities and sequelae of sepsis. Properly addressing health disparities in sepsis requires an honest critique of the systemic failures that exist in society and taking the initiative at the legislative and public health level to create tangible changes that will improve sepsis outcomes for all.

Advocacy organizations for sepsis

Globally, there is a critical importance to nonprofit organizations which may be rooted in patient advocacy for the voices of sepsis. These organizations may provide many different types of help, including memorializing people or loved ones who have lost their lives to sepsis or who have overcome septic shock, educating about sepsis, and advocating for change in practices or policies, amongst other priorities.
In **Table 1**, we provide examples of sepsis organizations that have advocated for patients and whose priority populations may be in their jurisdiction but could potentially have an impact globally. Of note, this list is a sampling of the organizations and is not inclusive of every organization across the globe. Of note, for both the Centers for Disease Control and Prevention and the World Health Organization, the website links are directly to the portions of their websites related to sepsis.

Community-based initiatives to promote sepsis education

While education of hospital systems and clinicians as well as nurses is important on a global scale, so too is the deployment of education to communities. Far too often, individual patients or their family members may not have heard of sepsis until they have had personal experiences. Sepsis education can occur through the work of sepsis advocacy organizations, as well as on a grassroots basis by having health systems educate about sepsis in community-based settings. This may first entail partnerships with community-based organizations or faith-based organizations, for instance, to gain buy-in from trusted leaders. Then, sepsis education can be delivered in familiar settings that the communities frequent regularly instead of requiring individuals to travel onsite to hospital systems. In addition, sepsis advocates could be mobilized and recruited to share

their sepsis stories to others. Furthermore, investment in community health workers as well as training them about sepsis may serve as potential avenues to reach communities well before individuals are hospitalized.

Table 1. List of sepsis-related organizations.

Organization	Website
African Sepsis Alliance	https://www.africansepsisalliance.org/
Asian Pacific Sepsis Alliance	https://www.asiapacificsepsisalliance.org/
Centers for Disease Control and Prevention	https://www.cdc.gov/sepsis/index.html
End Sepsis	https://www.endsepsis.org/
European Sepsis Alliance	https://www.europeansepsisalliance.org/
Global Maternal and Neonatal Sepsis Initiative	https://srhr.org/sepsis/
Global Sepsis Alliance	https://globalsepsisalliance.org/
Sepsis Alliance	https://www.sepsis.org/
The UK Sepsis Trust	https://sepsistrust.org/
The World Health Organization	https://www.who.int/news-room/fact-sheets/detail/sepsis#

Approaches to combat sepsis

The impact of sepsis worldwide can appear daunting; however, there are many steps we can take to reduce the global burden of sepsis. One of the first steps includes implementing ways to improve the accuracy in the identification and quantification of sepsis. Health systems should educate clinicians on appropriate and standardized documentation of sepsis cases. This will improve data collection and allow us to better quantify the current burden of sepsis as well as track and assess the efficacy of interventions over time. This in turn will allow us to better target areas of improvement and guide future health planning. Another important part of tackling sepsis is increasing awareness of the issue. Advocacy at the governmental level can help enact change and promote research on the topic. Sepsis prevention methods such as proper hygiene, water sanitation, and access to vaccinations also play a key role. Swift and timely recognition of sepsis at the population level can also help prevent death and disability as sepsis is a time-sensitive medical condition whose progression can be insidious and unpredictable.

Conclusion

The landscape of medicine is dynamic and our knowledge and understanding of sepsis in particular continues to develop and grow. Sepsis outcomes have improved dramatically throughout the years thanks to a combination of increased preventive care efforts, improved diagnostics and treatment, and greater awareness of sepsis in the community. However, there is still room for improvement in increasing sepsis research and data

for low- to middle-income countries, tackling large-scale issues such as climate change, and evaluating systemic causes of sepsis disparities. Addressing the global burden of sepsis involves cooperation and a coordinated effort at multiple levels including the governmental, healthcare, and population level. A global spotlight on sepsis will hopefully improve funding and promote further advocacy to create meaningful advances toward improving sepsis outcomes for all.

Competing interests

CH is the Chief Medical Officer of Sepsis Alliance and a member of its Board of Directors. US is a member of the Advisory Board for Sepsis Alliance.

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Chapter 97

Sepsis and septic shock: physiopathology and classification

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Introduction

Sepsis is a life-threatening clinical syndrome characterized by a dysregulated host response to infection, causing multiple organ dysfunctions and death. Sepsis represents a huge burden for patients and healthcare systems worldwide. In 2017 estimated cases of sepsis were 48.9 million, while sepsis-related deaths were 11 million, representing 19.7% of global deaths. This huge healthcare burden seems to be more present in low- and middle-income countries. Septic shock represents the most severe clinical subset of sepsis. It is a type of distributive shock, caused by the involvement of the circulatory system together with cellular and metabolic abnormalities, associated with a significantly higher risk of mortality compared to sepsis.

Immunological response to infection

The response to infection starts with the interaction of innate immune cells with microbial components called PAMPs (pathogen-associated molecular patterns), including bacterial endotoxins such as LPS. PAMPs bind to so-called pattern recognition receptors (PRRs) located on the surface of immune cells, such as Toll-like Receptors (TLRs), Nucleotide-Oligomerization Domains (NODs) and Retinoic Acid-inducible gene I (RIG-1). PRRs may also bind to endogenous signals, called danger-associated molecular patterns (DAMPs) or alarmins, which are released by injured cells during the inflammatory insult. These molecules are intracytoplasmic structures that

acquire new functions when released in the extracellular environment. Examples of DAMPs are S100 proteins, Heat Shock proteins (HSP) and ATP. The activation of immune cells caused by the binding of surface receptors to microbial components has various effects. For example, the binding of TLRs triggers a cascade of intracellular signaling, activating transcription factors, such as Nf-kB, and inducing the production of molecules involved in promoting inflammatory response, such as tumor necrosis factor α (TNFα), interleukin 1 (IL-1) and chemokines, as illustrated in **Figure 1**. Moreover, activated polymorphonuclear leukocytes migrate to the site of injury, releasing mediators that are responsible for the manifestations of local inflammation and increase microvascular permeability. Lastly, growing evidence suggests a role of a healthy microbiota in host defense. The trillions of commensal microorganisms colonizing the gut provide resistance against colonization and invasion against pathogens, by competing for space and nutrients, protecting the epithelial barrier and producing antibacterial peptides. The process of innate immune response to infection can be depicted as a balance of pro- and anti-inflammatory mediators, produced and released by macrophages in response to bacterial tissue invasion. If the mediators balance each other and the insult is resolved, homeostasis will be restored, and the tissue will start healing.

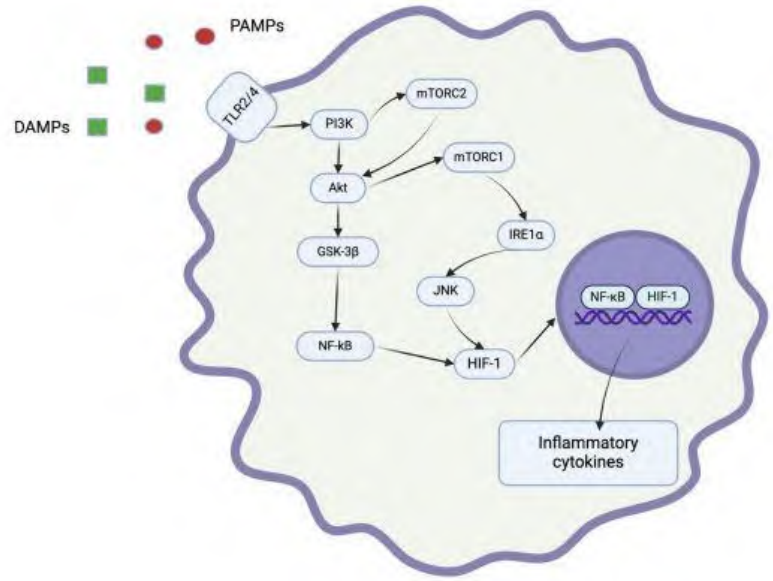

Figure 1. Illustration of one of the main signaling pathways activating immune response (created with BioRender.com). *Abbreviations*: PAMP Pathogen Associated Molecular Pattern, DAMP Danger Associated Molecular Pattern, TLR Toll-like Receptor, PI3K Phosphatidylinositol 3-kinase, AKT protein kinase B, GSK-3β Glycogen Synthase Kinase-3 beta, NF-kB Nuclear Transmutation of activated B cell, mTORC mammalian Target Of Rapamycin Complex, IRE1α Inositol-Requiring Enzyme 1 α, JNK Jun N-terminal Kinase, HIF-1 Hypoxia-Induced Factor-1.

Pathophysiology of sepsis

Sepsis results from a dysregulated and excessive host response to infection, with its pathophysiology being a complex interplay of immune, inflammatory and coagulation pathways. The transition from local to generalized response seems to be multifactorial, including the abnormal release of proinflammatory mediators, complement activation, a disrupted microbiota but also a genetical susceptibility of certain individuals.

One of the main factors seems to be the excess of proinflammatory mediators. When host response to infection is excessive, the binding of PRRs to PAMPs leads to an uncontrolled release of proinflammatory cytokines, historically defined as “cytokine storm”. For example, circulating levels of TNFα are higher in septic patients compared to non-septic ones with shock. Notably, when immune stimulation becomes persistent, not only PAMPs but also DAMPs concur to the vicious cycle of perpetrating immune activation via PRRs. Furthermore, there is evidence that activation of the complement system may have an important role in sepsis, as its uncontrolled activation can injure tissues and organs of the host, induce the release of tissue factor on endothelial cells and determine disseminated intravascular coagulation. In sepsis, the coagulation system results unbalanced, having a tendency towards thrombosis in the microvasculature. NETosis, a defense mechanism operated by neutrophils consisting in extrusion of decondensed nuclear chromatin and DNA mixed with granule-derived antimicrobial peptides in extracellular space, can also promote inflammation and tissue damage in sepsis, especially in the pathogenesis of disseminated intravascular coagulation and intravascular thrombosis. Apparently, genetic susceptibility may also play a role in sepsis. Various single nucleotide polymorphism (SNP), the most common form of genetic variation in humans, are associated with increased susceptibility to infection, more frequently the ones encoding for cytokines (IL-1 antagonist and TNF) and cell surface receptors (TLRs, CD14). Lastly, the disruption of microbiome balance may lead to a transition from homeostasis to disease, as indirectly demonstrated in large observational studies, and to increased susceptibility to further infections.

Systemic effects of sepsis

Passing from local to generalized response determines a widespread cellular injury, which is the precursor of organ dysfunction. As the mechanism of tissue damage is not yet fully understood, various models have been proposed. One of the pathogenetic models of widespread cellular injury in sepsis may be tissue ischemia caused by reduced peripherical oxygen exchange, which starts from microcirculatory and endothelial lesion. While microcirculatory lesions may result from altered coagulation, endothelial damage may be the result of the immune response. Production of reactive oxygen species (ROS), lytic enzymes, nitric oxide as well as NETosis operated by neutrophils produces endothelial damage. Also, erythrocytes lose their ability to deform in microcirculation, resulting in heterogeneous microcirculatory blood flow and, thus, reduced oxygen delivery. Another concurring mechanism is probably the so-called cytopathic injury: mediators of inflammation and its products may cause mitochondrial dysfunction through several pathways, including inhibition of respiratory enzyme complexes, oxidative stress damage and switch to anaerobic glycolysis, that results in the cytosolic conversion of pyruvate to lactate and, consequently, hyperlactatemia. Whatever the mechanism, altered mitochondria lead to cellular death determined by the inability to utilize oxygen, although present. During sepsis, several cell death pathways may be activated, including apoptosis, pyroptosis and autophagy-induced cell death. Apoptosis alters immune response by inducing death in lymphocytes and dendritic cells, determining immune suppression. Another mechanism is triggered by the aggregation of PRRs into macromolecular protein complexes, named inflammasome. Inflammosomes produce proinflammatory mediators, such as IL-1 and IL-18, and activate caspase-1, inducing programmed cell death by rapid rupture of the plasma membrane, termed pyroptosis. This pathway seems to concur in immune suppression by inducing cell death of monocytes and macrophages. Autophagy, a protective natural process implied in the removal of cytoplasmic substances or pathogens via autophagosome and consequent degradation via lysosome, seem to be inadequate in sepsis, aggravating tissue and organ injury and it may play a role in immune suppression.

The coagulation system and endothelial cells are also altered during sepsis. Sepsis-associated disseminated intravascular coagulation (DIC) is a systemic activation of coagulation with a suppressed fibrinolysis, together with a systemic inflammation that leads to organ dysfunction. Immune cells, through binding of their PRRs to PAMPs, produce tissue factor, that has been recognized as the main initiator of coagulation in sepsis. Furthermore, DAMPs molecules, NETosis, and leucocyte-derived extracellular vesicles, particularly neutrophil ones, all concur with the genesis of immunethrombosis. On the other hand, damage to the gel-like layer on the surface of endothelial cells, called glycocalyx, results in altered permeability, loss of antithrombogenicity, loss of anti-inflammation capability and, thus, microvascular dysfunction. In addition, activated platelets are promoted to aggregate and adhere to the damaged endothelium, providing a procoagulant membrane surface for further deposition of fibrin clot, but they also concur to perpetuate the endothelial damage by expressing ligands that alter endothelium. Stimulated platelet aggregation may also motivate sepsis-related thrombocytopenia.

Organ dysfunction in sepsis

The release of proinflammatory mediators together with cellular injury as described previously progresses to organ dysfunction, resulting in organ-specific manifestations. It has to be noted that multiple-organ dysfunction is common in sepsis.

Circulation

Hypotension due to diffuse vasodilation is the most severe expression of sepsis-induced organ dysfunction, as it concurs with the pathogenesis of other organ injuries. The aforementioned molecular and cellular mechanism of injury determines heterogeneous changes in microcirculation, with clinically significant vasodilation of arterioles in the systemic circulation. This results from unbalance of vasodilating agents (e.g. nitric oxide, histamine, kinins and prostaglandins) and endogenous vasopressors, determining reduced systemic resistance and hyporesponsiveness to vasoconstrictors such as epinephrine and norepinephrine. Nitric oxide (NO), a vasodilating agent, probably plays a pivotal role in sepsis. It is produced by NO synthase (NOS), which is induced during sepsis by proinflammatory mediators such as IL-1β and TNFα. NO produces its effects through guanylylcyclase stimulation, reducing myocyte intracellular calcium availability and sensitivity, and ultimately inducing vasodilation and hyporeactivity to endogenous vasopressors.

Heart

Sepsis-induced cardiomyopathy seems not to result from general hypoperfusion or hypoxia. Growing evidence demonstrates a non-ischemic myocardial depression as a pathogenesis of cardiac dysfunction, potentially having a self-protective meaning. One of the mechanisms proposed involves the downregulation of cardiac adrenergic receptors and/or their post-receptor signaling pathways, resulting in impaired response to catecholamines. Moreover, the release of DAMPs in systemic circulation may trigger cardiomyocytes to produce proinflammatory cytokines, such as IL-1, IL-6 and TNFα, which have been considered myocardial depressants by altering calcium balance for cardiac contractility. Mitochondria are also damaged during septic cardiomyopathy, resulting in microstructural breakdown, increase of membrane permeability and release of DAMPs, such as DNA and ATP, which may concur to systemic inflammation and altered cellular metabolism.

Lung

Sepsis-associated acute lung injury (ALI) finds its hallmark in the damage to the alveolar wall capillary barrier, which causes interstitial and alveolar pulmonary edema. One of the main protagonists of the pathogenesis of sepsis-associated ALI are macrophages, which can bind pathogen-associated molecules and release proinflammatory cytokines, concurring to alveolar damage. Neutrophils participate as well in the pathogenesis of ALI: their abnormal activation during ALI causes them to accumulate in the lungs and produce proinflammatory cytokines, damaging the epithelial and endothelial integrity. Lastly, oxidative stress damage, dysfunction of the coagulation system and abnormalities of alveolar surfactant, all concur with the pathogenesis and/or worsening of sepsis-associated ALI.

Gut and liver

Sepsis may determine the hyperpermeability of the intestinal barrier by dysregulating intestinal epithelial cells apopthosis. On the other hand, the physiological diversity of microbiota results disrupted, becoming dominated by multi-drug-resistant microorganisms. Disruption of the intestinal barrier favors PAMPs, such as LPS, and DAMPs to transfer into the systemic circulation, triggering an uncontrolled inflammatory response. When these molecules migrate to the liver through the portal circulation, inappropriate immune response results in impaired clearance of hepatic pathogenic bacteria and metabolic disorders, potentially favoring spillover of gut-derived toxins to the systemic circulation.

Kidney

Acute kidney injury (AKI) during sepsis may find multiple pathogenetic pathways, although its way of developing remains not fully understood. Hypoperfusion, leading to cellular hypoxia and necrosis (i.e. acute tubular necrosis or ATN), may be one of the mechanisms, although it has been demonstrated that sepsis-associated AKI may occur even with a preserved renal blood flow. Heterogeneity of blood flow, together with a decrease in the proportion of capillaries carrying continuous (nurturing) blood flow, has been proposed as the key mechanism of organ injury. This microcirculatory dysfunction may have multiple causes: endothelial injury, increased leucocyte recruitment, activation of the coagulation cascade and formation of microthrombi may alter the microvascular flow, inducing the release of DAMPs and PAMPs and significant tubular injury. In the kidney, tubular injury concurs to determine the loss of glomerular filtration rate (GFR) and increase in serum creatinine (SCr). Loss of GFR during sepsis may also be caused by a simultaneous constriction of the afferent arteriole and dilation of the efferent one, decreasing glomerular hydrostatic pressure. Moreover, the constriction of the afferent arteriole leads to intrarenal shunting through extraglomerular capillaries, concurring to a decrease in GFR.

Central nervous system

Sepsis-associated encephalopathy (SAE) is a very common phenomenon, occurring in 71% of patients diagnosed with sepsis. The pathogenesis of cerebral dysfunction is not yet fully understood, although evidence suggest alteration of the blood-brain barrier (BBB). Microglial cells, which are part of the neurovascular unit that constitutes the BBB, are activated by circulating proinflammatory cytokines. Activated microglia produce more proinflammatory mediators, but also nitric oxide, ROS and glutamate, resulting in aberrant neuronal functioning, cellular death and increased permeability of BBB. On the other hand, brain endothelial cells (BEC) are also affected: circulating toxins, such as LPS, and proinflammatory cytokines can alter tight junctions of the BBB, increasing its permeability, but can also activate BEC, resulting in leucocyte recruitment and infiltration, activation of coagulation cascade and local microthrombosis. In the pathogenesis of SAE, alteration of BBB seems intertwined with neuroinflammation. Excessive production of proinflammatory cytokines, such as

TNFα and high mobility group box-1 (HMGB1), results in deteriorative neuroflogosis. In a murine model, TNFα appears to be a key mediator of SAE, determining various injuries, such as brain edema, cellular apoptosis, leucocyte infiltration and astrocytes activation. Activated astrocytes play a pivotal role in perpetuating inflammatory brain injury, as their aberrant responses promote intractable neuroinflammation and cognitive impairment. Lastly, inflammation may be responsible of brain tissue ischemic injury by altering endothelial cells (EC). Injured EC produce various mediators promoting thrombogenesis and abnormal vasoconstriction. Consequently, this ischemic process exacerbates local inflammation, increasing leucocyte infiltration and immune dysfunction, resulting in a vicious cycle.

Classification

Classification of sepsis has evolved over time, reflecting advances in medical research. The latest update on the definition of sepsis was introduced in 2016 with the Third International Consensus Definition for Sepsis and Septic Shock (Sepsis-3). Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection. Organ dysfunction is quantified using the Sequential Organ Failure Assessment (SOFA) score. An increase of 2 points or more in the SOFA score indicates organ dysfunction and, thus, it may indicate sepsis in a correct clinical scenario. The SOFA score tool assesses the function of six organ systems: neurological, cardiovascular, respiratory, hepatic, renal and coagulation. The pathophysiology of organ injury and relative SOFA score item is presented in **Table 1**.

Table 1. Pathophysiology of organ injuries and related SOFA score item.

Organ injury	Pathophysiology	SOFA score Item
Cardiovascular system	• Unbalance of vasodilating agents and endogenous vasopressors, determining reduced systemic resistance and hyporesponsiveness to vasoconstrictors • Downregulation of cardiac adrenergic receptors resulting in impaired response to cathecolamines • Release of DAMPs may trigger the release of proinflammatory cytokines, causing myocardial depression • Mitochondria damage	MAP
Lung	• Damage to the alveolar wall capillary barrier caused by proinflammatory cytokines, oxidative stress damage, coagulation dysfunction and abnormalities in alveolar surfactant	PaO_2/ FiO_2
Liver	• Hyperpermeability of intestinal barrier and alteration of gut microbiota promote migration of pathogenetic molecules to the liver, determining inappropriate immune response	Bilirubin
Kidney	• Acute tubular necrosis • Heterogeneity of blood flow caused by endothelial injury, leucocyte recruitment and microthrombi formation may determine tubular injury and consequent reduction in GFR	Creatinine and urine output
Central nervous system	• Alteration of the blood-brain barrier • Neuroinflammation	GCS
Coagulation	• Endothelium damage • Overproduction of tissue factor • Alteration of the glycocalyx • Platelet aggregation	Platelets

Abbreviations. DAMPs: danger-associated molecular patterns, GCS: Glasgow Coma Scale. GFR: glomerular filtration rate. MAP: mean arterial pressure, PaO_2, arterial partial pressure of oxygen, FiO_2, fraction of inspired oxygen, SOFA: Sequential Organ Failure Assessment.

Septic shock is defined as a subset of sepsis in which underlying circulatory and cellular metabolism abnormalities are profound enough to substantially increase mortality. Clinically, septic shock is identified, in the setting of a suspected infection, by the need for vasopressor therapy to maintain a mean arterial pressure (MAP) over 65 mmHg and a serum lactate level higher than 2 mmol/L despite adequate volume resuscitation.

Conclusion

Sepsis is a life-threatening clinical syndrome, with a complex pathogenesis, multiple organ dysfunction and a high mortality rate if not treated promptly. Molecular pattern disruption, cellular death, and tissue and organ injury realize a fine physiopathological interplay which is yet to be fully understood. Preclinical and clinical research needs to further advance in its comprehension, trying to improve outcomes and/or implement strategies to prevent sepsis.

Competing interests

The authors have no financial and non-financial competing interests to declare.

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Chapter 98

Abdominal compartment syndrome

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Introduction

Intra-abdominal hypertension (IAH) and abdominal compartment syndrome (ACS) are critical conditions that pose significant risks to critically ill patients, influencing morbidity and mortality rates. The Abdominal Compartment Society (WSACS, www.wsacs.org) has provided standardized definitions and management guidelines to enhance the recognition and treatment of these conditions.

IAH, characterized by an elevated intra-abdominal pressure (IAP) equal to or above 12 mmHg, can affect a broad range of patients, including those undergoing trauma, burns and various surgical procedures but also medical patients like those with sepsis and pancreatitis. The fluid dynamics of the abdominal cavity, governed by Pascal's law, are crucial in understanding the effects of IAP on organ perfusion. Changes in mean arterial pressure (MAP) and IAP or central venous pressure (CVP) can alter abdominal perfusion pressure (APP) and renal perfusion pressure (RPP), leading to complications like acute kidney injury (AKI). Thus, achieving optimal perfusion pressures tailored to individual patient needs is essential in managing IAH and ACS.

Over the past few decades, there have been significant advancements in the understanding of IAH and ACS, particularly in their pathophysiology, diagnosis, and management. These developments have improved the identification of organ dysfunction mechanisms related to elevated IAP and have led to the creation of both medical and minimally invasive management techniques. Nevertheless, challenges persist, particularly in the application of these guidelines to individual patients, where dynamic and evolving clinical conditions demand a tailored approach to treatment.

A key area of interest is abdominal compliance, which refers to the capacity of the abdominal cavity for expansion and is influenced by the elasticity of the abdominal wall and diaphragm. Despite its importance, abdominal compliance remains an under-explored parameter in critically ill patients, although, it is crucial for comprehending the adverse effects of increased intra-abdominal volume on organ function and perfusion and it helps to understand organ-organ crosstalk interactions as seen in polycompartment syndrome or cardio-abdominal-renal syndrome (CARS).

This chapter aims to provide a comprehensive overview of IAH and ACS, focusing on their definitions, epidemiology, diagnosis, pathophysiology, prognosis, and management strategies, while also highlighting future research directions and key takeaways for clinical practice.

Historical background

The relationship between IAP and organ function was first identified in the late 19th century. Wendt's early work linked elevated IAP to renal impairment, while Marey observed the inverse effects of thoracic and abdominal pressures. Despite these early observations, the clinical significance of IAP remained underappreciated until the late 20th century. Emerson's 1911 work highlighted the cardiovascular and respiratory consequences of increased IAP, laying the groundwork for understanding abdominal compartment syndrome (ACS).

Definitions

The term ACS was first introduced by Fietsam *et al.* in the late 1980s to describe the physiological changes resulting from IAH following aortic aneurysm surgery. They observed that increased IAP in patients who received extensive fluid resuscitation led to increased ventilatory pressures, elevated CVP, and decreased urinary output, which dramatically improved upon abdominal decompression. Recognizing the need for standardization in this field, the WSACS, established in 2004 has since developed consensus definitions.

According to WSACS definitions, IAH is characterized by a sustained increase in IAP equal to or above 12 mmHg. Abdominal compartment syndrome (ACS) represents a complex and multifaceted condition characterized by sustained intra-abdominal pressure (IAP) above 20 mmHg, which is associated with new or worsening organ dysfunction. The development of ACS can result from various underlying causes, including trauma, burns, and surgery, but also medical conditions like sepsis, pancreatitis and other conditions that lead to increased abdominal volume and reduced compliance of the abdominal wall. Understanding the pathophysiology of ACS is crucial for the effective management of affected patients. The APP, calculated as the MAP minus the IAP, serves as an important parameter for assessing visceral perfusion. An APP below 60 mmHg is often used as a critical threshold in evaluating the severity of ACS.

The condition is classified into three types: primary, secondary, and recurrent intra-abdominal hypertension (IAH). Primary IAH typically arises from conditions within the abdominopelvic region, such as hemorrhage, surgery, or intra-abdominal infections. Secondary IAH, on the other hand, is associated with conditions outside the abdominopelvic region, such as severe sepsis, pancreatitis, or massive fluid resuscitation. Recurrent IAH describes cases where IAH reappears after an initial resolution, often due to underlying chronic conditions or inadequate initial management. The severity of IAH is graded based on the measured IAP, which guides clinical management decisions. Grade I IAH is defined as an IAP of 12-15 mmHg, Grade II as 16-20 mmHg, Grade III as 21-25 mmHg, and Grade IV as an IAP greater than 25 mmHg. As IAP increases, the risk of progression to ACS and associated organ dysfunction increases, affecting the neurological, cardiovascular, respiratory, renal, hepatic, and gastrointestinal systems, necessitating a proactive approach to management.

In children, the definitions and thresholds for IAH and ACS are adjusted due to physiological differences. Normal IAP values in healthy children are lower, around 3-5 mmHg, and the thresholds for IAH and ACS are also correspondingly lower. For instance, IAH in children is defined by an IAP of 10 mmHg, and ACS is defined as a sustained elevation in IAP of greater than 10 mmHg associated with new or worsening organ dysfunction that can be attributed to elevated IAP. The full list of established and potential new definitions is given in **Table 1A-E**.

Table 1A. Definitions regarding Intra-abdominal Hypertension according to the 2013 WSACS guidelines update; WSACS 2013 Definition statement (Adapted from Kirkpatrick AW, *et al.* 2013).

Topic	WSACS 2013 Definition statement
Intra-abdominal pressure (IAP)	IAP is the steady-state pressure concealed within the abdominal cavity.
Abdominal perfusion pressure (APP)	APP = MAP – IAP
"Normal" IAP	IAP is approximately 5-7 mmHg and around 10 mmHg in critically ill adults.
Intra-abdominal hypertension (IAH)	IAH is defined by a sustained or repeated pathological elevation in IAP ≥12 mmHg.
IAH grading	IAH is graded as follows: ● Grade I, IAP 12–15 mmHg; ● Grade II, IAP 16–20 mmHg; ● Grade III, IAP 21–25 mmHg; ● Grade IV, IAP > 25mmHg.
Abdominal compartment syndrome (ACS)	ACS is defined as a sustained IAP>20 mmHg (with or without an APP<60 mmHg) that is associated with new organ dysfunction/failure.
Primary IAH/ACS	Primary IAH/ACS is a condition associated with injury or disease in the abdominopelvic region that frequently requires early surgical or interventional radiological intervention.
Secondary IAH/ACS	Secondary IAH/ACS refers to conditions that do not originate from the abdominopelvic region.
Recurrent IAH/ACS	Recurrent IAH/ACS refers to the condition in which IAH/ACS redevelops following previous surgical or medical treatment of primary or secondary IAH/ACS.
IAP measurement	The reference standard for intermittent IAP measurements is via the bladder with a maximal instillation volume of 25 mL of sterile saline. IAP should be expressed in mmHg and measured at end-expiration in the complete supine position after ensuring that abdominal muscle contractions are absent and with the transducer zeroed at the level of the midaxillary line.
Poly-compartment syndrome	A poly-compartment syndrome is a condition where two or more anatomical compartments have elevated compartmental pressures.
Abdominal compliance	Abdominal compliance quantifies the ease of abdominal expansion, is determined by the elasticity of the abdominal wall and diaphragm, and is expressed as the change in intra-abdominal volume per change in intra-abdominal pressure in L/mmHg.
Open abdomen (OA)	An OA is any abdomen that is left temporarily open after creating a surgical defect for exposure of abdominal contents. It may include temporary abdominal closure with only skin and fascia. The technique of temporary abdominal closure should be explicitly described.
OA classification	The open abdomen is classified with the following grading system: **1 – No fixation** ● 1A: clean, no fixation. ● 1B: contaminated, no fixation. ● 1C: enteric leak, no fixation. **2 – Developing fixation** ● 2A: clean, developing fixation. ● 2B: contaminated, developing fixation. ● 2C: enteroatmospheric/cutaneous fistula, developing fixation. **3 and 4 – Frozen abdomen** ● 3: frozen abdomen, no fistula. ● 4: frozen abdomen with enteroatmospheric/cutaneous fistula.
Lateralization of the abdominal wall	Lateralization of the abdominal wall refers to the phenomenon whereby the musculature and fascia of the abdominal wall, most well seen by the rectus abdominis muscles and their enveloping fascia, move laterally away from the midline with time.

Table 1B. Definitions regarding Intra-abdominal Hypertension according to the 2013 WSACS guidelines update; Pathophysiology, WSACS 2024 Potential new definitions (Adapted from Kirkpatrick AW, *et al.* 2013)

Topic: Pathophysiology	WSACS 2024 Potential new definitions
Major body compartments	There are 4 major body compartments: head, chest, abdomen, and extremities.
Filtration gradient (FG)	FG is the mechanical force across the glomerulus and equals the difference between GFP and PTP, while GFP is the difference between MAP and RVP
Filtration gradient and IAH	In the presence of IAH, PTP may be assumed to equal RVP and IAP, and thus GFP can be estimated as difference between MAP and IAP. The FG can then be calculated by the formula, MAP– 2*IAP.
Respiratory abdominal variation test (RAVT)	RAVT is a non–invasive test assessing RAV during gradual increase in tidal volume (in mechanically ventilated patients) and provides indirect measure of Cab.
Abdominal pressure variation	Abdominal pressure variation is an indirect measure of Cab and can be calculated as (IAPei – IAPee)/IAPmean.
Abdominal perfusion pressure (APP)	APP is the difference between MAP and IAP and should be kept above 60 mmHg.
Positional abdominal variation test (PAVT)	PAVT is a non–invasive test assessing RAV during gradual changes in HOB (also in spontaneous breathing) and provides indirect measure of Cab.
RAV	RAV is an indirect measure of Cab and can be calculated as IAPei – IAPee (delta IAP).
Pascal's law	The abdominal cavity/compartment is considered as being primarily fluid in character following Pascal's law.

Table 1C. Definitions regarding Intra-abdominal Hypertension according to the 2013 WSACS guidelines update; Measurement, WSACS 2024 Potential new definitions (Adapted from Kirkpatrick AW, *et al.* 2013)

Topic: Measurement	WSACS 2024 Potential new definitions
Normal IAP and anthropometry	The normal IAP differs regarding the patient population and anthropometry and can be non–pathologically increased 10–15 mmHg in obese patients, pregnancy, etc.
Continuous IAP (CIAP)	Continuous IAP can be used to keep track of changes in IAP during treatment.
Gold standard CIAP	Different techniques exist to perform continuous IAP monitoring (e.g., gastric, bladder, direct). A gold standard yet needs to be identified.
Clinical assessment	Clinical assessment and estimation of IAP is inaccurate.
Gastric pressure	The gastric route can be used as alternative for intermittent IAP measurement with a maximal instillation volume of 50–75 mL of water or nutritional fluid.
Awake patients	IAP measurement can also be performed in awake or spontaneously breathing patients.
Normal IAP in healthy	IAP is approximately 5–7 mmHg in healthy adults. Modify: IAP is approximately 5–7 mmHg in healthy adults.
Normal IAP in ICU	Normal IAP is approximately 10 mmHg in critically ill adults.
Effect of HOB	After IAP measurement in the supine position, IAP should also be measured in the "resting" position of the patient, e.g., the normal HOB is at 30–45° position or prone position.

Table 1D. Definitions regarding Intra-abdominal Hypertension according to the 2013 WSACS guidelines update; Extended definitions, WSACS 2024 Potential new definitions
(Adapted from Kirkpatrick AW, *et al.* 2013)

Topic: Extended definitions	WSACS 2024 Potential new definitions
IAH Duration	IAH duration can be chronic, acute, subacute or hyperacute
Hyperacute IAH	Hyperacute IAH is defined as IAH that only lasts for second or minutes (e.g., coughing, sneezing).
Acute IAH	Acute IAH is defined as IAH that develops within hours (e.g., ruptured abdominal aortic aneurysm).
Subacute IAH	Subacute IAH is defined as IAH that develops within days (e.g., fluid overload and capillary leak).
IAH categories	The four distinct IAH categories are defined as medical, surgical, trauma or burns.
Chronic IAH	Chronic IAH is defined as IAH that lasts for months or years (e.g., ovarian tumour, ascites, pregnancy).
Sustained IAH	Sustained increase in IAP is defined as a pathological value during a minimum of three standardized measurements that are performed 1–2 hours apart for ACS and 4–6 hours apart for IAH.
Localized IAH	Localised IAH and ACS is defined as a local increase in IAP that does not lead to a systemic elevation (e.g., pelvic trauma, liver or spleen trauma).
Organ dysfunction	Organ dysfunction/failure is assessed by (a daily) SOFA or equivalent scoring system (qSOFA); organ failure is defined as a SOFA organ system sub–score of >2.

Table 1E. Definitions regarding Intra-abdominal Hypertension according to the 2013 WSACS guidelines update; Management, WSACS 2024 Potential new definitions (Adapted from Kirkpatrick AW, *et al.* 2013)

Topic: Management	WSACS 2024 Potential new definitions
Medical management	Medical management is defined as a nonsurgical intervention with the purpose to lower increased IAP and consists of five treatment options: improvement of Cab, decrease of intra–abdominal volume, decrease of intra–luminal volume, fluid management, organ support.
Four questions	For further fine–tuning and classification of IAH/ACS four questions need to be answered. 1. What is the duration of IAH/ACS? 2. Is an intra–abdominal problem responsible for the IAH/ACS? 3. What is the aetiology of the IAH/ACS? 4. Is there a local compartment syndrome?
Closure of OA	When left open with a TAC, the open abdomen should be closed as soon as possible (best within one week).

Recognition and awareness

Early recognition of IAH and ACS is of paramount importance in the management of critically ill patients. Despite the growing body of literature on the subject, under-recognition of the syndrome persists. Several surveys have highlighted a general lack of clinical awareness among physicians regarding IAH and ACS. Many intensive care units (ICUs) still do not routinely measure IAP, let alone continuous IAP, a tool that recently became available and there is no consensus on the optimal timing for measurement, management or decompression. As noted by Ivatury, this widespread under-appreciation may be linked to failure to anticipate

and f instead of measurement relying on the clinical assessment of IAH and ACS. Initially understood in isolated experimentally controlled scenarios, our comprehension has expanded to recognize IAH as a "second-hit" phenomenon following ischemia-reperfusion injury or a “third hit” phenomenon in patients with global increased permeability syndrome (GIPS).

Anticipation and frequent monitoring of IAP is essential for timely diagnosis of IAH and intervention for ACS. Although awareness has increased, many clinicians still fail to recognize the syndrome due to its complex presentation and the overlap of its symptoms with other critical conditions. ACS should be suspected in any critically ill patient who shows unexplained signs of organ dysfunction, particularly when conventional treatments fail to improve the patient's condition. Regular training and education about the importance of monitoring IAP and recognizing the signs and symptoms of ACS are crucial steps in improving clinical outcomes.

Underlying risk factors

ACS is defined as increased IAP accompanied by evidence of end-organ dysfunction. In the ICU, multiple factors can contribute to acute deterioration of cardiopulmonary, renal, hepatosplanchnic, or neurologic functions. Recognizing IAP as an independent risk factor for organ function deterioration is essential. Timely identification of underlying risk factors and predisposing conditions that lead to IAH and ACS is crucial for effective management. Indications for IAP monitoring should be based on the presence of these risk factors.

Conditions and risk factors associated with IAH and ACS can be categorized into four groups (**Table 2**):

1. Conditions that decrease abdominal wall compliance (e.g., obesity, fluid accumulation, abdominal surgery, burns with eschar formation).
2. Conditions that increase intraluminal contents (e.g., bowel obstruction, gastric dilation).
3. Conditions related to abdominal collections of fluid, air, or blood (e.g., ascites, hemoperitoneum, pneumoperitoneum).
4. Conditions associated with capillary leak and fluid resuscitation (e.g., sepsis, major trauma, burns, severe acute pancreatitis).

Table 2. Classical IAH risk factors: When to monitor IAP?

1. Related to increased intra-luminal contents
● Gastroparesis
● Gastric distention
● Ileus
● Volvulus
● Colonic pseudo-obstruction
● Abdominal tumour
● Retroperitoneal/ abdominal wall hematoma
● Enteral feeding
● Intra-abdominal or retroperitoneal tumor
● Damage control laparotomy

(cont.)

Table 2. Classical IAH risk factors: When to monitor IAP? *(cont.)*

2. Related to increased intra-luminal contents
● Gastroparesis ● Gastric distention ● Ileus ● Volvulus ● Colonic pseudo-obstruction ● Abdominal tumour ● Retroperitoneal/ abdominal wall hematoma ● Enteral feeding ● Intra-abdominal or retroperitoneal tumor ● Damage control laparotomy
3. Related to increased intra-abdominal contents abdominal fluid, air or blood collections
● Liver dysfunction with ascites ● Massive incisional hernia repair ● Abdominal infection (pancreatitis, peritonitis, abscess, etc.) ● Haemoperitoneum ● Pneumoperitoneum ● Laparoscopy with excessive inflation pressures ● Major trauma ● Peritoneal dialysis (CAPD)
4. Related to capillary leak and fluid resuscitation
● Acidosis* (pH below 7.2) ● Hypothermia* (<33°C) ● Coagulopathy* ● Polytransfusion ● Polytrauma ● Global increased capillary leak syndrome (GIPS) ● Sepsis ● Severe sepsis or bacteraemia ● Septic shock ● Massive fluid resuscitation ● Major burns ● Abdominal infection
5. Predisposing factors for decreased Cab
Related to anthropometry and patient demographics ● Male gender ● Young age (elastic recoil) ● Obesity (weight, BMI), especially central obesity and metabolic syndrome ● Android composition (sphere, apple shape) ● Increased visceral fat ● Waist-to-hip ratio >1 ● Increased sagittal abdominal diameter ● Short stature

(cont.)

Table 2. Classical IAH risk factors: When to monitor IAP? *(cont.)*

6. Predisposing factors for decreased Cab (cont.)
Related to comorbidities and/or increased non-compressible IAV
● Fluid overload and fluid accumulation syndrome ● Bowels filled with fluid ● Stomach filled with fluid ● Tense ascites ● Hepatomegaly ● Splenomegaly ● Abdominal fluid collections, pseudocyst, abscess ● Sepsis, burns, trauma and bleeding (coagulopathy)
Related to abdominal wall
● Head-of-bed (HOB) elevation > 30-45° ● Umbilical hernia repair ● Muscle contractions (pain) ● Bodybuilders (6 pack) ● Interstitial and anasarca oedema (skin) ● Abdominal burn eschars (circular) ● Tight abdominal surgical closure ● Abdominal velcro belt or adhesive drapes ● Prone positioning ● Pneumoperitoneum ● Pneumatic anti-shock garments ● Abdominal wall bleeding ● Rectus sheath hematoma ● Correction of large hernias ● Gastroschisis, omphalocoele
Related to diaphragm
● Mechanical ventilation (IPPV) ● Fighting with the ventilator ● Use of accessory muscles ● Use of positive end-expiratory pressure (PEEP >10) ● Presence of auto-PEEP (tension pneumothorax) ● COPD emphysema (diaphragm flattening) ● Basal pleuropneumonia

These categories encompass a wide range of clinical scenarios, making it clear that IAH and ACS can develop in both surgical and non-surgical patients. It is crucial to maintain a high index of suspicion for ACS in at-risk populations and to monitor IAP in patients with relevant predisposing conditions. We must be aware that secondary IAH and ACS are mainly iatrogenic due to overzealous crystalloid fluid administration in the setting of capillary leaks.

Epidemiology

IAH and ACS are increasingly recognized as significant contributors to morbidity and mortality in critically ill patients. The incidence of IAH in the intensive care unit (ICU) varies widely, on admission around 25-30% of patients present with IAH, with some studies reporting that up to 50% of ICU patients may develop IAH within the first week, particularly those with risk factors such as severe trauma, major abdominal surgery, sepsis, or

large-volume fluid resuscitation. The development of ACS, though less common (around 5% in medical patients), represents a severe and often life-threatening progression of IAH, with mortality rates that can exceed 50% in some patient populations or when left untreated.
The variability in reported incidence rates is due in part to differences in patient populations, clinical practices, and the criteria used to diagnose IAH and ACS. Some of the most significant risk factors for the development of IAH and ACS include major trauma, severe burns, abdominal surgery, sepsis, and conditions that lead to significant fluid shifts or accumulation within the abdominal cavity. Understanding these risk factors and maintaining a high index of suspicion in at-risk patients is crucial for early diagnosis and intervention.

Diagnosis

The diagnosis of IAH and ACS relies on accurate measurement of IAP. The most widely accepted method for measuring IAP is via the bladder, where a pressure transducer is used to measure the pressure transmitted through the bladder wall, reflecting the pressure within the abdominal cavity. This method is minimally invasive, cost-effective, and can be performed at the bedside, making it the gold standard for IAP measurement in clinical practice.
IAP should be measured at end-expiration with the patient in a supine position to ensure accuracy and zeroed at the level where the midaxillary line crosses the iliac crest. It is important to consider the patient's baseline IAP, as certain conditions, such as obesity or pregnancy, may result in chronically elevated IAP without significant pathologic consequences, although (pre-eclampsia has been linked to IAH above 14 mmHg. Normal IAP is around 5-7 mmHg and in critically ill patients, an IAP of 10 mmHg is usually observed, while values above 12 mmHg indicate the presence of IAH.
Clinical signs of IAH and ACS are often nonspecific and may be easily attributed to other conditions, making early diagnosis challenging. Common clinical signs include abdominal distension, ileus, oliguria, increased ventilatory pressures, and hemodynamic instability. However, these signs are not pathognomonic for IAH or ACS and should prompt further investigation, including IAP measurement, in at-risk patients.
In addition to direct measurement of IAP, advanced imaging techniques such as ultrasound and computed tomography (CT) can provide valuable information about the presence of abdominal fluid collections, bowel distension, bowel edema, and other signs of increased intra-abdominal pressure. While these imaging modalities can support the diagnosis of IAH and ACS, they should be used in conjunction with clinical assessment and IAP measurement, rather than as standalone diagnostic tools.
Regular monitoring of IAP is essential in patients with multiple risk factors for IAH, particularly those who have undergone major abdominal surgery, experienced large-volume fluid resuscitation, or are suffering from sepsis or major burns. Serial measurements or even better continuous IAP can help track the progression of IAH and guide timely interventions to prevent the development of ACS.

Pathophysiology and impact on organ systems

The pathophysiology of ACS involves a complex interplay between the contents of the abdominal cavity and the compliance of the abdominal wall and diaphragm. As intra-abdominal volume increases, the pressure within the abdominal cavity rises, leading to compression of abdominal organs, reduced venous return, and impaired perfusion of vital organs. This pressure can also be transmitted to the thoracic cavity, further compromising respiratory and cardiovascular function. The resulting organ dysfunction can affect nearly all major

systems in the body, making ACS a life-threatening condition that requires prompt recognition and management.

Understanding these effects is crucial for effective management and treatment strategies. Elevated IAP triggers a cascade of detrimental impacts across various organs, each manifesting in unique clinical presentations. **Figure 1** illustrates the pathophysiologic impact of IAH and ACS on end-organ function.

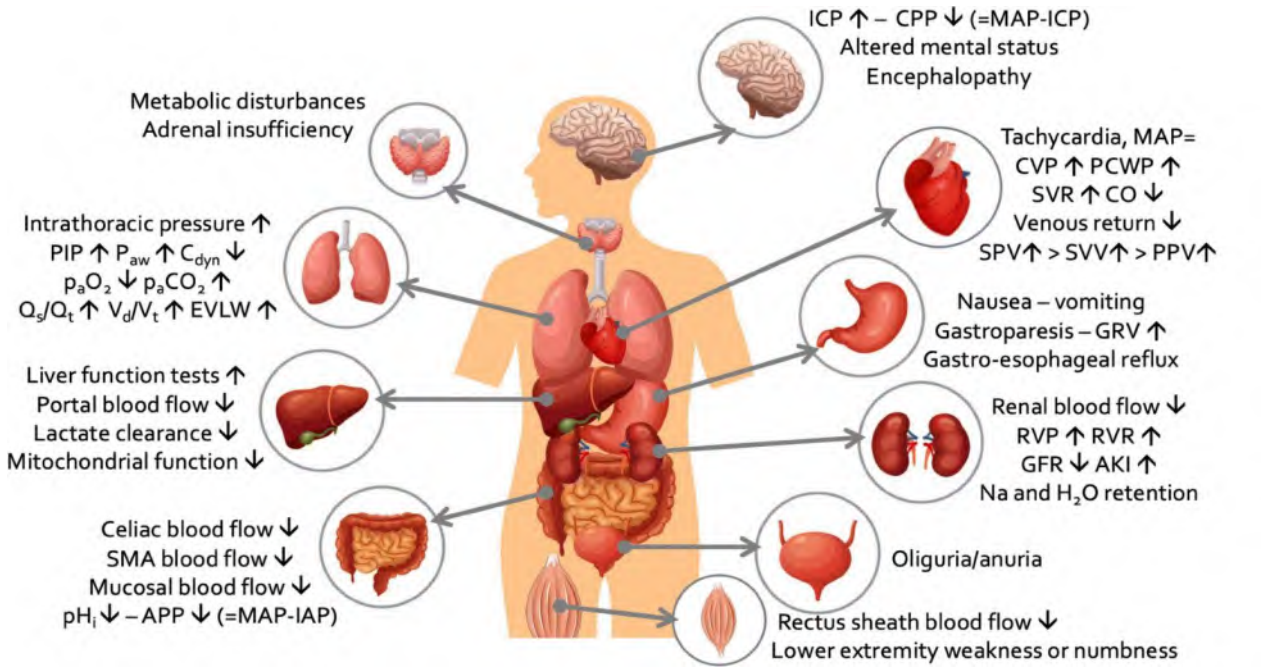

Figure 1. Summary of the most important pathophysiologic effects of increased intra-abdominal pressure on end-organ function within and outside the abdominal cavity (Adapted from: Regli A, *et al.* 2019).

Abbreviations. AKI, acute kidney injury. APP, abdominal perfusion pressure. Cdyn, dynamic respiratory compliance. CO, cardiac output. CPP, cerebral perfusion pressure. CVP, central venous pressure. EVLW, extravascular lung water. GFR, glomerular filtration rate. GRV, gastric residual volume. HR, heart rate. IAP, intra-abdominal pressure. ICP, intracranial pressure. ITP, intra-thoracic pressure. MAP, mean arterial pressure. PIP, peak inspiratory pressure. Paw, airway pressures. PCWP, pulmonary capillary wedge pressure. pHi, intra-mucosal gastric pH. PPV, pulse pressure variation. Qs/Qt, shunt fraction. RVP, renal venous pressure. RVR, renal vascular resistance. SMA, superior mesenteric artery. SPV systolic pressure variation. SVR, systemic vascular resistance. SVV, stroke volume variation. Vd/Vt, dead-space ventilation.

The *cardiovascular system* is particularly susceptible to the effects of elevated IAP, as increased pressure within the abdominal cavity can compress the inferior vena cava, reduce venous return, and increase systemic vascular resistance. These changes can lead to decreased cardiac output, hypotension, and ultimately shock, particularly in patients who are already hemodynamically unstable, hypovolemic or under mechanical ventilation with PEEP.

The *respiratory system* is also severely affected by elevated IAP, as the increased pressure within the abdominal cavity restricts diaphragmatic movement, reducing lung volumes and compliance. This can lead to hypoxemia and hypercapnia, complicating the management of patients who require mechanical ventilation. Additionally, the elevation of the diaphragm increases intrathoracic pressure, which can further reduce venous return and exacerbate cardiovascular instability. The level of IAP affects lung protective ventilation strategies and higher opening pressures are needed for lung recruitment.

Renal function is highly sensitive to increases in IAP, as elevated pressure within the abdominal cavity can reduce renal perfusion pressure, leading to a decrease in glomerular filtration rate (GFR) and subsequent acute kidney injury (AKI). This effect is further compounded by the direct compression of the kidneys and renal vasculature, which impairs renal blood flow and increases the risk of renal ischemia. The development of oliguria or anuria in the setting of elevated IAP is a critical warning sign that may necessitate prompt intervention to prevent irreversible renal damage.

The *gastrointestinal system* is also highly vulnerable to the effects of elevated IAP. Reduced splanchnic blood flow can lead to intestinal ischemia, increasing the risk of bacterial translocation and subsequent sepsis. This can contribute to the development of multiple organ dysfunction syndrome (MODS), a common complication in patients with severe IAH and ACS. Maintaining adequate APP is crucial to mitigating these risks and preventing the progression to multiple system organ failure (MSOF). Acute gastrointestinal injury (AGI) can manifest through bowel edema and ischemia, contributing to the development of acute intestinal distress syndrome (AIDS), which parallels the pathological processes observed in acute respiratory distress syndrome (ARDS). Fluid accumulation in the bowel wall leads to diminished bowel contractility and further IAP increase and ileus.

Hepatic dysfunction may also occur as a result of reduced portal and hepatic arterial blood flow, leading to impaired metabolism and detoxification processes. Measurement of indocyanine green (ICG) plasma disappearance rate can provide valuable insights into hepatic perfusion and function under IAH conditions.

Neurological complications of elevated IAP include increased intracranial pressure (ICP), which can result from elevated CVP and impaired venous drainage from the brain. This can lead to reduced cerebral perfusion pressure (CPP) and an increased risk of ischemic brain injury. These effects are particularly concerning in patients with pre-existing neurological conditions or those who have sustained traumatic brain injuries.

In addition to these systemic effects, elevated IAP can also impact the *endocrine and metabolic systems*, leading to alterations in glucose metabolism, insulin resistance, and increased production of stress hormones such as cortisol. These changes can exacerbate the metabolic derangements commonly seen in critically ill patients and contribute to the development of hyperglycemia, a known risk factor for poor outcomes, together with a disruption of the renin-angiotensin-aldosterone system (RAAS), causing salt and water retention posing significant challenges in critically ill patients.

The polycompartment syndrome (PCS) refers to the concurrent involvement of multiple body compartments (e.g., abdominal, thoracic, limb, and cranial) in response to elevated pressures. IAH and ACS play central roles in PCS development, affecting intracranial, intrathoracic, and cardiovascular pressures, leading to compounded physiological stress. The interrelated pressures necessitate comprehensive monitoring and management strategies to address the complex interactions between different compartments.

Cardio-Abdominal-Renal Syndrome (CARS) represents a complex interplay between the heart, abdomen, and kidneys, where IAH and venous hypertension/congestion play pivotal roles in exacerbating acute kidney injury (AKI). Elevated IAP has been identified as a critical risk factor for AKI across various clinical settings, including post-emergency abdominal surgery, orthotopic liver transplantation, and in critically ill patients. Studies have demonstrated that IAH can lead to a significant reduction in renal perfusion and function, often manifesting as oliguria or anuria at higher pressures.

In patients with acute decompensated heart failure (ADHF), the combination of low cardiac output and systemic venous congestion exacerbates the risk of AKI. Increased CVP and renal venous pressure (RVP) due to right ventricular dysfunction and elevated IAP result in decreased renal perfusion pressure (RPP). This venous congestion impairs renal function, often leading to worsening renal function, a common occurrence in heart failure patients. Elevated IAP further complicates this scenario by compressing renal veins and the inferior vena cava, thereby reducing venous return and increasing SVR.

Understanding and addressing the pathophysiological mechanisms underlying CARS, including the role of IAP, PCS and venous congestion, are essential for improving outcomes in critically ill patients. Clinicians must be vigilant in monitoring IAP and employing appropriate therapeutic strategies to mitigate the adverse effects on renal function and overall patient prognosis

Management

Prevention of IAH and ACS is best achieved through early detection and continuous monitoring of IAP. Regular assessment of IAP in high-risk patients allows for timely interventions that can prevent the progression of IAH to ACS. Continuous IAP monitoring, particularly in critically ill patients, helps in identifying rising pressures early and enables prompt medical or surgical interventions to mitigate the adverse effects on organ function. Managing patients with IAH involves a comprehensive approach centered on four primary principles: 1) reducing IAP and mitigating the consequences of ACS, 2) providing general intensive care support, 3) considering surgical decompression when necessary, and 4) optimizing care post-decompression to address any specific adverse effects. Early detection and continuous monitoring of IAP are crucial in preventing IAH and ACS, enabling timely interventions that can significantly improve patient outcomes.

Medical treatment

Before resorting to surgical decompression, various less invasive medical treatments should be optimized. The relationship between abdominal contents and IAP is exponential, meaning small increases in volume can lead to significant rises in pressure, especially when abdominal wall compliance is reduced. Medical treatments aim to improve abdominal wall compliance, evacuate intraluminal contents, drain abdominal fluid collections, correct capillary leak and positive fluid balance, and apply specific treatments. The WSACS has developed a 4-pillar medical management algorithm with a stepwise approach encompassing these strategies, emphasizing the need for flexibility and clinician expertise in tailoring interventions to individual patients.

1. **Improvement of abdominal wall compliance**
    - Sedation helps increase abdominal wall compliance, while NMB has been shown to reduce IAP effectively. However, fentanyl and other opioids can increase IAP due to stimulation of active phasic expiratory activity.
    - Proper body positioning and the use of pressure-relieving surfaces can significantly affect IAP.
    - Techniques such as percutaneous procedures to increase abdominal capacity have shown benefits in both experimental models and clinical settings, such as in burn patients.

2. **Evacuation of intra-luminal contents**
    - In critically ill patients with ileus, non-invasive evacuation methods include gastric tube placement, rectal tubes, enemas, and possibly endoscopic decompression.
    - These methods can be supported with prokinetic agents like erythromycin, metoclopramide, and neostigmine. These measures help reduce intra-abdominal volume, thereby lowering IAP.

3. **Evacuation of abdominal fluid collections**
    - Draining tense ascites can significantly reduce IAP. This is particularly beneficial in patients with liver cirrhosis and secondary ACS in burn patients.
    - For localized fluid collections, CT-guided fine needle aspiration can be effective.

4. **Correction of capillary leak and positive fluid balance**
    - Initial fluid loss should be compensated to prevent splanchnic hypoperfusion. However, managing fluid balance is critical as these patients tend to retain large volumes of sodium and water, exacerbating tissue edema.
    - Diuretic therapy combined with albumin can help mobilize edema, but renal replacement therapy (RRT) may be necessary in cases of anuria.
    - The WSACS recommends avoiding positive cumulative fluid balance after acute resuscitation and addressing inciting issues.

5. **Specific treatments**
    - **Continuous negative abdominal pressure**: Applying continuous negative abdominal pressure has been shown to decrease IAP and improve lung volumes.
    - **Targeting abdominal perfusion pressure (APP)**: Similar to targeting cerebral and coronary perfusion pressures, maintaining an appropriate APP and RPP can help reduce the risk of worsened splanchnic perfusion and subsequent organ dysfunction.
    - **Pharmacologic interventions**: Octreotide, vitamin C, and melatonin have shown promise in reducing inflammation and oxidative damage associated with IAH.

Surgical management

In cases where medical management is insufficient to control IAP, surgical decompression may be necessary. Decompressive laparotomy is the definitive treatment for refractory IAH and ACS, and involves making a midline incision to open the abdominal cavity and rapidly reduce IAP. While this procedure can be life-saving, it is associated with significant risks, including the development of an open abdomen, which requires meticulous management to prevent infection and promote delayed primary closure.

The use of negative pressure wound therapy (NPWT) has been shown to be beneficial in managing the open abdomen, as it helps to remove exudate, reduce bacterial load, and promote wound healing. NPWT can also help to stabilize the abdominal wall and prevent the development of large ventral hernias, a common complication of decompressive laparotomy.

Future directions

Future research in the field of IAH and ACS should focus on refining diagnostic criteria, developing less invasive monitoring techniques, and improving treatment strategies. One area of growing interest is the role of abdominal compliance in the pathophysiology of IAH. Understanding the factors that influence abdominal compliance could lead to the development of new therapeutic approaches that target this aspect of the disease.

The integration of continuous IAP monitoring into routine critical care practice is another promising area of development. Continuous monitoring could enhance the early detection of IAH, allowing for timely interventions that could prevent the progression to ACS. Additionally, there is a need for further research into the long-term outcomes of patients who survive ACS, as this could inform strategies for rehabilitation and long-term management.

Conclusion

ACS represents a severe manifestation of IAH and is associated with high morbidity and mortality in critically ill patients. Early recognition and timely intervention are crucial to prevent the progression of IAH to ACS and mitigate its impact on multiple organ systems. The standardization of definitions and management guidelines by the World Society of the Abdominal Compartment Syndrome (WSACS) has been instrumental in advancing the understanding and treatment of these conditions.

Effective management of IAH and ACS requires a multidisciplinary approach, incorporating both medical and surgical strategies. Optimizing fluid balance, improving abdominal wall compliance, and reducing intra-luminal and intra-abdominal contents are key components of medical management. In cases of refractory IAH, surgical decompression remains the definitive treatment, despite its associated risks.

Continuous monitoring of IAP is essential for patients at risk of developing IAH and ACS. Early detection allows for timely interventions that can prevent the onset of ACS and improve patient outcomes. As research continues to evolve, the development of less invasive monitoring techniques and the refinement of treatment strategies will be critical in enhancing the care of patients with IAH and ACS.

In conclusion, IAH and ACS are critical conditions that require prompt recognition, continuous monitoring, and comprehensive management to improve outcomes in critically ill patients. The ongoing efforts of the WSACS in research, education, and guideline development will continue to play a pivotal role in the fight against these life-threatening conditions.

Competing interests

The author has no financial and non-financial competing interests to declare.

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Chapter 99

Immunological profile of the surgical critical patient

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Introduction

The immunological response in a surgical patient refers to the body's reaction to the stress and trauma caused by surgery. Surgery is considered a significant physiological insult, following the pathology itself as a trigger, and the body's immune system plays a crucial role in the healing and recovery process. The traditional paradigm in immunology divided the immune response into two main phases: the immediate or innate response and the delayed or adaptive response.

The innate immune response is the front line of the host to eliminate invading pathogens. It is typically rapid and can be triggered without the selective events that underlie adaptive immunity. It can be mediated through cell-dependent mechanisms (phagocytosis and cytotoxicity) or secreted factors, including antimicrobial peptides, complement factors, cytokines/chemokines, acute-phase proteins, proteases, and other less-categorized molecules.

Immunological memory is defined as “the ability of the immune system to respond more rapidly and effectively to pathogens that have been encountered previously”. It was long thought that memory was an exclusive property of the adaptive immune system.

However, in the last decades, studies in plants, and invertebrates, that both lack adaptive immunity, and, more recently, in mammals, have shown that innate immune cells can also perform this function of "immunological memory".

So, features of "trained immunity" have been reported in various innate immune cell populations including monocytes/macrophages, natural killer (NK) cells, dendritic cells (DCs), innate lymphoid cells and neutrophils.

The ability of innate immune cells to remember and respond accordingly to secondary challenges has thus been termed “innate immune memory”. The innate immune memory phenotype is highly dependent on the nature and intensity of external stimuli and can result either in enhanced activation, also known as “trained immunity”, or unresponsiveness, also known as “tolerance” (in this context, the term tolerance is distinct from self-tolerance, defined as a lack of immunological response to self-antigens).

Immediate or innate response

Innate immunity is comprised of different components including:

- Physical barriers (tight junctions in the skin, epithelial and mucous membrane surfaces).
- Anatomical barriers; epithelial and phagocytic cell enzymes (lysozyme), phagocytes (neutrophils, monocytes, macrophages).
- Inflammation-related serum proteins (complement, C-reactive protein, lectins such as mannose-binding lectin).
- The release of pro-inflammatory molecules, such as cytokines and chemokines, leads to localized swelling, redness, and heat at the surgical site. This inflammatory response helps recruit immune cells to the area and plays a role in tissue repair.
- Surface and phagocyte granule antimicrobial peptides (defensins, cathelicidin)
- Cell receptors that sense microorganisms and signal a defensive response (Toll-like receptors).
- Cells that release cytokines and inflammatory mediators (macrophages, mast cells, natural killer cells).

Innate immune cells comprise a broad and expanding range of myeloid and lymphoid cell types.

- *Neutrophils* play a crucial role in phagocytosing (engulfing and digesting) bacteria and cellular debris to prevent infection and initiate the healing process.
- *Monocytes* play a significant role in defending the body against infections and other harmful substances. When needed, they can migrate into various tissues throughout the body and differentiate into macrophages or dendritic cells, depending on the specific signals they receive. Key functions of monocytes include phagocytosis, antigen presentation, inflammation, tissue repair and healing. Monocyte elevated levels can indicate various conditions, including infections, autoimmune diseases, and certain cancers. Understanding the role of monocytes and their functions is important for comprehending the immune response and the body's defense mechanisms against diseases.
- *Macrophages* are long-lived cells that monitor tissues and offer the earliest response to an invasion. Macrophages take over the task of phagocytosis and also release growth factors that promote tissue repair.
- *Natural Killer (NK) cells:* NK cells are important in the early defense against viruses and tumor cells. They also contribute to tissue repair and wound healing. Recent studies have shown that NK cells exhibit adaptive memory-like properties, as they can be primed for enhanced IFNγ production upon restimulation.

Delayed or adaptive response

Immunological memory is a fundamental aspect of the adaptive immune system, which helps the body recognize and respond more effectively to previously encountered pathogens. This memory allows the immune

system to mount a faster, stronger, and more targeted response upon re-exposure to the same pathogen. Two main types of adaptive immune responses exhibit immunological memory.

A. *Cell-mediated immunity (T cell memory)* - This involves the activation and expansion of specific T cells, which are responsible for recognizing and destroying infected cells. T cells that encounter a specific antigen during an initial infection undergo clonal expansion, producing a population of memory T cells. These memory T cells remain in the body for an extended period, sometimes for a lifetime, ready to respond rapidly upon re-exposure to the same antigen. They can quickly recognize and eliminate infected cells, preventing the spread of the pathogen.
B. *Humoral immunity (B cell memory)* - B cells are responsible for producing antibodies, which are proteins that bind to specific antigens on pathogens, marking them for destruction by other immune cells or neutralizing their activity. During an initial infection or vaccination, B cells that recognize the pathogen undergo clonal expansion and differentiation into plasma cells, which produce large amounts of antibodies. Some of these B cells also become memory B cells. If the same pathogen enters the body again, memory B cells can quickly differentiate into plasma cells, producing a rapid and robust antibody response. This helps to eliminate the pathogen before it can cause widespread infection. Immunological memory is the basis for the effectiveness of vaccines. Overall, immunological memory is a crucial aspect of the immune system's ability to protect the body from recurring infections and provides the basis for long-lasting immunity against many diseases. The adaptive immune response takes longer to develop and is specific to the particular pathogens or foreign substances encountered during surgery. It involves the activation of T and B lymphocytes and leads to the formation of memory cells for long-term protection.

Key components of the adaptive immune response include:

- T lymphocytes: T cells recognize specific antigens presented by antigen-presenting cells (APCs) and can activate other immune cells or directly attack infected or damaged cells.
- B lymphocytes: B cells produce antibodies that can neutralize pathogens and foreign substances encountered during surgery.
- Memory cells: some of the T and B cells formed during the adaptive response become memory cells, which "remember" the encountered pathogens or antigens. This results in a quicker and more robust immune response if the same pathogen is encountered in the future.

Factors affecting immunological response in surgical patients.

Several factors can influence the immunological response in surgical patients:

- *Age.* Older patients may have a weaker immune response compared to younger individuals.
- *Nutritional status*. Malnutrition can impair the immune system, leading to increased susceptibility to infections and delayed wound healing.
- *Pre-existing health conditions*. Chronic illnesses or immunosuppressive conditions may compromise the immune response.
- *Type and duration of surgery*. The extent and complexity of the surgery can impact the immune response.
- *Anesthesia.* Certain anesthetic agents can affect the immune system.
- *Post-operative care*. Proper wound care and infection prevention measures are essential for optimal immune function and recovery. It's important to note that while the immune response is vital for healing

and defense against infection, an excessive or prolonged immune response can lead to complications, such as excessive inflammation or immunosuppression. Thus, providing appropriate surgical care and managing the patient's immune response are critical aspects of ensuring a successful surgical outcome.

When analyzed surgical patient profile for hematologic biomarkers [WBC, lymphocyte, monocyte count and serum concentrations of interleukin IL-6 (IL-6), procalcitonin (PCT) and C reactive protein (CRP)] at various time points (Admission, prior to any therapeutic intervention, immediately after surgery and during postoperative follow-up) the absolute number of WBC and monocytes are increased, whereas lymphocyte levels were found pronounced reduced (**Figure 1A** and **Figure 1B**).

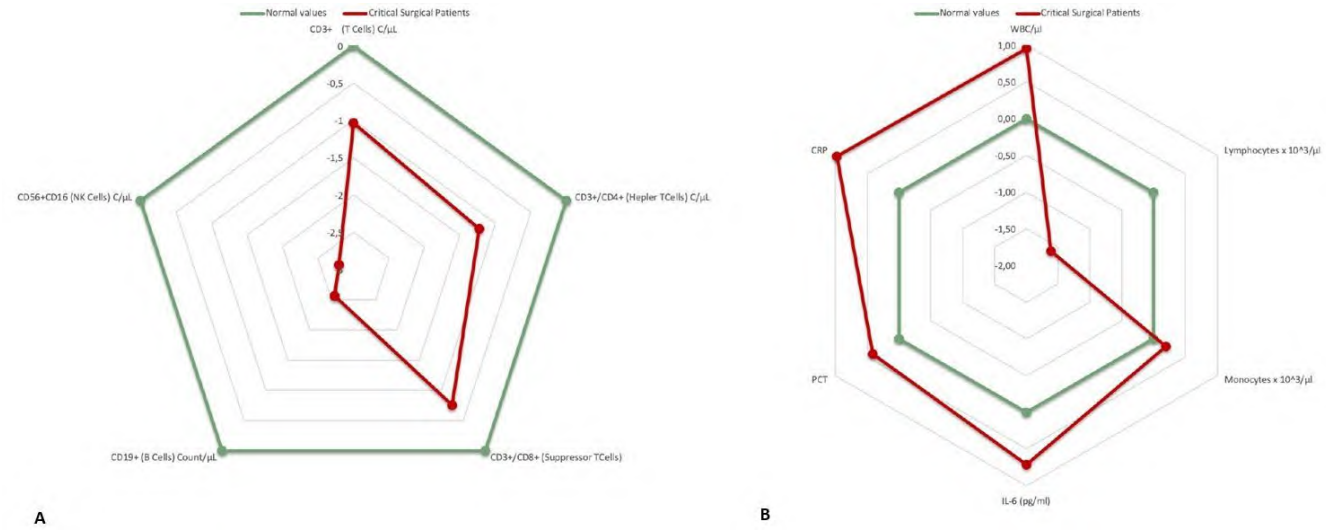

Figure 1A. Lymphocyte typing. **Figure 1B.** blood count and inflammation indices.

The status of the patient's immune system through the lymphocyte typing is confirmed weak. Lymphocytes are an essential part of the adaptive immune response to infection and their subsets play a complex and well-documented role in sepsis. We observe a drop in the absolute number of total lymphocytes in surgical patients, either with or without Open Abdomen Treatment, which is associated with a decrease in all lymphocyte populations investigated (Total T-cells, T-helper cells, Cytotoxic T cells, CD16/ CD56 Natural Killer and CD19 B-lymphocytes). In particular, we observe a pronounced reduction for Natural Killer and B-lymphocytes and document a decrease for CD3 T cells, CD4 T lymphocytes, CD8 T cells, CD16/ CD56 Natural Killer cells and CD19 B-lymphocytes (**Figure 1-4**).

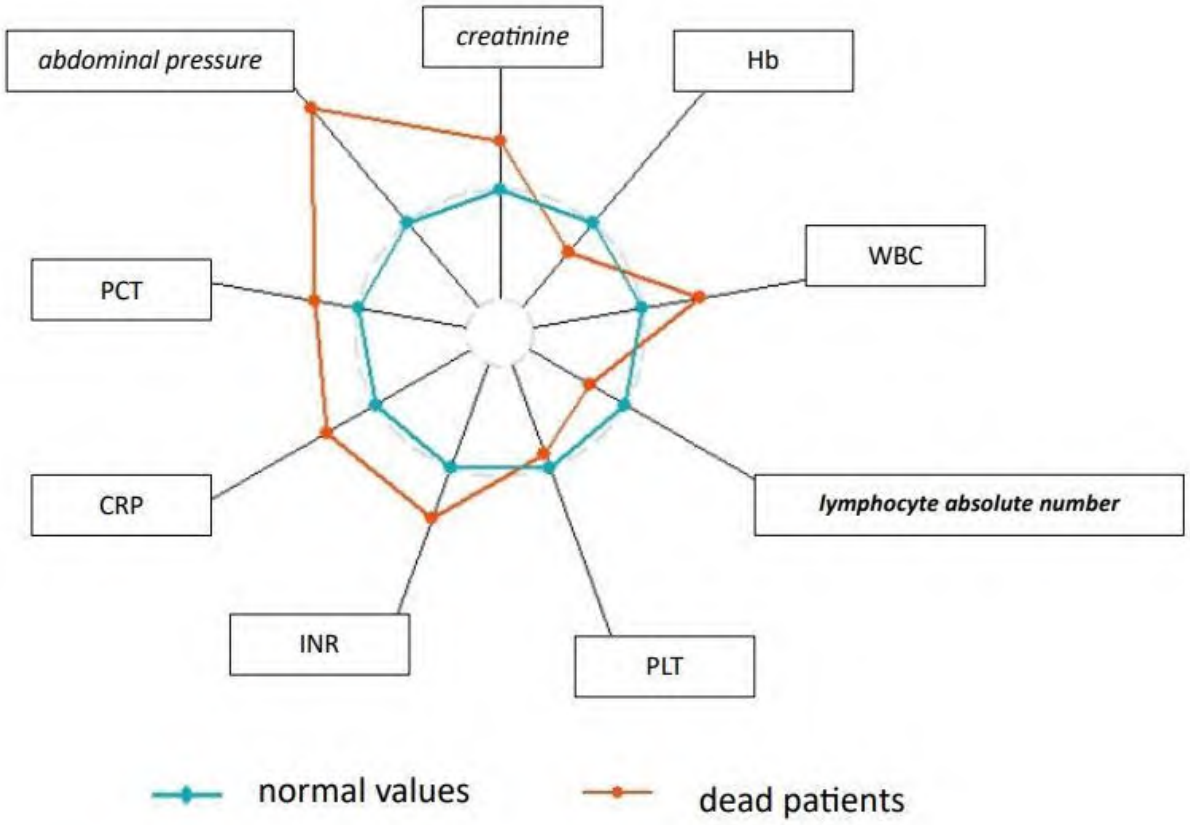

Figure 2. Humoral-immunological assessment of Patients with Open Abdomen - **Dead patients**. *Abbreviations*. CRP: C-reactive protein. Hb: hemoglobin. INR: normalized ratio. PCT: procalcitonin. PLT: platelets. WBC: white blood cells.

A strong inflammatory response affects immune homeostasis. Immunosuppression is a risk factor for poor prognosis of critically ill patients, but current monitoring of the immune status in clinical practice is still inadequate. Profound and persistent lymphopenia can occur for many reasons: migration of cells into infection sites, associated with the expansion of immunosuppressive cell populations such as regulatory T-lymphocytes and myeloid-derived suppressor cells, or excess catabolism, caused by several factors including chemotherapy, immunosuppressive therapy, certain viral infections, septic shock, extended burns and systemic granulomatosis. Previous studies indicated that lymphopenia may occur early in the course of sepsis and that decreases in specific lymphocyte subsets may help identify fragile patients at higher risk of disease progression. All these considerations reveal an additional line of evidence that it's helpful to investigate lymphocytes, in comparison with other biochemical markers commonly used to stratify outcomes of patients in the evolution of sepsis. Consequently, lymphocyte subsets can be regarded as a valuable tool in the establishment of an immune prognostic score for sepsis. Upcoming studies will aim to explore different trajectories of the above-mentioned hematologic biomarkers and evaluate their relationship with prognosis in surgical, not only, critically ill patients.

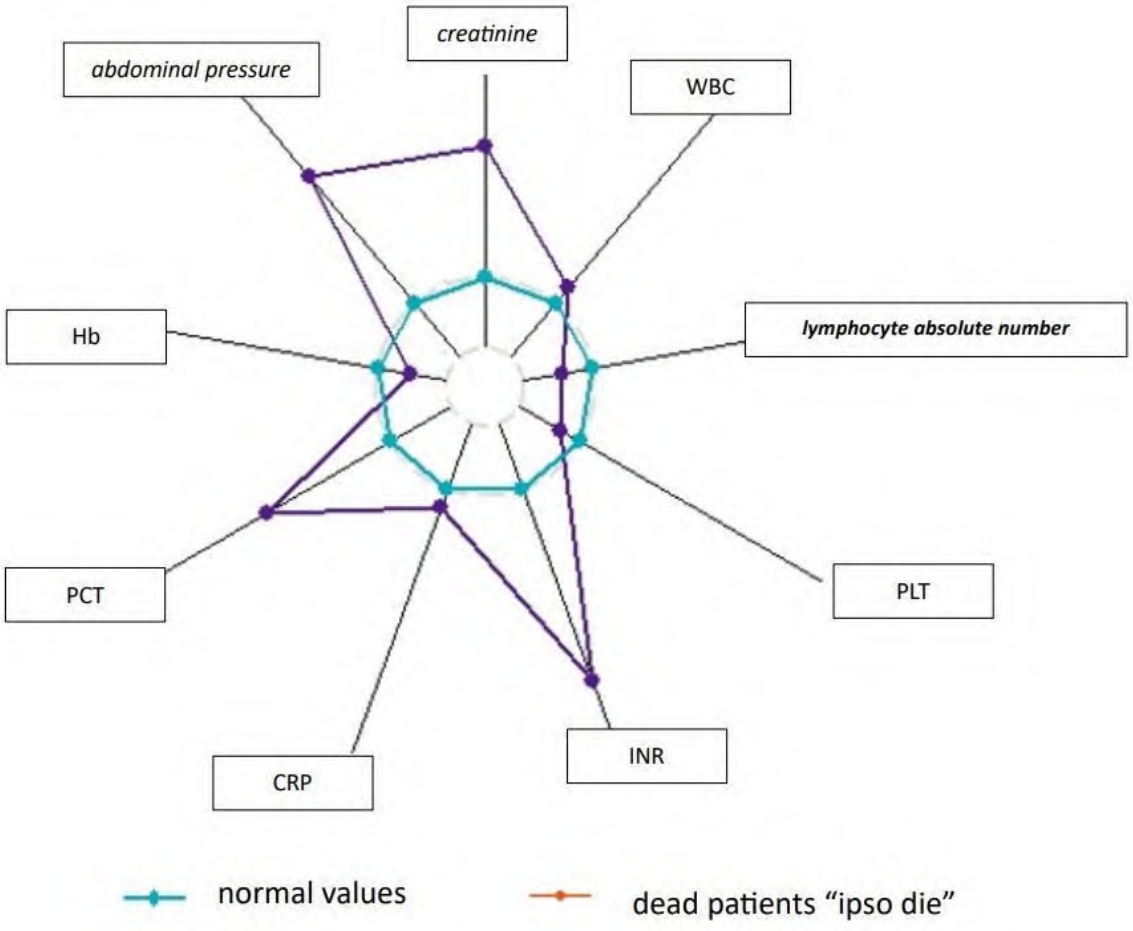

Figure 3. Humoral-immunological assessment of Patients with Open Abdomen - **Dead patients “ipso die”**. *Abbreviations*. CRP: C-reactive protein. Hb: hemoglobin. INR: normalized ratio. PCT: procalcitonin. PLT: platelets. WBC: white blood cells.

Every year, worldwide, 50 million patients develop sepsis. Thanks to the huge advances in resuscitation and to the growing understanding of the mechanisms of sepsis, the in-hospital and 28-day mortality of sepsis is decreasing, although the late mortality is still high. Thanks to these advances in ICU assistance, patients passed by a single organ failure from the failure of two or more organs, a clinical entity recognized in the 1970s and defined as Multiple Organ Failure (MOF). MOF has always been considered as the result of the activation of proinflammatory mediators during infections and sepsis. At the dawn of its identification, it was defined as the epilogue of an uncontrollable infection. But as time passes, it starts to be investigated whether MOF was the cause or the consequence of an infectious phenomenon.

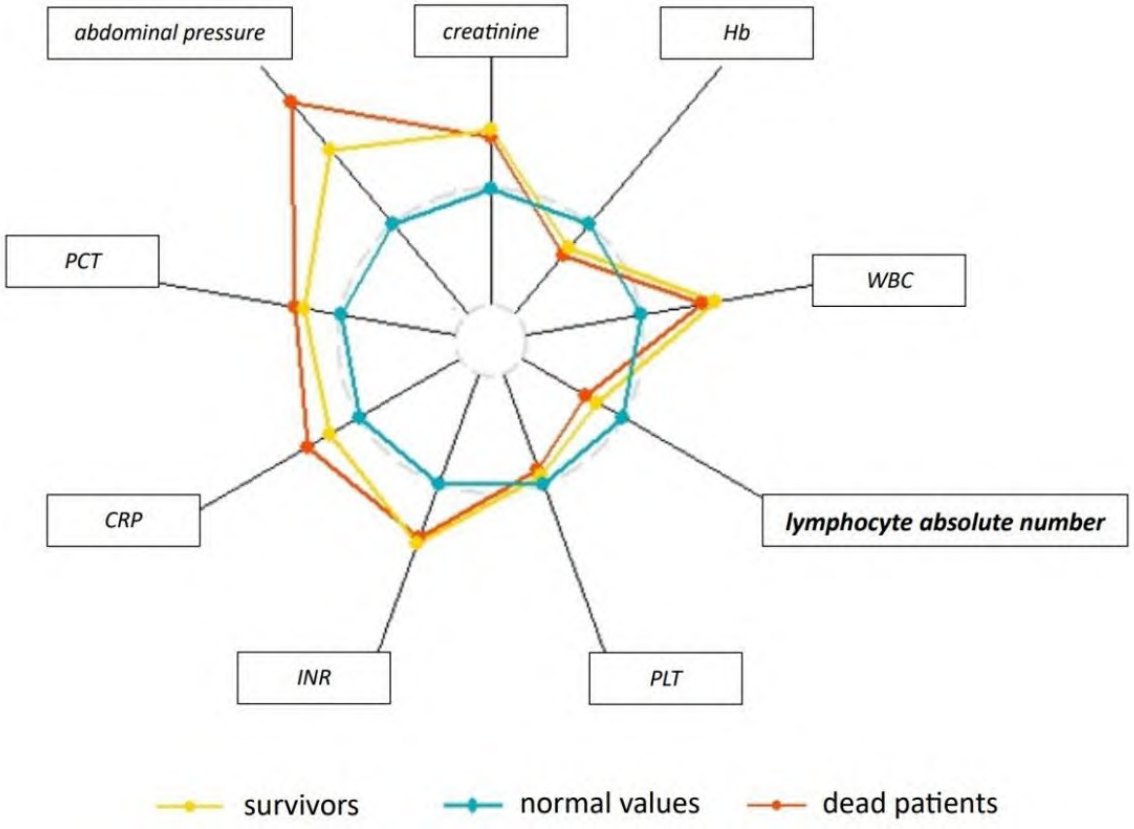

Figure 4. Humoral-immunological assessment of patients with open abdomen - Survivors *versus* dead patients. *Abbreviations*. CRP: C-reactive protein. Hb: hemoglobin. INR: normalized ratio. PCT: procalcitonin. PLT: platelets. WBC: white blood cells.

It was only in the 1990s that MOF was described as a bimodal event, in which an initial insult causes the early MOF that is followed by a period of improvement until a second late MOF in two-thirds of cases. To explain this phenomenon, the SIRS/CARS model was proposed. According to this model, when the patient suffers an insult, the immunity system is activated with the production of pro-inflammatory mediators, configuring the Systemic Inflammatory Response Syndrome (SIRS). If this insult is severe enough, patients develop MOF. All this process is a reaction to the exposure to infectious products, such as pathogen-associated molecular patterns (PAMPS), or endogenous danger signals (damage-associated molecular patterns [DAMP] and alarmins) acting through TLR or nucleotide-binding oligomerization domain (NOD) signaling pathways. Those processes result in very dangerous and complex in peritoneum. The early MOF that follows is characterized by the overproduction of multiple proinflammatory mediators, the PMN activation, an endothelial injury with inadequate perfusion and consequently tissue damage. The result is the activation and overexpression of early response genes, driven in large part by nuclear factor JB (NF-kB) activation. When the compensatory anti-inflammatory response is activated, causing the Compensatory Anti-inflammatory Response Syndrome (CARS), the doors to late MOF and multiple infections are opened. While the early MOF and SIRS seem to be associated with an excessive innate immune response, the development of late MOF and CARS seem to be associated to a suppressive adaptative immune response. The adaptative immune changes in severe sepsis are an increase in T-Reg cells with a parallel T-cells anergy, a macrophage paralysis with a decrease in cytokines production and bacterial clearance and lymphocyte depletion. Despite therapeutic efforts, several patients

didn’t recover from the late MOF, rather they developed a Chronic Critical Illness (CCI), configuring a new late MOF phenotype, defined as Persistent-Inflammation-Immunosuppression-Catabolism Syndrome (PICS).

Persistent Inflammatory Catabolic Syndrome (PICS)

PICS seems to replace, or rather integrate, the concept of late Multi-Organ Failure (MOF), typical of those surgical patients in Intensive Care Units (ICU) who failed to recover. As a matter of fact, the incidence of MOF is progressively reducing in ICU, thanks to the huge advances in resuscitation and the growing understanding of the mechanisms of sepsis. Rather, the MOF is giving way to PICS, a condition that affects critically ill surgical patients who do not recover after the first days in ICU for no recognizable reason.

PICS23 is defined as a condition of persistent inflammation and impaired immune response that affects surgical patients who reside in ICU for at least 10 days after surgery, with persistent high concentration of inflammatory markers, as C-reactive protein (CRP), values which suggest immunosuppression, as low lymphocytes count, and markers of increased catabolism, as high creatinine values, low serum albumin values, low Retinol Binding Protein (RBP) and weight loss. To understand how PICS fits into this panorama, it is important to understand each possible scenario after an insult. When an insult occurs, such as sepsis or trauma, the early immune response is activated. The old SIRS/CARS model that saw the SIRS preceding the CARS, has been overcome. Indeed, now it is clear how SIRS and CARS are two simultaneous and complementary responses to an insult. Respectively, the patient could develop early MOF and eventually die, fitting the criteria for late MOF or experiencing a PICS. From a clinical point of view, patients affected by PICS experien ance loss of weight despite nutritional intervention, poor wound healing and recurrent nosocomial infections, until discharge to a long-term acute care facility (LTAC) and an indolent death. From a biological point of view, PICS is characterized by a suppression of macrophage activity, paralyzed monocytes, anergy of T cells and an increase of Myeloid-Derived Suppressor Cells (MDSC), resulting in an ineffective and impaired immune response (**Figure 5**).

The peculiarity of PICS, and consequently the difficulty in understanding its pathophysiological assumptions, lies in the combination of a latent inflammatory state and a persistent immunosuppression. Normally, the response to an insult such as sepsis, IAI, trauma or surgery, is mediated by the so-called "emergency granulopoiesis/myelopoiesis”. Thanks to emergency myelopoiesis, hemopoietic stem cells differ in "myeloid-derived suppressor cells" (MDSC) rather than lymphocytes. These cells do not mature in granulocytes but possess both the ability to accentuate the acute inflammatory response and at the same time suppress lymphocyte function, hesitating in an immunosuppressive mechanism.

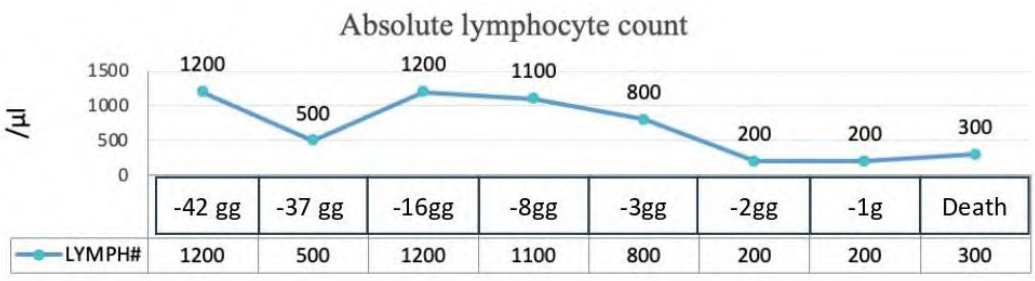

Figure 5. Absolute lymphocyte number in a PICS.

Cytokines modulation shows a rise of pro-inflammatory cytokines involved in early response and amplification of inflammatory responses such as IL-6, IL-8 and TNF-α and no changes in anti-inflammatory cytokine IL-10, particularly IL-8 is progressively increased at the early disease phase with a definitive drop. IL-8 release may result in amplification of systemic inflammation. IL8 is involved in neutrophil recruitment, mediates innate immune activation, and is also a potent promoter of angiogenesis. Numerous cell types, such as macrophages and B-lymphocytes, secrete this cytokine; moreover, immature B cells can secrete more IL-8 than mature B cells. A prolonged presence of inflammation-induced IL-8 in circulation may cause variable degrees of tissue damage. Decrease in NK cells, innate immune cells that perform antitumor and antimicrobial functions.

All these considerations could be inserted in the routine clinical approach to the surgical patient in order to avoid any kind of perioperative complication, to stratify the surgical risk, and to monitor the clinical course of those complex surgical patients real “open doors” to critical clinical events.

Competing interests

The authors have no financial and non-financial competing interests to declare.

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Chapter 100

The management of sepsis and septic shock in patients with surgical infections

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Introduction

Surgical infections often lend themselves to operative or procedural interventions that compliment antimicrobial use and other efforts in the management of septic patients at risk for septic shock. Prompt identification of at-risk patients is paramount for their successful treatment. Antimicrobials, source control as well as close monitoring and aggressive resuscitation are at the center of therapy for these patients. This chapter focuses on the updates on sepsis management utilizing the current definitions of sepsis and septic shock to ensure early identification with empiric therapy and continual reassessment to drive de-escalation. Further examination includes options to influence antimicrobial selection and duration including the use of cultures, biomarkers, and antibiograms. Additionally, the role of pharmacokinetics and pharmacodynamics to assist with dosing regimens for individual medications is incorporated. Adjunctive therapies including ventilatory management, glycemic control and corticosteroids are also part of the contemporary treatment algorithms and are mentioned in this chapter. Many of the published guidelines use similar approaches in both sepsis and septic shock; the most recent 2021 Surviving Sepsis Campaign differentiates these clinical situations in certain circumstances for which patient outcome balanced with appropriate antimicrobial stewardship demonstrates optimal results. These differences are highlighted in this chapter.

Definitions

Surgical infection. Surgical infections refer to infections that occur in patients who have undergone surgery or have an infection whose treatment is amenable to procedural interventions such as debridement, drainage, or excision. These infections may occur at the site of a surgical procedure or in the tissues or organs affected by surgery. These infections can involve the skin, underlying tissues, or internal organs and may be caused by bacteria, viruses, fungi, or other microorganisms. Intra-abdominal infections comprise most surgical infections resulting in sepsis and the second most common source of sepsis overall.

Sepsis. Sepsis is a potentially life-threatening condition that arises when the body's response to infection causes systemic inflammation. The normal immune response becomes dysregulated during the cytokine

cascade leading to organ dysfunction. Key signs and symptoms of sepsis include tachycardia, fever, tachypnea, and mental status changes. Hence, their role in many of the early identification tools for sepsis.

Septic Shock. Septic shock is a severe and potentially life-threatening condition that occurs when sepsis progresses to a point where there is profound circulatory dysfunction, leading to hypotension. Mortality is significantly increased due to circulatory, cellular, and metabolic abnormalities. Clinical identification of septic shock also involves a therapeutic vasopressor requirement to maintain a mean arterial pressure of 65 mmHg or greater, and persistent serum lactate levels greater than 2 mmol/L despite adequate fluid resuscitation.

Early identification

Throughout multiple iterations, the Surviving Sepsis campaign proposes a performance improvement program for sepsis and septic shock to include early screening of high-risk patients allowing for prompt identification and initiation of treatment. This recommendation has been changed from a best practice statement in the 2016 guidelines to a strong recommendation in the 2021 guidelines.

In addition to aggressive monitoring to identify the source(s) of infection through careful clinical examination, cultures and radiographs, there are several scoring systems in use to promote early identification of sepsis and septic shock. The tools include the Systemic Inflammatory Response Syndrome (SIRS) Criteria, National Early Warning Score (NEWS), The Modified Early Warning Score (MEWS), Sepsis-related Organ Failure Assessment (SOFA), and Quick Sequential Organ Failure Assessment (qSOFA).

Table 1 provides an overview of the multiple scoring systems each of which uses varying physiologic and laboratory data to assess risk. Although there is no one ideal screening tool, the 2021 guidelines provide a strong recommendation with moderate-quality evidence against using qSOFA alone compared with SIRS, NEWS, or MEWS due to its poor sensitivity. Ultimately the choice depends on the clinical setting, available resources, and the specific patient population. Combining these tools with clinical judgment often provides the most effective strategy for early sepsis identification. Furthermore, serum lactate remains a recommendation albeit a weak one because it may not be available in resource-limited locations. It is meant to compliment the initial assessment while improving the pretest probability in patients who are suspected, but not confirmed, of having sepsis. Serum lactate's greatest value is in directing early resuscitation.

Table 1. Screening tools.

	Components	Strengths	Limitations
SIRS	**Two or more of the following:** 1. Temperature >38°C or <36°C 2. Heart rate > 90 beats per minute 3. Respiratory rate >20 breaths per minute or $PaCO_2$<32 mmHg 4. White blood cell count >12,000/mm³, <4,000/mm³, or >10% immature (band) forms	High sensitivity	Low specificity
NEWS	**Based on six physiological parameters:** 1. Respiratory rate 2. Oxygen saturation 3. Temperature 4. Systolic blood pressure 5. Pulse rate 6. Level of consciousness or new confusion	High sensitivity and specificity, well-validated in various settings	Requires more data points and can be complex to implement

Abbreviations. NEWS: National Early Warning Score, SIRS: Systemic Inflammatory Response Syndrome.

(cont.)

Table 1. Screening tools *(cont.)*

	Components	Strengths	Limitations
MEWS	1. **Heart Rate (HR)** • Scoring: ○ 0 points: 51-100 beats per minute (bpm) ○ 1 point: 41-50 or 101-110 bpm ○ 2 points: 111-129 bpm ○ 3 points: ≤40 or ≥130 bpm 2. **Respiratory Rate (RR)** • Scoring: ○ 0 points: 9-14 breaths per minute ○ 1 point: 15-20 breaths per minute ○ 2 points: 21-29 breaths per minute ○ 3 points: ≤8 or ≥30 breaths per minute 3. **Systolic Blood Pressure (SBP)** • Scoring: ○ 0 points: 101-199 mmHg ○ 1 point: 81-100 mmHg ○ 2 points: 71-80 mmHg ○ 3 points: ≤70 or ≥200 mmHg 4. **Temperature** • Scoring: ○ 0 points: 36.1-38.0°C ○ 1 point: 35.1-36.0°C ○ 2 points: 34.1-35.0°C ○ 3 points: ≤34.0 or ≥38.1°C 5. **Level of Consciousness** Assessed using the AVPU scale (Alert, Verbal response, Pain response, Unresponsive) • Scoring: ○ 0 points: Alert ○ 1 point: Responds to Voice ○ 2 points: Responds to Pain ○ 3 points: Unresponsive **Total MEWS Score**: Sum of the individual scores from each parameter. **Risk Stratification**: **Low Risk (0-2):** Standard monitoring. **Medium Risk (3-4)**: Increased frequency of monitoring and potential intervention. **High Risk (≥5)**: Urgent clinical review and likely intensive monitoring and intervention.	Higher scores are associated with an increased risk of mortality and ICU admission	More complex scoring system
SOFA	**Evaluates the following systems:** 1. Respiratory (PaO_2/FiO_2 ratio) 2. Coagulation (platelet count) 3. Liver (bilirubin level) 4. Cardiovascular (mean arterial pressure or administration of vasopressors) 5. Central nervous system (Glasgow Coma Scale) 6. Renal (creatinine level or urine output)	Comprehensive, valuable in ICU setting	More complex and time-consuming, requires lab results.

Abbreviations. MEWS: The Modified Early Warning Score, SOFA: Sepsis-related Organ Failure Assessment.

(cont.)

Table 1. Screening tools *(cont.)*

	Components	Strengths	Limitations
qSOFA	**Presence of two or more of the following:** 1. Altered mental status (Glasgow Coma Scale < 15) 2. Respiratory rate ≥ 22 breaths per minute 3. Systolic blood pressure ≤ 100 mmHg	Simple, quick to administer, useful in non-ICU settings	Lower sensitivity and should not be used alone

Abbreviations. qSOFA: Quick Sequential Organ Failure Assessment.

Management

Source control

Source control is a critical aspect of managing surgical infections and is directed at removing infected fluid or tissue and preventing ongoing contamination. Examples of source control include abscess drainage, debridement of dead, damaged or infected tissue and removal of infected devices such as implants or catheters. Both the Surgical Infection Society 2016 and the updated 2024 intra-abdominal guidelines provide a strong recommendation for definitive source control with the least invasive approach resulting in the resolution of organ dysfunction and inflammatory response. Furthermore, the 2024 guidelines differentiate the timing of source control in the patient with septic shock. In this subset, the strong recommendation is for source control within six hours based on studies that demonstrated significant increases in mortality when it was delayed. The 2021 Surviving Sepsis guidelines provide a more general best practice statement emphasizing rapid identification and intervention as soon as is logistically practical to include the removal of infected devices.

Resuscitation

The facets of volume resuscitation include the type and amount of fluid complimented by monitoring techniques. The updated 2021 guidelines have downgraded from strong to weak the recommendation of at least 30 ml/kg of intravenous crystalloid within the first three hours due to the poor quality of the associated studies. Moreover, these guidelines now recommend using only a balanced crystalloid solution rather than normal saline to minimize the risks associated with saline including hyperchloremic metabolic acidosis. The authors again offer a weak recommendation although now with moderate-quality evidence against using gelatin for resuscitation and maintain the strong recommendation against using starches. They make no recommendation due to insufficient evidence of using restrictive *versus* liberal fluid strategies in the first 24 hours in patients who continue to demonstrate hypoperfusion. However, they include albumin as a suggested option rather than crystalloid alone for those patients who received a large volume resuscitation.

Norepinephrine remains strongly recommended as the first-line vasopressor agent with the addition of vasopressin followed by epinephrine as a weak suggestion if unable to maintain adequate perfusion. The goal for vasopressor use is defined as a mean arterial pressure (MAP) > 65 mmHg. Moreover, a weak recommendation exists against the use of levosimendan, a calcium-sensitizing drug with both inotropic and vasodilation effects, which has been added for patients with persistent septic shock and cardiac dysfunction due to its lack of benefit and safety profile. To allow for more prompt delivery of vasopressors, current recommendations promote peripheral intravenous access rather than through a central line during the initial infusion resulting in a faster time to achieve the goal MAP. Monitoring capillary refill as an adjunct now has a weak recommendation as well. These new updates are meant to be used in conjunction with the unchanged components from the 2016 paper to include early admission to the ICU and trending lactate levels to guide resuscitation.

Antimicrobial therapy

Timing of antimicrobials

Antimicrobial therapy is a cornerstone in the management of sepsis, aimed at eradicating the infection causing the systemic inflammatory response. A key aspect of antimicrobial therapy in sepsis management includes early administration. An important change is the distinction in the 2021 recommendations to include a differentiation between septic shock patients and those with sepsis. Although a goal of antimicrobials within one hour remains in place for patients with a high likelihood of sepsis and septic shock, for those patients whose diagnosis of sepsis is in question and who do not meet the definition of shock, the guidelines suggest the pursuit of noninfectious causes allowing for up to a three-hour interval to initiate antimicrobial administration if there remains a concern for infection. This update is a major change. Efforts to promote antimicrobial stewardship and a concerted, thoughtful approach to diagnosis and treatment are emphasized. A recent study demonstrated this approach did not result in a higher mortality when antimicrobials were given outside of the one-hour window in those patients who did not meet septic shock criteria. Moreover, the authors recommend against the use of procalcitonin to influence antimicrobial initiation as it has been shown to be of no benefit.

Empiric therapy

Initial empirical antibiotic therapy should cover a wide range of pathogens, including both Gram-positive and Gram-negative bacteria as failure to choose correctly is associated with an increase in morbidity and mortality in patients with sepsis or septic shock. Antibiograms aide in the initial selection of antibiotics based on the differences in organisms and susceptibility patterns found in each hospital. Now a best practice statement, those patients at high risk for methicillin-resistant *Staphylococcus aureus* (MRSA) based on factors such as the site of infection, medical history, chronic organ failure, current medications, indwelling devices, the state of the immune system, recent infections/colonization, and recent antimicrobial treatments should have an initial regimen that includes an anti-MRSA agent. Of equal import, the authors for the 2021 guidelines offered a weak recommendation to avoid empiric MRSA coverage in low-risk patients.

Similarly, they differentiate patients at low risk for fungal infection and suggest against empiric anti-fungal agents. For those patients at high risk for fungal infections, including but not limited to those with neutropenia, immunosuppressed, total parenteral nutrition, and exposure to extensive broad-spectrum antibiotics, an echinocandin empirically is the drug of choice in patients with sepsis or septic shock. If the suspicion for resistant *Candida* species is low then azoles can be considered. If there is echinocandin toxicity or intolerance, then liposomal amphotericin B is an alternative. There remains no recommendation for antiviral use.

Double coverage is meant to include the use of two different classes of antimicrobials and specifically is designed for multidrug-resistant (MDR) Gram-negative pathogens.

This weak recommendation is for those at high risk, particularly those with known colonization of an MDR. Furthermore, the authors suggest not using two medications for low risk and when susceptibilities are available in the septic and septic shock patient as outcomes are not improved. These suggestions are meant to balance optimal outcomes while minimizing the risk of toxicity, resistance and *Clostridiodes difficile* infection.

Dosing

Patients with sepsis and septic shock have metabolic derangements that can significantly impact the effectiveness of antimicrobials which include an increased likelihood of hepatic and renal dysfunction, immune dysfunction, and an increased volume of distribution due to aggressive fluid resuscitation. These changes alter drug clearance and affect drug binding. Such issues can influence many of the drug classes; hence the

general best practice statement encourages the use of pharmacokinetic and pharmacodynamics (PK/PD) principles to optimally dose these medications. The guidelines do offer a specific weak recommendation for using a prolonged infusion of beta-lactams. Beta-lactams have demonstrated improved short-term mortality with prolonged infusion thereby producing a longer duration of plasma concentration above the pathogen minimal inhibitory concentration (MIC).

De-escalation

Daily de-escalation assessments are recommended over a fixed duration of therapy. These include discontinuation of unnecessary antimicrobials or narrowing the spectrum of coverage. Utilization of sensitivity data assists these efforts and is a key component of good antimicrobial stewardship. Moreover, it has directly been shown to improve short-term mortality. Therefore, patients with clinical improvement even with negative cultures should have early discontinuation of all antimicrobial therapy as should patients who have a noninfectious cause of their shock identified.

Duration

The shortest duration of therapy with optimal outcomes either equivalent to or better than the longer duration of therapy should be the goal. Many studies over the last two decades have demonstrated no difference in outcomes with shorter *versus* longer courses of antimicrobial treatment. This finding is consistent across multiple locations of infection including lung, urine, blood and abdominal. Consequently, in patients with adequate source control, the most recent surviving sepsis guidelines suggest using shorter over a longer duration of antimicrobial therapy. More specifically, the Surgical Infection Society guidelines 2024 make a strong recommendation with high-quality evidence for 96 hours of treatment after adequate source control for intra-abdominal infections. Additionally, they recommend the use of organ system dysfunction and measures of systemic inflammation to predict failure of source control. This recommendation of assessing the adequacy of source control mirrors the 2021 guidelines evaluating the adequacy of antimicrobial therapy. The authors suggest the use of procalcitonin along with a clinical examination to assist with discontinuation of antibiotics.

Adjuncts

Ventilation

For those patients with respiratory failure coincident with their septic shock, the 2021 guidelines now offer a weak recommendation for the use of high-flow nasal oxygen instead of noninvasive ventilation. For those with sepsis-induced acute respiratory distress syndrome (ARDS) the strong recommendations for low tidal volume strategy, an upper limit of 30 cm H2O for plateau pressures, avoidance of incremental positive end-expiratory pressure (PEEP) titration, and proning for over 12 hours in severe cases remain in place. A new suggestion is the use of veno-venous extracorporeal membrane oxygenation (ECMO) when conventional measures fail recognizing that not all centers will be able to offer this option.

Glycemic control

Glycemic control is an important aspect of managing sepsis, as both hyperglycemia and hypoglycemia are associated with poor outcomes in critically ill patients. The goals and strategies for glycemic control in sepsis have evolved, and current guidelines emphasize the need for careful management to avoid extremes of blood glucose levels. The current guidelines strongly recommend initiation of insulin therapy for glucose levels above 180 mg/dl with a range of 144-180 mg/dl.

Steroids

The use of corticosteroids in sepsis has been a topic of extensive research and debate. Corticosteroids can help modulate the inflammatory response in sepsis and potentially improve outcomes, but their use must be carefully considered due to potential side effects. More recently, the data has supported its use in limited circumstances; hence the change in recommendations both in the 2021 and the focused 2024 updates. For patients in septic shock who continue to require vasopressors then corticosteroids are suggested as a weak recommendation. Furthermore, the 2024 guidelines specifically recommend against a higher dose so currently the approach is 200 mg/d given as 50 mg IV every 6 hours after 4 hours of norepinephrine at a dose at least 0.25 mcg/kg/min has failed to meet resuscitation endpoints.

Sodium bicarbonate

The updated guidelines differentiate patients based on the degree of acute kidney injury and pH. Routine use of sodium bicarbonate is not supported in patients with hypoperfusion resulting in lactic acidemia. Therefore, a weak recommendation against its use to improve hemodynamics is included. For the subset of patients with an acute kidney injury network score of 2 or 3 and a pH of less than 7.2, there is a weak suggestion for the use of sodium bicarbonate due to lower mortality found in this group with its use.

Vitamin C

Although absent in the 2016 guidelines, a weak recommendation against the use of Vitamin C is included in the 2021 update due to an updated meta-analysis that failed to show reduced mortality with its use.

Blood purification

This process uses an absorption cartridge within an extracorporeal circuit through which the blood passes. Previous guidelines offered no recommendation for or against blood purification techniques. However, the authors for the latest guidelines offer a weak suggestion against the use of polymyxin B hemoperfusion due to its questionable benefits, resource utilization and lack of feasibility in low-income areas. There is not enough evidence to make recommendations on other techniques of blood purification.

Conclusion

The management of surgical patients is very similar to nonsurgical patients with sepsis or septic shock. Differences include more potential for operative source control as most of these patients have an intra-abdominal pathology. Another challenge with surgical patients is their perioperative SIRS making differentiating expected post-operative physiology from the onset of sepsis difficult. Utilizing scoring systems with a vigilant approach to postoperative clinical examination is crucial to identify sepsis early or rule out infection.

For patients with a high likelihood of a septic source, early intervention is ideal and should be within six hours with an intraabdominal pathology. To incorporate antimicrobial stewardship efforts the newer guidelines have differentiated those with sepsis from septic shock allowing more time to investigate whether the patient has a noninfectious source mimicking sepsis. For patients without shock, a delay of three hours to the first dose of antimicrobials is recommended for this evaluation thereby avoiding unnecessary antimicrobials when a noninfectious source is identified while having no detrimental impact on the patient who ultimately is found to have an infection. For those in shock, receipt of antimicrobials within one hour after cultures are taken remains the goal. The choice of anti-infective is similar for patients with or without shock and is based on individual risk factors. Patients with low risk for MRSA or fungal infections should not have an anti-MRSA or

anti-fungal agent, respectively included in their initial treatment nor should patients with low risk for MDR be treated with two Gram-negative agents.

Additional adjuncts for septic surgical patients that show a benefit include but are not limited to low-dose corticosteroids when patients have ongoing vasopressor requirements despite adequate volume resuscitation, reasonable blood sugar control, optimization of oxygenation through noninvasive techniques and use of optimal PEEP in concert with low tidal volume strategy with sepsis-induced ARDS. Blood purification, routine sodium bicarbonate administration and vitamin C offer no advantage and should not be used. The successful management of sepsis and septic shock in patients with surgical infections depends on many factors with the active role of the surgical team being vital to optimize patient outcomes.

Competing interests

The authors have no financial and non-financial competing interests to declare.

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Chapter 101

Adjuvant therapies for sepsis and shock of abdominal origin

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Introduction

Sepsis represents a life-threatening condition with a huge impact on healthcare costs. Fragile persons, immunocompromised patients, neonates and pregnant women are particularly keen on being affected by infection with potentially severe consequences. According to WHO, 48.9 million cases of sepsis and 11 million sepsis-related deaths worldwide were estimated in 2020 (accounting for 20% of all global deaths), with higher rates in lower middle-income countries. In-depth, Intra-abdominal infection (IAI) represents a potentially fatal medical condition and a common cause of surgical emergencies. The infection starts within the abdomen cavity and can potentially spread beyond the primary affected organ with potentially further complicating factors (e.g., perforation, peritonitis or abscess formation). IAI can lead to significant morbidity and mortality if not promptly and effectively managed, consequently, timely diagnosis, intervention and a multidisciplinary approach are crucial to improve outcomes. Source control and antimicrobial therapy represent above all the first therapeutic approach.
Even more, it is important to notice that Sepsis is characterized by a dysregulated host response to infection with consequent organ dysfunction and death. This maladaptive response leads to an uncontrolled activation of the inflammatory system involving both the innate and the adaptive immune response.
Consequently, immune modulation has appeared as a promising adjuvant therapy in septic patients. Nowadays, immune modulation may serve as a complementary therapy with the potential to affect both pro-inflammatory and anti-inflammatory responses. The array of immune-modulating drugs available is constantly growing. A crucial aspect of adjuvant therapies is selecting the optimal timing for drug administration during sepsis to maximize treatment effectiveness. Therefore, a deep understanding of the role of the systemic inflammatory response is essential. In this chapter, we aimed to provide an overview of the current available adjuvant therapies that can be used during sepsis and shock of abdominal origin.

Sepsis and shock of abdominal origin: an overview

Intra-abdominal infection (IAI) can involve any of the abdominal viscera and it can be classified based on both the source of origin (i.e. healthcare-acquired *vs.* community-acquired) and on the extent of infection (i.e., uncomplicated and complicated). Healthcare-acquired infection represents a particular challenge for clinicians due to the underlying healthcare status (hospitalized patients, immunocompromised, previous antibiotics treatment) and for the probability of being due to multi-drug resistant (MDR) agents. Complicated Intra-Abdominal Infection (cIAI) refers to an infection that spreads beyond the primary affected organ or to an infection characterized by complicating factors such as perforation, peritonitis or abscess formation. cIAI can lead to significant morbidity and mortality if not promptly and effectively managed. The extent of the infection is influenced by several factors. Above all, host defense plays a central role in containing the infection resulting in the possible formation of abscess with or without peritonitis.

Intra-abdominal infections are often polymicrobial, involving multiple types of bacteria. The combination of aerobic and anaerobic bacteria can lead to complex infections that are more challenging to treat. The microorganisms involved in abdominal sepsis are typically those found in the gastrointestinal tract (from the gastroenteric tract, biliary tract or genitourinary system). The percentage of microorganisms involved in abdominal sepsis can vary depending on the specific type of infection, the patient's demographics, and the healthcare setting. However, certain microorganisms are more commonly associated with abdominal sepsis. Among Gram-negative bacteria, *Escherichia coli* represents one of the most common Gram-negative bacteria responsible for intra-abdominal infections, followed by *Klebsiella* species. *Pseudomonas aeruginosa* is generally characterized by its resistance to antibiotics and association with hospital-acquired infections. Other possible Gram-negative microorganisms found in abdominal sepsis are represented by *Enterobacter* species and *Proteus* species. Gram-negative bacteria are particularly dangerous in abdominal sepsis due to their multiple virulence factors: Endotoxins (Lipopolysaccharides, LPS), Exotoxins, and Enzymes (Beta-lactamases).

Gram-positive bacteria also play a significant role in abdominal sepsis, although they are generally less common than Gram-negative bacteria. *Enterococcus* species (e.g., *Enterococcus faecalis*, *Enterococcus faecium*), part of the normal gut flora, are responsible of for 10-20% of abdominal sepsis. *Streptococcus* species are found in approximately 5-10% of the abdominal sepsis. Then, the prevalence of *Staphylococcus aureus* is around 2-5%. Gram-positive bacteria contribute to the pathogenesis of abdominal sepsis through various mechanisms: Exotoxins (e.g., enterotoxins produced by *S. aureus*), biofilm formation (especially *Enterococcus* and *Staphylococcus* species), enzymes (hyaluronidase and fibrinolysin).

Anaerobic bacteria are a significant component of the microbiota involved in abdominal sepsis, particularly due to their prevalence in the gastrointestinal tract. These bacteria thrive in low-oxygen environments and can contribute to severe intra-abdominal infections. *Bacteroides fragilis* represents the most isolated anaerobe in intra-abdominal infections. It plays a key role due to its virulence and resistance to multiple antibiotics. In addition, *Clostridium* species, including *Clostridium perfringens*, can cause gas gangrene and severe intra-abdominal infections (5-10%). Finally, *Candida albicans* and non-*albicans* species (5-10%) can cause secondary infections in immunocompromised patients or those with prolonged antibiotic use.

The interaction between microorganisms and the immune response in abdominal sepsis is a complex and dynamic process. Indeed, sepsis is characterized by a dysregulated host response to infection and involves a complex interplay between an overactive inflammatory response and subsequent immune suppression. This imbalance can lead to tissue damage, organ failure, and increased susceptibility to secondary infections. The innate immune response plays a crucial role in the initial defense against infection in abdominal sepsis. This response is characterized by the rapid recognition and elimination of pathogens and involves various cells, receptors, and signaling pathways. Immune cells recognize pathogens through specific receptors (Pattern

Recognition Receptors (PRRs) - recognize pathogen-associated molecular patterns (PAMPs)) and respond vigorously to the infection with the release of large quantities of pro-inflammatory cytokines (e.g., TNF-α, IL-1β, and IL-6). The adaptive immune response is slower to develop than the innate immune response but is more specific and has memory capabilities. It involves the activation and coordination of T and B lymphocytes, which specifically target and eliminate pathogens.

The hyperinflammatory phase, often referred to as a "cytokine storm," leads to widespread inflammation. As the body attempts to counterbalance the excessive inflammation, it shifts towards an anti-inflammatory state, a process known as Compensatory Anti-inflammatory Response Syndrome (CARS). This phase is marked by the release of anti-inflammatory cytokines (i.e., IL-10 and TGF-β), which suppress the immune response to mitigate tissue damage caused by the initial hyperinflammatory phase. However, this compensatory response may lead to immunosuppression, which is characterized by reduced function and increased apoptosis of key immune cells (T cells, B cells, and dendritic cells). T-cell exhaustion, indicated by high levels of inhibitory receptors such as PD-1 and CTLA-4, further reduces their functionality. Neutrophils, which are crucial for early pathogen clearance, may become dysfunctional, showing reduced phagocytic ability and contributing to ongoing infection and secondary infections. This cyclical imbalance between hyperinflammation and immunosuppression results in a prolonged and inefficient immune response. The hyperinflammatory response can cause significant tissue damage and organ dysfunction, while the later immunosuppressive phase increases susceptibility to secondary infections and sepsis-related complications. Understanding these phases and their underlying mechanisms is crucial for developing targeted therapies. Current treatments focus on managing the immediate threat of infection and inflammation through antibiotics and supportive care. Future therapies may include immunomodulatory treatments aimed at balancing the inflammatory and anti-inflammatory responses, thereby preventing the deleterious effects of both hyperinflammation and immunosuppression.

Adjuvant therapies for sepsis and shock of abdominal origin

Given the well-established central role that dysregulation of the immune response plays in the pathophysiology of sepsis, the possibility of modulating the host's immune response to facilitate recovery of septic patients certainly appears attractive. The Surviving Sepsis Campaign guidelines dedicate ample space to considering the available evidence in order to recommend or not recommend certain immunomodulatory treatments; however, the use of corticosteroids in patients who do not respond to fluid therapy and medium-high doses of vasopressor drugs remains the only immunomodulatory therapy for which a favorable recommendation is given. Key considerations of adjuvant therapy for abdominal sepsis are presented in **Figure 1**. An overview of the different adjuvant therapies and targets are shown in **Table 1** and **Figure 2**.

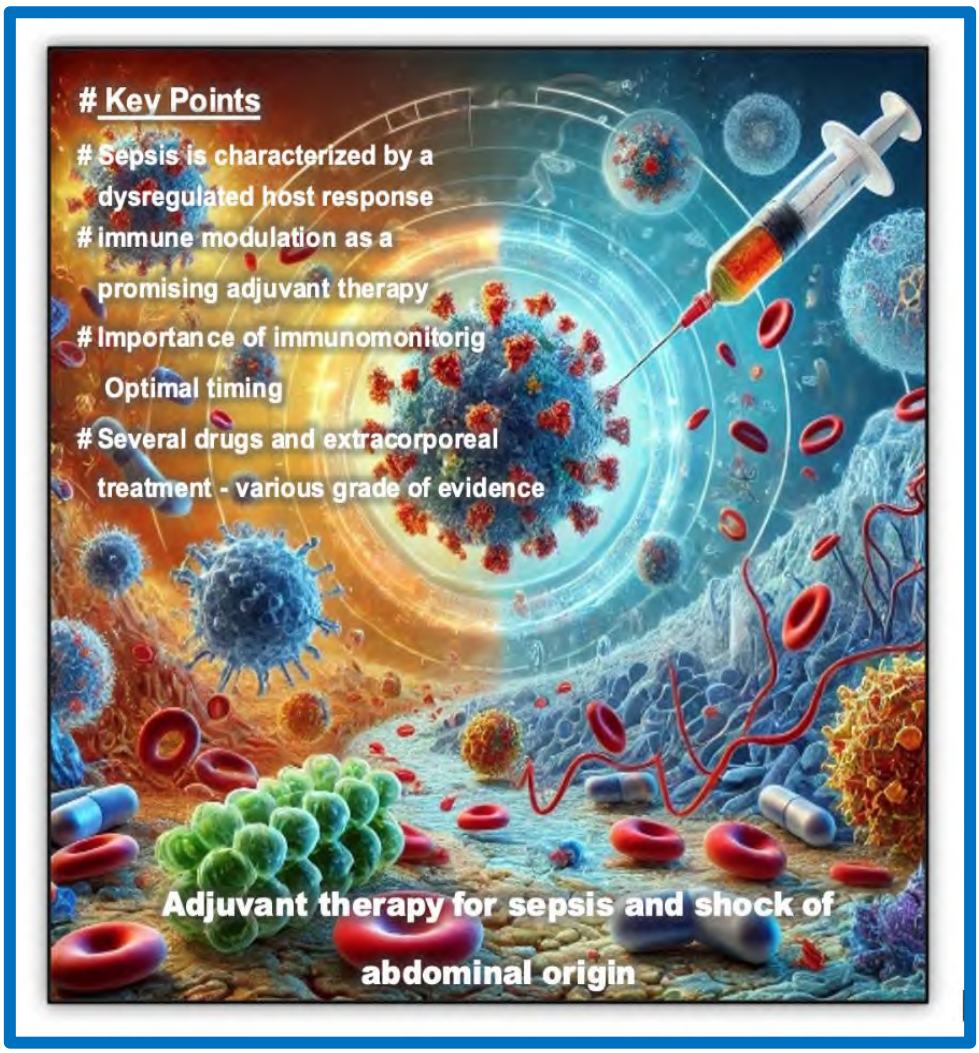

Figure 1. Key considerations of adjuvant therapy for abdominal sepsis (Fictional image created with the assistance of DALL·E 2 (https://openai.com >dall-e-2).

Table 1. Overview of the different adjuvant therapies.

Adjuvant therapy	Characteristics	Biomarkers	Evidence
Steroids	Immune response modulation, promotion of cardiovascular stability, stimulation of organ restoration.	No significant effect on sepsis biomarkers highlighted; interesting insights come from genomic studies.	Currently recommended in patients who do not respond to fluid therapy and medium-high doses of vasopressor drugs.
Immunoglobulins	antigen neutralization; modulation of cytokine responses and immune cell function; interference with activated complement; direct anti-apoptotic effect on lymphocytes; regulation of endothelial cell function, leukocyte adhesion and capillary perfusion.	Low immunoglobulin levels in serum/plasma detected in septic patients.	Currently not recommended as standard treatment in sepsis and septic shock but may be beneficial in certain subtypes of patients.

(cont.)

Table 1. Overview of the different adjuvant therapies *(cont.)*

Adjuvant therapy	Characteristics	Biomarkers	Evidence
Vitamin C	Protection from oxidative stress; maintenance of immune functions; increase in hemodynamic reserve.	Low levels of L-ascorbic acid in septic patients.	Currently not recommended as standard treatment in sepsis and septic shock but may be beneficial in certain subtypes of patients (particularly those with severe sepsis or septic shock, including abdominal sepsis.
Interferon-y	Stimulation of innate immune response to infections.	HLA-DR expression on monocytes.	Currently not recommended as standard treatment in sepsis and septic shock, but evidence in favor derives from case series.
Recombinant human proteins (rhGM-CSF)	Generation and differentiation of myeloid cells; modulation of innate immune effector functions.	HLA-DR expression on monocytes.	Currently not recommended as standard treatment in sepsis and septic shock as it did not prove effective in preventing infections in patients with sepsis-induced immunoparalysis.
Monoclonal antibodies (Nivolumab)	Monoclonal antibody directed against PD-1; already approved in cancer treatment.	Yet to be identified.	First clinical trial in septic patients is underway.
Monoclonal antibodies (Adrecizumab)	Monoclonal antibody directed against adrenomedullin with implications on endothelial barrier function.	Adrenomedullin plasma levels.	Encouraging results from animal models (murine and porcine), safety trials performed in humans.
Monoclonal antibodies (MEDI3622)	Monoclonal antibody directed against ADAM-17; has a role in regulation of neutrophil migration and phagocytosis	Yet to be identified	Limited to preclinical field.

The failure of large trials investigating the application of immunomodulatory therapies in sepsis is probably due to the heterogeneity of the populations involved, which therefore does not allow us to identify the subtypes of patients or the most appropriate timing to demonstrate a benefit. However, the growing push towards the personalization of therapy in all areas of medicine and the increasingly detailed knowledge of the complex interactions between pro- and anti-inflammatory factors that make up the inflammation cascade could contribute to a renewed interest in this type of therapy.

The finding of low levels of endogenous immunoglobulins (IVIG) in septic patients led to the development of a line of research aimed at establishing whether possible supplementation with intravenous immunoglobulins could improve the outcome of this population. The rationale behind using IVIG in sepsis is based on its immunomodulatory effects, which could help counteract the overwhelming inflammatory response and improve patient outcomes. IVIG contains pooled antibodies from thousands of donors, providing a broad range of immunoglobulins (primarily IgG). It seems that immunoglobulins can play a role both in the early phases of sepsis, in which they directly stimulate antimicrobial functions and at the same time modulate the

hyperactivation of the immune system and in the later phases characterized by profound depression of innate and adaptive immunity. Some RCTs have explored the use of IVIG in patients with sepsis, including those with abdominal sepsis.

These studies have produced mixed results. Some trials reported improved survival rates, reduced hospital stays, and better control of infection, while others showed minimal or no significant benefit. Even more, several meta-analyses have been conducted to assess the overall effectiveness of IVIG in sepsis. The analyses from systematic review and meta-analysis generally suggest that IVIG might reduce mortality in certain subgroups of sepsis patients, particularly those with septic shock or severe sepsis, including abdominal sepsis. In a systematic review of neonatal and pediatric patients, Dinleyici *et al.* found that adjunctive treatment with IgM-enriched immunoglobulin may reduce the risk of mortality compared with controls (OR 0.41; 95% CI 0.32-0.55). Even more, in a 2023 systematic review, Pan *et al.* found that standard Immunoglobulins were effective in reducing mortality compared with a group of patients not receiving immunoglobulin (RR 0.70, 95% CI 0.57-0.86, p=0.0006) in adult patients, whereas, standard immunoglobulins were not effective in reducing mortality in neonates (RR 0.93, 95% CI 0.81-1.05, p=0.10). The same group of authors found that IgM-enriched Immunoglobulins were effective in the treatment of sepsis (RR 0.55, 95% CI 0.40-0.76, p=0.0003). A recent study from the Hellenic Sepsis Study Group analyzed 65 cases of septic shock treated with IgM-enriched Immunoglobulins and another 62 propensity-matched non-treated comparators with documented infections by MDR Gram-negative bacteria. Mortality after 28 days was 38.5% under IgM-enriched Immunoglobulins compared to 62.9% of matched comparators (p=0.008) providing promising data on the use of polyclonal IgM-enriched immunoglobulin preparations as adjunctive of antimicrobial treatment for the management of severe infections caused by MDR Gram-negative bacteria. Nevertheless, in summary, the data available in the literature show contrasting results, in the absence of high-quality clinical evidence, the latest Surviving Sepsis guidelines (2021) have maintained its recommendation against the use of intravenous immunoglobulins, also due to the non-negligible adverse effects that can arise from this therapy. However, the debate around the clinical benefit of immunoglobulins continues to flourish. Due to the lack of evidence and conflicting results on the real efficacy of adjuvant therapy and at the same time the need to improve the mortality of sepsis, a panel of experts was established in 2024 by SIAARTI in order to evaluate the potential role of adjuvant therapy in sepsis. The expert concluded that the use of Immunoglobulin within 6h was to be considered appropriate in case of septic shock with severe hyperinflammatory response due to toxin-related syndromes. In detail, the expert highlighted the appropriateness of using preparation inclusion gals IgM component.

At present, routine use of high-dose vitamin C is not recommended in the treatment of sepsis and septic shock. Interest in this therapy had grown in consideration of its potential beneficial effects linked to protection from oxidative stress, the maintenance of immune functions and the increase in hemodynamic reserve, being vitamin C a crucial cofactor involved in the biochemical process of catecholamine synthesis. Furthermore, in sepsis of abdominal origin, a study demonstrated that parenteral vitamin C supplementation after surgery showed anti-apoptotic effects on circulating neutrophils. Despite the large number of studies conducted in the wake of these considerations, convincing evidence in favor of its use on a large scale is still lacking; moreover, non-negligible adverse effects such as hemolysis, although rare, can be present with deleterious consequences, especially in frail patients such as those with underlying renal dysfunction.

Some steps of the inflammatory cascade have been looked at with greater interest. TNF-alpha and IL-1beta are the main proinflammatory mediators in the acute phase response, having a pivotal role in attracting neutrophils to the site of infection; at the same time, however, their action contributes to triggering endothelial dysfunction, which paves the way for the development of multi-organ failure that can be observed in severe cases of septic shock. The conclusions drawn from the clinical trials that have investigated the potential role

of anti-TNF alpha and anti-IL1beta drugs in the treatment of sepsis cannot permit to recommend their use on a large-scale basis; however, some post-hoc analyses have suggested their effectiveness in some subpopulations. For example, Anakinra is a recombinant human interleukin-1 receptor antagonist drug and has been shown to reduce mortality in patients whose septic state was accompanied by liver dysfunction and disseminated intravascular coagulation; at the same time, therapies with anti-TNF-alpha monoclonal antibodies appear effective in reducing mortality if administered in the early stages of sepsis, i.e. before the onset of shock.

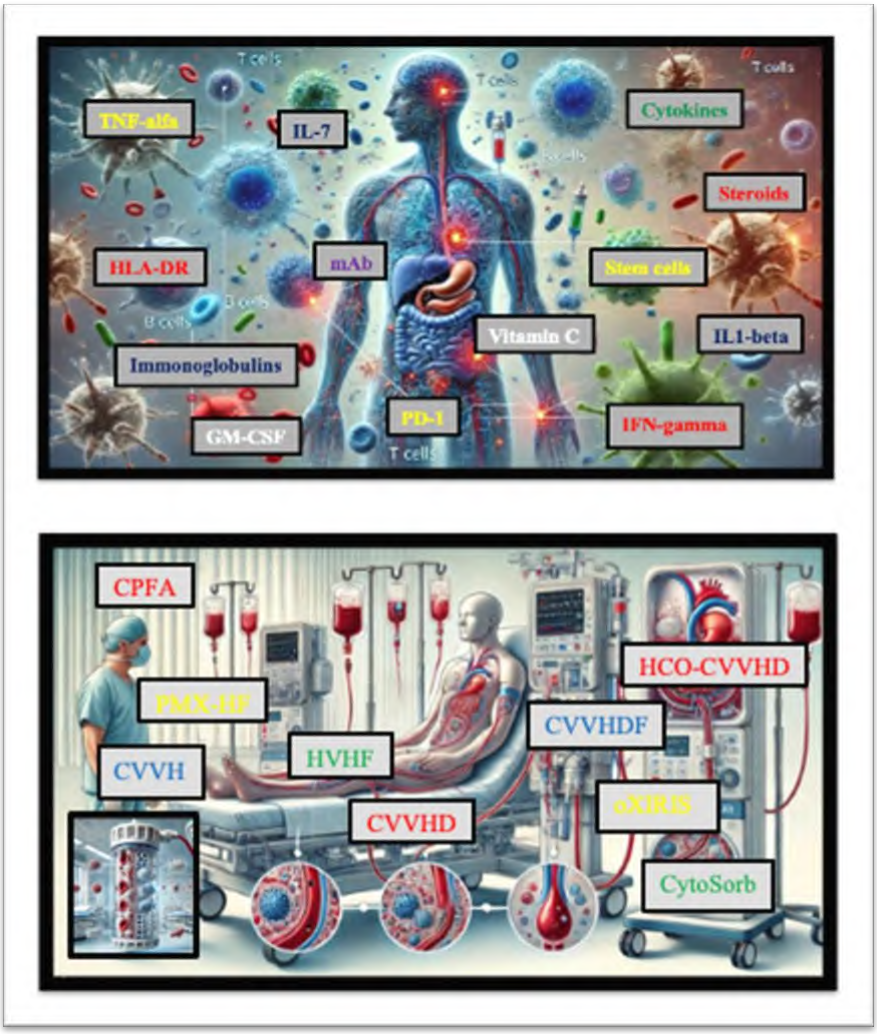

Figure 2. Graphical overview of different adjuvant therapies (Fictional image created with the assistance of DALL·E 2 (https://openai.com >dall-e-2).

Abbreviations. TNF-alfa: Tumor necrosis factor alfa, IL-7: Interleukin 7, IL1-beta: Interleukin 1 beta, HLA-DR: human leukocyte antigen DR isotype, mAb: monoclonal antibody, GM-CSF: Granulocyte macrophage colony-stimulating factor, PD-1: Programmed cell death protein 1, IFN-gamma: Interferon-gamma. CPFA: Coupled plasma filtration adsorption, PMX-HF: polymyxin B hemoperfusion, CVVH: continuous veno-venous hemofiltration, HVHF: High-volume haemofiltration, CVVHD: continuous veno-venous hemodialysis, CVVHDF: continuous veno-venous hemodiafiltration, HCO-CVVHD: high cut-off continuous veno-venous hemodialysis.

Other points in the inflammatory cascade can be targeted by monoclonal antibodies. Generally speaking, the action of monoclonal antibodies can be targeted either directly against the pathogen or some of its components (e.g., bacterial toxins) or against some specific element of the inflammatory cascade with the aim of modulating its function. Three monoclonal antibodies directed against bacteria have been approved by the

FDA: raxibacumab and obiltoxaximab against Bacillus anthracis toxin, and bezlotoxumab against *Clostridium difficile* toxin. Monoclonal antibodies directed against the ADAMTS17 protease, against adrenomedullin and against complement factor C5a are under development, but at the moment their successes remain mostly confined to the preclinical field. A further promising application of monoclonal antibodies is to target so-called immune checkpoints, such as the one involving programmed cell death protein-1 (PD-1) and its ligand (PD-L1), based on the knowledge that one of the mechanisms behind T lymphocyte dysfunction in sepsis-induced immunosuppression is the upregulation of PD-1 and PD-L1. In the wake of the success that nivolumab, the monoclonal antibody against PD-1, has had in the oncology field, studies are underway to evaluate its effectiveness in the treatment of sepsis with encouraging results on mouse models.

Another target of immunomodulatory therapies is the sepsis-induced immunoparalysis phase. One strategy to intervene in this phase is to stimulate the immune response through the use of human recombinant molecules analogous to endogenous mediators such as proinflammatory cytokines or colony growth-stimulating factors; the activity of these molecules can be monitored by evaluating the expression levels of HLA-DR by monocytes. IFN-gamma is a powerful stimulant of innate immunity in response to infections, the use of which is already consolidated in the treatment of primary immunodeficiency. Studies conducted in models *in vitro* and *in vivo* hint that it could be able to reverse sepsis-induced immunoparalysis. A case series has investigated the use of interferon-gamma in the therapy of sepsis-induced immunoparalysis with promising results, but there is a lack of randomized clinical trials to evaluate its real impact on the outcome of these patients.

The use of recombinant human GM-CSF, which is already a cornerstone of the treatment of patients with neutropenia following chemotherapy, has also been evaluated with interest as an immunostimulant during sepsis-induced immunoparalysis. Despite the favorable premises deriving from previous evidence, a randomized clinical trial was unable to demonstrate an effect in the prevention of infections in patients with sepsis-induced immune paralysis. Promising results in the reversal of sepsis-induced lymphopenia also appear to derive from the use of recombinant human Interleukin-7.

Finally, interesting ideas derive from a rapidly growing area in all sectors of medical research, namely that of mesenchymal stem cells. Mesenchymal stem cells are multipotent cells with the capacity to differentiate into cells from all three lineages and are thought hopeful in sepsis treatment for the abilities of tissue regeneration and immune regulation, and for anti-inflammatory and anti-bacterial functions. The first clinical trials applying mesenchymal stem cell therapy to the setting of sepsis are currently underway, but *in vitro* and animal model studies have provided a good evidence base to encourage further research in this area, although there are concerns about potential long-term side effects including an increased risk of cancers.

Extracorporeal blood purification therapies for sepsis and shock of abdominal origin

As aforementioned described, a key feature in sepsis and septic shock is mediated by numerous pro- and anti-inflammatory cytokines synthesized in response to PAMPs and damage-associated molecular patterns (DAMPs) released by the interaction between host cells and the pathogen. In this context, extracorporeal blood purification therapies have become attractive as adjuvant therapy in sepsis and septic shock. An overview of the possible modalities, characteristics and indications of Extracorporeal blood purification therapies are shown in **Table 2**.

Table 2. Overview of the possible modalities, characteristics of the filter and indication of extracorporeal blood purification therapies.

Blood purification technique	Modality	Characteristics of the filter	Indications
HVHF	Convection	Standard high flux membrane.	Renal dose > 35 ml/kg/h (if >45 ml/kg very high HF). High renal dose allows for high convective flow of larger molecules (cytokine). RCTs haven't shown benefit from this approach.
HCO-membrane	Diffusion	High cutoff membrane: larger pore size than a standard hgh flux.	Better in CVVHD modality to reduce albumin loss. Removal of molecules with molecular weight up to 50kDa.
Cytosorb	Haemoadsorption	polystyrene-divinylbenzene copolymers coated with polyvinylpyrrolidone.	It allows for the reduction of bilirubin, myoglobin, cytokines (i.e. IL-6, IL-10, and TNF-a).
Toraymyxin	Haemoadsorption	polymiyxin B.	Benefit on patients with EAA between 0,6 and 0,9.
oXiris	Convection/Diffusion + Haemoadsorption	polyacrylonitrile methalysulfonate coated with polyethyleneimine and unfractioned heparin.	Same as toraymyxin and cytosorb but with the possibility of also performing kidney replacement therapy.
CPFA	Haemoadsorption on plasma + Hemodiafiltration on blood	The blood first passes through a plasma filter. The plasma is then circulated in a sorbent to remove pro-inflammatory substances. It is subsequently reconstituted with the blood in the circuit, and before returning to the patient, it flows through a CRRT hemofilter.	RCTs have shown the potential harm of this method.

Abbreviations. HVHF: Hugh Volume HemoFIltration, HCO: High Cut-Off, CPFA: coupled plasma filtration adsorption, EAA: Endotoxin Activity Assay, RCT: randomized controlled trial, CRRT: continuous renal replacement therapy.

The rationale behind these methods has a similar background, although it differs in conceptual elaboration: Ronco hypothesized that cutting the peaks of cytokine concentrations could bring them to a non-toxic level, in what is called the “peak concentration hypothesis”. According to Honoré, removing cytokines from the blood compartment creates a concentration gradient that forces them out of the tissues. Peng suggested that removing cytokines/chemokines could restore leukocyte trafficking in tissues, improving damage to healthy tissues and promoting repair in infected ones, the so-called “cellular theory”. Di Carlo's “mediator delivery hypothesis” posits that the use of high-volume hemofiltration (HVHF) stimulates lymphatic flow and thus the removal of inflammation mediators due to the high volume of reinfusion fluid.

Cytokines have different molecular weights, ranging from 8.4kDa (i.e., IL-8) to 51kDa (i.e., TNF-alpha), so the modality of renal replacement therapy (RRT) and the cutoff of the membrane used influences the clearance of the solute to be removed. The removal of cytokines can occur non-specifically using common blood purification techniques or selectively using hemoperfusion techniques with specific sorbents. Indeed, High-volume ultrafiltration techniques use convection as the primary mechanism for solute removal, where plasma is driven across the membrane by a pressure gradient, dragging solutes along with it, the so-called “solvent

drag" process. The amount of plasma "filtered" during High Volume Ultrafiltration treatment is usually more than 50 ml/kg/h. This process is highly efficient for the removal of small to medium-sized molecules, including cytokines. Furthermore, the use of high cut-off membranes in hemofiltration allows for a more effective clearance of medium-molecular-weight molecules (e.g., cytokines), due to the characteristics of larger pore size of such membranes. Then, Hemadsorption involves the use of adsorptive cartridges that selectively bind and remove cytokines and other inflammatory mediators from the blood. During Adsorption techniques, blood passes through the adsorption cartridges, where cytokines are bonded to the adsorptive material.

About non-selective blood purification techniques, HVHF can represent a potent immunomodulatory treatment for sepsis. IVOIRE trial, a multicenter randomized controlled trial, examined the impact of HVHF on 28-day mortality in septic shock and AKI. However, no difference in mortality was observed between septic patients with AKI and amine support who received 35 or 70 ml/kg/h of renal dose. In fact, the 137 patients in the study were treated with Continuous Veno-Venous Hemodiafiltration (CVVH) with a flow distribution of one-third pre and two-thirds post for 96 hours (with high-flux filter change every 48 hours). The 28-day mortality was not significant (HVHF 37.9% *vs.* slow continuous venovenous hemofiltration, SVHF, 40.8%, p=0.94), as well as at 60 and 90 days. Additionally, there were no differences in terms of duration of mechanical ventilation, RRT, or ICU or hospital stay. In contrast, the group treated with 70 ml/kg/h had increased clearance of electrolytes and antibiotics, although these were underdosed in both groups. Similar data were recorded in Zhang's observational study comparing 50 *vs.* 85 ml/kg/h, and as reported in Clark's meta-analysis, the evidence does not show a benefit in using HVHF in patients with Sepsis-associated -AKI(SA-AKI) possibly due to subtherapeutic antibiotic levels, the cornerstone of sepsis therapy. It should be noted that Clark's study is significantly confounded by the timing of RRT initiation. Given the molecular weight of cytokines, another approach attempted was using membranes with larger pore sizes than the classic high-flux membranes commonly used in RRT treatments: the high cut-off membranes. Although observational studies showed a reduction in vasopressor use and even mortality (37.5% in the High Cutoff Continuous Veno-Venous Hemodialysis, HCO-CVVHD, group *vs.* 87.5% in the Continuous Veno-Venous Hemodiafiltration, CVVHDF, group), the randomized High Cutoff Sepsis (HICOSS study) study was prematurely interrupted due to the lack of improvement in 28-day mortality and no difference in vasopressor use between the HCO-membrane group and the standard treatment group. It should also be noted that HCO significantly increases albumin loss.

CytoSorb is a blood purification device already used for the removal of bilirubin and myoglobin. CytoSorb also allows the absorption of cytokines. Up to now, the use of CytoSorb during sepsis has not provided definitive results in terms of mortality. Currently, its use in septic patients is not supported by positive evidence, likely because the cytokine storm does not subside after a few hours of treatment or due to non-selective removal of other molecules such as coagulation factors and antibiotics. Therefore, the scientific community stresses the need for RCTs to identify the appropriate setting for the method. bCoupled plasma filtration adsorption (CPFA) is another extracorporeal blood purification therapy that absorbs both proinflammatory and anti-inflammatory mediators. CPFA is not recommended as therapy because 3 RCTs have demonstrated its inefficacy in reducing mortality and even highlighted its dangers: the COMPACT-2 study showed that in the intervention arm, mortality was 32.8% *vs.* 12.5% in the control group with p=0.02. These results led to the early discontinuance of this technique.

Of notable importance is the removal of Endotoxin, a major component of lipopolysaccharide (LPS) on the outer cell of Gram-negative bacteria and one of the most emblematic PAMPs. Endotoxin interacts with TLR-4 and initiates a series of intracellular signals pathways leading to the transcription of pro-inflammatory gene products. High blood levels of endotoxin trigger severe organ dysfunctions, leading to the development of acute kidney injury, altered myocardial contractility, disseminated intravascular coagulation, and acute lung injury due to alveolar endothelial alterations. For this reason, methods have been developed to remove LPS

from the blood. Polymyxin B-immobilized fiber column direct hemoperfusion allows endotoxin clearance using an extracorporeal circuit. PMX Hemoperfusion (PMX-HP) was developed in Japan in the 1990s and several clinical trials conducted in Japan showed encouraging results. In 2010, the EUPHAS randomized controlled trial was conducted enrolling patients with septic shock who underwent emergency surgery for abdominal infection. Patients were randomized in PMX treatment *versus* standard of care. 28-day mortality was 32% in the PMX group compared with 53% in the standard of care treatment group (unadjusted hazard ratio (HR): 0.43; 95% confidence interval (CI), 0.20-0.94; adjusted HR, 0.36; 95% CI, 0.16-0.80). Adjusting for SOFA score, this difference became statically significant with a significant reduction in 28-day mortality in the PMX hemoperfusion (adjusted HR, 0.36; 95% CI, 0.16-0.80; p=0.01). In abdominal sepsis, encouraging data emerged also from patients enrolled in the EUPHRATES trial that examined the impact of polymyxin B hemoperfusion (PMX) on mortality in patients with endotoxic shock measuring endotoxin activity (EAA) in the blood of the patients. The post-hoc analysis, enrolling patients with EAA between 0.6–0.89, showed a significant difference in mortality in PMX-treatment patients (p=0.005). Contrarily, in the 2015 ABDOMIX study, comparing PMX treatment with standard of care in patients with peritonitis and septic shock undergoing emergency surgery, the authors failed to find a significant difference in 28-day mortality. It should be noted that the 2021 Surviving Sepsis Campaign guidelines weakly recommend against it, citing it as “expensive, resource-intensive, potentially reducing health equity, and infeasible in low-income economies”. Crucial is the accurate selection of patients who may benefit from this treatment to ensure study results are not misleading. Important results are expected from the ongoing TIGRIS study (NCT03901807).

Another interesting membrane is the oXiris membrane, a single-use device that allows the performance of standard hemofiltration modalities with hemoadsorptive activity. This letter feature is a consequence of the polyethyleneimine that creates a negatively charged surface capable of binding endotoxin and various cytokines, such as TNF-a, IL-1, IL-6, IL-8, and IL-10. A recent meta-analysis analyzed 14 studies comparing the use of the oXiris membrane with classic dialysis membranes used in CRRT. Most of the analyzed studies were conducted on patients with intra-abdominal infections. oXiris proved effective in reducing 28-day mortality and improving hemodynamic stability compared to patients treated with standard membranes. It should be noted that experts recommend the use of blood purification techniques in patients with sepsis and concurrent acute kidney injury, and this membrane allows for achieving both objectives: modulation of cytokines and endotoxin, and kidney support.

Another key element in extracorporeal blood purification therapy, as highlighted by the SIAARTI-SIN joint commission, is the timing of initiation of these techniques. A single-center analysis on ICU patients with endotoxin shock, predominantly of abdominal origin, showed that introducing a therapeutic flowchart for PMX treatment significantly reduced mortality, allowing for early recognition of organ dysfunction and the early use of extracorporeal blood purification techniques. It should be emphasized that in the absence of SA-AKI, extracorporeal purification methods pose more risks than benefits, making it a challenging method to pursue outside of RCTs.

It remains valid, as shown earlier by data from EUPHAS2, that patient selection may allow for an earlier approach aimed at modulating the inflammatory drive with subsequent sequential therapy to support multiorgan failure.

Conclusion

The interplay between microorganisms and the immune response in abdominal sepsis is intricate and can lead to significant morbidity and mortality. Effective management requires a thorough understanding of the

pathogens involved and the immune dysregulation that occurs. Early diagnosis, appropriate antimicrobial therapy, surgical intervention for source control, and supportive care are critical for improving patient outcomes. Additionally, ongoing research into immunomodulatory therapies holds promise for future treatment strategies.

Competing interests

The authors have no financial and non-financial competing interests to declare.

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Chapter 102

Prognosis and predictors of mortality in patients with sepsis of abdominal origin

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Introduction

Sepsis is defined as a potentially fatal organ dysfunction induced by a dysregulated host response to infection. The incidence of sepsis has risen, apparently due to the increasing ageing of the population; several studies have evidenced a relationship between age and incidence of sepsis and a higher number of people with disease comorbidities. Up to 49.9 million cases of sepsis and 11 million sepsis-related deaths were recorded globally in 2017. Intra-abdominal infection (IAI) is characterized as an inflammatory reaction to bacteria and their toxins in the peritoneum. IAI is the second most frequent cause of sepsis, with an estimated mortality rate of around 30.0%. Early diagnosis and treatment of infection in this group of patients is associated with improved outcomes and reduced mortality.
The purpose of our review was to describe clinical scores and biomarkers influencing morbidity and mortality in patients with sepsis of abdominal origin.

Biomarkers

Definition

A biomarker is a molecule that can be measured in a biological sample objectively, systematically, and precisely, as an indicator of normal or pathological processes, or pharmacological responses to a therapeutic intervention. They can be used for the evaluation of pathophysiological processes in various aspects such as prevention, diagnosis, treatment, prognosis, and disease progression, among others.
The ideal biomarker should, in general, be easy to measure, low in cost, and high in sensitivity and specificity, and should provide additional information for the clinical assessment. The main studies analyzing the utility of different biomarkers are summarized in **Table 1**.

Table 1. Studies that have shown the utility of different biomarkers as prognosis factors in abdominal sepsis.

Study	Biomarker	N	Conclusions
Reith *et al.*	PCT	246	Median PCT values on days 1, 4 and 10 associated with higher mortality
Suarez-de-la-Rica *et al.*	PCT and lactate	121	High lactate values and high peak PCT concentrations (>100 ng/ml) associated with mortality
Rau *et al.*	PCT	82	PCT > 10 ng/mL predicts the development of multiple organ failure
Schroder *et al.*	PCT	24	Higher PCT levels in non-survivors
Gukasjan *et al.*	PSP	91	PSP was the only independent predictor of death
Fu *et al.*	mHLA-DR	46	mHLA-DR expression was depressed in the more severe group of patients
Bösch *et al.*	Preseptin and IL-6	31	Presepsin had the highest predictive value for mortality

Abbreviations. PCT: procalctitonin; PSP: pancreatic stone protein; mHLA-DR: monocyte human leukocyte antigen-DR; IL-6: interleukin-6.

Procalcitonin

Procalcitonin (PCT) is a prohormone of calcitonin that is produced in response to the release of endotoxin or mediators released in response to bacterial infections and has a strong correlation with the severity and extent of infection. Procalcitonin, as a biomarker for bacterial infections, has been widely studied for its prognostic role in sepsis. Several studies have evaluated its role as a prognostic factor in abdominal sepsis.

A study by Reith *et al.*, which involved 246 patients with intra-abdominal sepsis focused on the association between median PCT levels and mortality rates at different intervals following surgery. Median PCT values on days 1, 4 and 10 after surgery were associated with higher mortality (4.9 ng/mL in survivors *vs.* 13.8 ng/mL in non-survivors on day 1; 4.8 ng/mL *vs.* 13 at day 4 and 0.4 ng/mL *vs.* 13.25 at day 10; $p<0.01$).

Our group performed a retrospective multicenter observational study that explored the utility of PCT, lactate and C-reactive protein (CRP) to predict mortality in critically ill patients with complicated intraabdominal infection. We included a total of 121 patients, and we found an association of peak PCT (>100 ng/ml) with overall mortality.

Two other additional studies support the prognostic value of procalcitonin (PCT) in intra-abdominal infections:

1. Rau *et al.*: this study was conducted on 82 patients with secondary peritonitis, showing that PCT levels > 10 ng/mL could predict the development of multiple organ failure (multiorgan dysfunction syndrome).
2. Schroder *et al.*: in this smaller study of 24 patients with septic shock in a surgical ICU, higher PCT levels were found in non-survivors. Most patients had intraabdominal infections.

Lactate

Lactate is the most widely used biomarker as an indicator of organ dysfunction and deficit of perfusion and is commonly elevated in sepsis. It was included in the definitions of septic shock in 2016. Our group observed an association of peak lactate values >1.8 mmol/L and lactate value at 24h >5.87 mmol/L with hospital mortality and ICU mortality, respectively, in surgical patients with complicated intra-abdominal infection. Interestingly, mortality was better predicted if high lactate values and high peak PCT concentrations (>100 ng/ml) were combined in a single dummy variable. To our knowledge, this was the first study that assessed the value

of lactate as a prognostic factor in abdominal sepsis. Recently, Park *et al.* did not find an association between initial lactate and 28-day mortality in 219 patients admitted to ICU due to IAI.

C-reactive protein (CRP)

C-reactive protein (CRP) is another commonly used biomarker for inflammation and sepsis. It is less specific for bacterial infections compared to PCT. A recent study performed in critically ill septic patients (that included patients with abdominal sepsis) showed that a CRP level > 100 mg/L on ICU admission was a SAPS-3 independent prognostic factor for ICU and 30-day mortality. Notwithstanding, when only patients with abdominal sepsis were analyzed, we found no differences in CRP values between survivors and non-survivors. This result was not surprising, because all patients had inflammation derived from tissue injury.

Pancreatic stone protein (PSP)

PSP is an acute-phase reactant, that is essentially produced in the exocrine pancreas and other organs in response to systemic stress, with higher levels according to the severity of inflammation. PSP provokes polymorphonuclear cell activation by binding to their surface. Gukasjan *et al.* performed a study that investigated the value of PSP to predict organ failure and death in critically ill patients with secondary peritonitis. PSP had higher diagnostic accuracy to discriminate organ failure than white blood cell counts, CRP, interleukin-6, and PCT and it was the only independent predictor of death.

Monocyte human leukocyte antigen-DR (mHLA-DR)

The HLA-DR is a glycosylated cell surface membrane protein expressed on antigen-presenting cells, constitutively expressed on monocytes too. This protein presents antigen to T-helper cells resulting in the liberation of pro-inflammatory cytokines. Down-regulation of HLA-DR in monocytes may worsen prognosis in septic patients. Several studies have shown an important association between lower m-HLA-DR expression and mortality, but only one was exclusively performed in patients with abdominal sepsis. In this last study, forty-six critically ill patients with severe intra-abdominal infections were included. mHLA-DR expression was depressed in the more severe group of patients.

Interleukin-6 (IL-6)

IL-6 is an established blood marker of inflammation, usually raised in patients with sepsis. In a study performed on critically ill patients with suspicion of infection, IL-6 had a higher diagnostic value for infection than PCT, CRP and preseptin, and it was a predictor of 28-day mortality as well. Specifically in abdominal sepsis, higher preoperative IL-6 values were associated with 90-day mortality in patients undergoing emergency surgery due to an abdominal infection.

Preseptin

Presepsin is a 13 KDa polypeptide made by proteolytic cleavage of soluble forms of a cluster of differentiation CD14. CD14 is expressed mostly on most immune system cells, as well as cartilage, brain, liver, and intestinal cells. It is released after the binding of lipopolysaccharide (LPS) to monocytes, causing an enhanced immune response. Since presepsin is produced immediately after the onset of an infection it can be detected early in the development of sepsis.

Excellent predictive capacity for severity and mortality was recently found in sepsis of several origins. In a multicenter retrospective trial that enrolled patients with sepsis presepsin levels were higher in non-survivors, while PCT values were not different. Preoperative presepsin had the highest predictive capacity of 90-day mortality before emergency abdominal surgery in 31 patients with abdominal infection when it was

compared with CRP, PCT, IL-6, endotoxin and white blood cells (WBC). In this last study, endotoxin, a part of the membrane of Gram-negative bacteria, showed a low predictive capacity. Only IL-6 and presepsin showed significant predictive capacity in ROC analyses, although it was slightly higher for presepsin.

Clinical scores

Our group found that the SAPS II score of ≥47 and SOFA score at admission ≥ 7 were associated with ICU and hospital mortality, respectively, in critically ill patients with complicated intra-abdominal infections. Both scores showed a significant prognostic performance (AUC >0.7, p<0.05) at admission and 72 hours after in the case of SOFA.

SAPS II has been demonstrated to be a good prognostic tool in abdominal sepsis in other previous studies. SAPS III has been recently associated with mortality as well. In a study performed in 163 patients with secondary peritonitis SOFA score at admission but not APACHE II was an independent predictor of mortality. Other research showed an association between SOFA score on day 4 and mortality in sepsis of abdominal origin.

Source control and adequate antibiotic administration

Early administration of appropriate antibiotics is critical for reducing mortality in sepsis. Park *et al.* found specifically in patients with abdominal sepsis that the non-survivor group had a tendency of delayed antibiotic administration compared with that in the survivor group, although significant difference was not observed (217.5 ± 422.8 min *vs.* 171.4 ± 238.8 min, p= 0.495).

Adequate source control is essential in sepsis, and it is an independent predictor of mortality in sepsis caused by intra-abdominal infection. Azuhata *et al.* found that the time to initiation of surgery was an important determinant of survival in patients with gastrointestinal perforation and septic shock. The survival rate was 0% for times greater than 6 hours.

Conclusion

PCT and lactate values seem to be good predictors of mortality in abdominal sepsis. IL-6 and presepsin may be useful as well. A combination of biomarkers as PCT and lactate may increase their predictive value. SAPS II and SOFA are clinical scores with important predictive capacity. Specifically in abdominal sepsis, quick source control is of vital importance to improve the prognosis of our patients.

Competing interests

The authors have no financial and non-financial competing interests to declare.

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Chapter 103

Challenges related to surgical infection prevention and management

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Introduction

The major challenges related to surgical infections are not the need to elucidate new therapeutic targets or develop innovative technology but rather to utilize our currently available knowledge, diagnostics, and interventions to provide data for improved precision medicine in our approach to the individual patient condition and their unique infectious risks.

Surgical infections are healthcare-associated infections occurring after an operation. Due to the enormous volume of surgical procedures annually, associated infections affect millions of patients yearly and mandate that every effort be made to work toward prevention. Multiple international societies and national organizations have developed guidelines and best practices to prevent these infections, but despite these efforts, many patients succumb to infection; leading to morbidity, mortality, and increased hospital cost. On average patients undergoing elective surgery will be diagnosed with a surgical site infection in 2-5% of cases and upwards of 20% in high-risk procedures depending on the site and surgical indication. While the rate is low, this has major implications for both patient morbidity and hospital costs accrued over time. It is of the utmost importance that we critically evaluate current policies and procedures and develop improved precision in our individualized patient care to better prevent infection in all surgical patients.

The data supporting these strategies has been mixed, but with implementation, there has been some slow, positive impact. A major unresolved issue remains whether these approaches used as blanket strategies, assuming all patients with similar disease scenarios will respond similarly, are equally effective or optimal for the individual patient and whether they are harmless and without unintended consequences in any specific patient. Another major challenge is the common error incurred within the concept of “The enemy of good is better”. Increasingly aggressive strategies to prevent infection have led to many unproven, questionable practices, such as longer courses of antibiotic treatment and unproven sterility practices that contribute to increases in antibiotic resistance, questionable stewardship practices, excessive cost and environmental blight. Below, several areas addressing the prevention and management of surgical infection are introduced, and potential future directions for better prevention practices for more effective infection prevention are proposed.

Preoperative infection prevention challenges

The goal of primary prevention should always be employed for infection control. Major organizations including the World Health Organization (WHO), the Centers for Disease Control and Prevention (CDC, USA), and many other national organizations have prevention practice guidelines that should be adhered to whenever possible. An ongoing challenge is the lack of consistency and fidelity in the application of these recommendations for SSI prevention and therapy. Ongoing investigations and improvements in implementation science are critical to achieving global utilization and consistent application of these recommendations. Currently, the average time to broad implementation of newly proven therapies exceeds 17 years. This is unacceptable going forward and successful techniques and modalities to educate, train and disseminate new knowledge will be critical.

In patients with malnutrition identified on routine screening panels, enteral supplementation with varying multi-nutrient enhanced formulas has been suggested to help prevent SSI, but with significant variability of results and overall low-quality evidence. The impact of uncontrolled diabetes mellitus, as monitored by an elevated A1C, on wound complications and healing and proven need to control and lower A1C prior to elective surgery is broadly accepted and increasingly applied. The discovery of new glucagon-like peptide-1 (GLP-1) agents as effective weight loss therapy along with other less studied potential metabolic benefits requires extensive RCTs to define how these therapies can be implemented to optimize weight loss to minimize infectious complications and enhance healing of the surgical wound. Similarly, the WHO and other experts recommend that prior to surgery patients taking one of many biologic agents, particularly immunosuppressive agents such as anti-tumor necrosis factor (TNF) medications and other biologic mediator inhibitors, an explicit discussion of benefits *versus* risks occur and decision for discontinuation should be individualized to the patient and procedure. Unfortunately, most of these recommendations carry moderate to low evidentiary support, and it is challenging to apply these general principles to any one patient as most of the studies are quite heterogenous. The current need for large RCTs to definitively prove efficacy in infection prevention and wound healing enhancement in holding these critical and increasingly common agents is an ongoing major challenge. Currently, recommendations are to continue most agents as being nondetrimental to the surgical processes but based on extremely heterogenous and mostly historical controls.

Perioperative antibiotics are still recommended for most clean and clean-contaminated cases to cover endemic bacteria at the site of planned surgery. There are well-established practices regarding pre-operative administration of antibiotics prior to incision on many procedures. Antibiotics should have coverage of common skin flora including *Staphylococcus aureus* and coagulase-negative Staph. In general, cefazolin remains the antibiotic of choice administered within 30 minutes of incision time. The addition of broader spectrum antibiotics for clean-contaminated cases varies based on the organ system involved. Overall, these exposures make up 1 in 5 of all inpatient antibiotic exposures, and with the threat of antibiotic resistance on the rise, some have called this standard practice into question. The balance of risk benefits of impact on preventing infectious complications *versus* the environmental impact on hospital and patient flora is currently unknown. However, increasing hospital-acquired and also prior patient colonization-related infections both in-hospital and community-acquired are known to be caused by resistant bacteria. Adequate and appropriate testing protocols are not established or supported by current screening processes.

Colonization with MRSA has been linked to increased postoperative infection and mortality in select patient populations. The addition of vancomycin for patients screened MRSA positive through any method, most commonly nasal swab, has been adopted into practice. If it is to be used, vancomycin or fluoroquinolones require a longer administration time preoperatively to achieve adequate tissue levels, so should be administered within 120 minutes and an hour before incision time. While preoperative screening for MRSA

colonization is standard practice in many facilities, compliance and efficacy remain uncertain. Studies have confirmed that expanded antibiotic coverage for resistant bacteria does improve outcomes, including the prevention of SSI. In the setting of rising antibiotic resistance there is interest in better coverage of additional organisms based on individual patient microbiomes, similar to the practice of adding vancomycin for patients with known MRSA colonization). Some efforts have been made to identify which patients might benefit from individualizing antibiotics based on pre-existing conditions particularly cancer with metastatic disease, congestive heart failure, chronic obstructive pulmonary disease (COPD), and diabetes mellitus, which have been associated with higher risk for development of antibiotic-resistant infections. Further studies are needed to confirm whether these patients benefit from broader spectrum coverage at the time of their operations.

Compliance based on appropriate preoperative screening and also not using expanded coverage treatment in cases where it is inappropriate remains a significant issue and challenge to antibiotic stewardship. Because of the growing resistance patterns of many bacteria, one strategy utilized when organisms present are not known prior to surgery is to target a narrower spectrum of bacteria that are known through institutional screening data to be problematic based on the specific patient and case being performed. In addition, ongoing debated strategies such as oral antibiotics preoperatively for colorectal surgery and topical antibiotics for dermatologic procedures have evidentiary support for effective surgical site infection prevention with the added benefit of narrower spectrum treatment and lower risks of antibiotic resistance.

The WHO currently recommends environmental decolonization practices for high-risk procedures. However, the direction of transmission of these bacterial strains has been questioned whether from hospital to patient or patient to hospital, and since the latter seems more consistently the case, broader environmental decontamination practices may not be effective for SSI prevention. In a recent study of elective spine procedures, comparing an individual patient's microbiome based on a sample of nares, back, and rectal samples, more than half of the subsequent SSI-causing bacteria were resistant to the standard prophylaxis employed. Up to 86% of bacteria causing SSIs were found in the patient's own microbiome, which calls into question the overall impact of universal blanket practices of expanded sterility and current antibiotic selection. In addition, when comparing SSI bacterial microbiome based on the spinal level of incision; cervical, thoracic, or lumbosacral, there was a marked difference in bacterial species. Common skin flora was more likely to be isolated from the upper spine and subsequent SSI and enteric pathogens were more common in the lumbosacral region, a group for which standard Gram-positive prophylaxis is ineffective. The current inability to match the preoperative antibiotic spectrum to the individual patient's surgical anatomic site microbiome explains, in part, the ongoing inability to further impact the incidence of SSI. Routine surgical site microbiome analysis is feasible and a future potential goal in providing optimal prophylaxis.

Perioperative management

Routine measures such as pre-operative bathing with antimicrobial agents shown to have no impact on bacterial resistance patterns or plain soap is recommended in all cases when feasible. The choice of agents used is unproven since there does not seem to be a clinically significant effect on infectious complications. Selective use of hair removal using clippers and not shaving is recommended. Shaving has been shown to be detrimental by exposing increased levels of skin pore bacterial colonization. Immediately pre-operatively in the OR, the recommendation from the CDC is to use an alcohol-based anti-septic solution unless contraindicated. Recent data from patients undergoing elective clean cardiac or abdominal surgeries demonstrate alcohol povidone-iodine solution was a non-inferior preparation solution compared to alcohol-chlorhexidine solutions.

Whether there is a differential effect in contaminated or higher-risk procedures is not well studied with variably reported outcomes and requires controlled definitive trials.

Intraoperative infection prevention challenges

Several additional pre- and intra-operative treatment options are also employed to prevent surgical infections. Targeting tight glucose control, normothermia, euvolemia and adequate oxygenation are all recommended interventions known to affect the wound and healing process and as such provide an enhanced environment to aid in infection prevention. High glucose levels are proven to impair the immune system and tissue healing. Tight blood glucose control for both diabetic and non-diabetic patients is known to reduce SSI, with again the caveat to avoid over-treatment and detrimental effects of hypoglycemia. Thus, there remains controversy due to a lack of evidence regarding the range of control that should be targeted in the individual patient and specific clinical settings. Patients undergoing longer operative procedures are at risk of hypothermia, and a body temperature less than 36C has been linked to an increase in infectious and SSI outcomes. Maintenance of core body temperature by passive warming either with hot air or electrical warming devices has been shown to significantly reduce the risk of SSI. Inadequate circulating volume and permissive hypoxia can impair oxygen delivery and tissue and wound levels. There is a known impact on the host immune and reparative processes necessary for normal wound healing that has been shown to variably correlate with an increased risk of SSI. The use of intra-operative and perioperative goal-directed fluid management based on hemodynamic and cardiac output monitoring, targeting euvolemia has been associated with a decrease in SSI. In a meta-analysis of patients undergoing general anesthesia, increasing perioperative FiO_2 also reduces SSI. What is missing is the ability to selectively monitor and maintain a specific oxygen tension at the injured tissue level critical for each unique wound. The deleterious effects of over-resuscitation and hyperoxia are also recognized and similar to the over-aggressive treatment of hyperglycemia leading to a potentially net negative impact on the host overall.

The broadly accepted explanation for where surgical site infections develop is during intraoperative contamination. Techniques to reduce infections from host sources have been employed and demonstrated benefit. In all cases, delicate treatment of all tissues to avoid unnecessarily compromised healing and all efforts possible to prevent or minimize gross contamination along with the removal of grossly infected or diseased tissue for optimal source control are critical. Use of these principles with additional wound protectors, removal of contaminated instruments, and change in drapes, gowns, and gloves prior to closure have greatly reduced SSI in colonic resections and other similar procedures. For orthopedic prosthetic joint surgeries, vancomycin powder is often sprinkled in the field to prevent contamination and infection with *Staphylococcus aureus*, however, results of effectiveness are mixed. Recent meta-analysis demonstrates a preventive effect of wound irrigation with antiseptic and antibacterial solutions prior to wound closure. Since there is a potential impact on the induction of bacterial resistance with the use of antibiotic solutions, the preference is the use of a non-toxic antiseptic solution. Further controlled trials are needed to confirm these observations on heterogeneous patient populations with variable contamination sources.

Evaluation of the site by obtaining bacterial culture during an operation would seem a reasonable way to evaluate for the presence of pathogenic bacteria, and there is some correlation with a positive intraoperative culture and later development of SSI. However, there remains a large portion of these wounds that even if contaminated on intraoperative culture do not go on to develop an SSI. In addition, an alternative theory that SSI develops from a remote site on the patient due to translocation from the patient's own microbiome may bridge this gap in understanding. Support for this theory can be seen in cases in which aggressive MRSA

prevention strategies, preoperative decolonization, preoperative MRSA-targeted antibiotics, and intraoperative vancomycin powders, are used while the SSI that develops is due to polymicrobial, Gram-negative bacteria. Again, well-constructed and matched RCTs are lacking to better define aspects of the clinical scenario and therapeutic protocols definitively shown to prevent or reduce SSI.

Post-operative infection prevention and management

Diagnosis and timing of postoperative surgical infections varies based on the type of surgery performed, infectious agent, and other patient factors. Early preemptive treatment is paramount in many of these infections, but there are some studies showing diagnosis of these infections can be delayed as long as two weeks to one month after surgery.

Early identification and treatment of wounds at risk for SSI are essential to reduce postoperative infections, but prediction models for patients at the highest risk and therefore most likely to benefit from earlier intervention remain sparce. Clinical prediction tools are varied and the implications for practice are not well-defined or data-driven.

Multiple ongoing trials are using biological markers to better predict which patients are going to develop infectious complications and sepsis after surgery and trauma. However, while these markers correlate with risk and outcomes, the overall immunologic response among patients is similar without a clear separation of levels of specific markers that make identification of levels of clinical relevance wanting. In addition, the host response to infection may vary within significant overlapping of levels based on underlying genetic and immunologic phenotypes and haplotypes such that choosing the optimal treatment in an individual patient becomes clinically irrelevant and currently of little use without better additional prediction models to identify which patients will have worse outcomes. Several studies have shown differences in the immune cell response of patients with infection and sepsis including sub-phenotypes of plasma proteins that differ from patient to patient. Certain immune cells may be upregulated in the early moments of sepsis leading to worse immunosuppressive responses which can worsen host response and ultimately clinical outcomes). Given these findings, tools with greater accuracy and accurately timed to the phase of disease need to be developed to allow application in a focused patient-specific manner.

Currently, protocols that protect the healing wound and removing conditions supportive of bacterial overgrowth are variably applied and reported to have an impact on SSI. While the routine use of drains has been debated, a consensus is their use causes a greater risk of contributing to an SSI rather than preventing one. In conditions where significant dead space is created (such as a large chronic subcutaneous hernia sac in a morbidly obese patient) and likely to collect serum and blood, the appropriate use of drains to collapse dead space and remove fluid collections is still potentially advantageous. Data to decide are currently lacking. A similar approach in removing toxic and bacterial-favoring wound conditions is wicking of high-risk wounds and more recently the increasingly broadly used implementation of vacuum-assisted dressings to remove fluid and toxic agents. Again, the absence of well-controlled trials to confirm the efficacy of these approaches remains a major challenge in the field. An ongoing RCT comparing vacuum-assisted dressings *versus* routine wound care for laparotomy incisions will be completed soon and hopefully contribute higher-quality data to this debate. This is a critical need since international recommendations are for routine use in low-resource settings with a potential impact on access to other limited resources.

Recently, the utilization of various forms of mobile telemonitoring has been added to post-operative monitoring of the wound allowing for earlier identification of concerning wound developments and/or early SSI to allow intervention and minimizing the ultimate impact of the process. The use of mobile technology (i.e.

widely accessible smartphones) or computer-accessible programs is in its infancy and challenges us with needing the protocols to implement with the best opportunities for successful impact as proven by controlled prospective trials. While erratically utilized currently, the potential of this approach and the improved use of resources for maximal benefit need extensive investigation to reap the benefits of these technologies.

Postoperative antibiotic management

Currently, a shorter course, if any, of routine treatment or postoperative antibiotics is advised. Please refer to the chapter on non-perforated appendicitis and diverticulitis. Postoperative antibiotic prophylaxis lasting longer than 24 hours is not recommended in clean and clean-contaminated cases due to a lack of decrease in surgical site infection and an increase in the development of resistant organisms and in antibiotic-related complications such as *Clostridium difficile* infection (CDI). While a recommendation with a high level of evidence, the actual adherence to this practice is universally low, with less than 1/3 of hospitals implementing these policies effectively and consistently. The practice of a four-day course of antibiotics for intra-abdominal infection after source control has been widely adopted and has raised the question for similar pathology treatment in thoracic cases such as empyema decortication, which has historically been treated with a long course of postoperative antibiotics. Evidence suggests a shorter course after decortication might be sufficient and longer courses are just portending harm without benefit. Even in theoretically higher-risk procedures like orthopedic procedures with metal implants, extending the course of antibiotics postoperatively has no effect on infection prevention and may increase the risk of CDI without notable benefit.

In certain cases, however, extending antibiotic therapy may have some benefit. Patients undergoing pancreatectomy with a high risk of postoperative pancreatic fistula may benefit from a longer course of postoperative antibiotics). It should be noted in these cases that true source control cannot be reliably achieved, and these decisions should be individualized based on the patient, pre-existing conditions, surgical plan, and overall risk assessment. They should not be universally applied to all patients which does present challenges in quality assurance and antibiotic stewardship practices.

The challenge remains in not only identifying the appropriate utilization of these principles but also when and in whom to not utilize these protocols. Overriding all of these challenges is the lack of data from the use of implementation science to study and identify the means and processes necessary to ensure their correct implementation.

Conclusion

Many of the processes affecting the development of SSI have been elucidated. The remaining major challenges require valid, high-quality data to prove that our current care based on logical hypotheses but lacking high-level evidentiary data is indeed optimal. There are abundant challenges created by the lack of data that require investment in well-constructed randomized control trials (RCTs); based on our extensive understanding of wound infection biology, rather than relying on poorly controlled, historical comparisons. We need to move forward from inadequately studied interventions applied, too frequently, in a ubiquitous blanket fashion. We need to provide high-level evidence using improved host biologic, physiologic, and anatomic discriminators to improve our accuracy in patient selection. This improvement in patient selection will support the safe and appropriate use of therapeutic interventions that could potentially be harmful and/or wasteful

approaches. A precision medicine treatment approach is needed for each unique patient and their disease process. Lastly, we need data from implementation science on how to best achieve acceptance and consistent implementation of proven therapies.

Competing interests

The authors have no financial and non-financial competing interests to declare.

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Chapter 104

The art and science of surgical infections

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Introduction

What is the role of specialty in surgical infectious disease?
Surgical infections encompass a wide range of infections related to surgical procedures or requiring surgical intervention to treat. They can be broadly categorized into two categories:

1. Surgical site infections (SSIs) are a significant complication in the postoperative period and are among the most common healthcare-associated infections. These infections occur at the site of a surgical incision. SSIs can be superficial, affecting only the skin and subcutaneous tissues, or they can be deep, involving deeper tissues such as muscles and organs or implanted devices. They are a major concern due to their potential to cause significant morbidity and extend hospital stays.
2. Infections requiring surgery for treatment include conditions where surgical intervention is necessary to manage or treat an infection. Common examples are intra-abdominal infections, such as infected pancreatic necrosis, diverticulitis, cholecystitis, and appendicitis. These infections often require timely surgical management to prevent further complications.

Additionally, some infections are of particular concern to the surgeon due to additional infection risks associated with surgery in patients with some specific infections. These, in particular, include viral illnesses such as HIV, Hepatitis B, and C and also include unusual infections such as prion disease.

The importance of addressing surgical infections

Surgical infections are a significant concern in clinical practice, substantially affecting patient outcomes, including prolonged hospital stays, increased morbidity, and healthcare costs. These infections pose a formidable challenge to surgical practice, as they can range from superficial SSIs to deep organ-space infections. Despite advances in surgical techniques, antibiotic prophylaxis, and aseptic protocols, the incidence of surgical infections remains a persistent problem globally.
Surgical infections are in many ways different from other infectious diseases due to the inherent local nature of many of these infections, whether necrotizing soft tissue infection or post-operative surgical site infection.

A common characteristic of most of these infections is the need for source control as well as antimicrobial therapy to cure such infections. Many practitioners of surgical infectious disease are surgeons, with training that highlights the uses (and sometimes limitations) of surgical source control to assist in the complete cure of this disease.
This introduction sets the stage for a detailed discussion on surgical infections, highlighting the importance of ongoing research and adherence to best practices to mitigate these challenging and costly complications.

Case

A 45-year-old male with a history of recurrent acute pancreatitis complicated by a pancreaticocutaneous fistula underwent a distal pancreatectomy and splenectomy. Intraoperative findings were notable for significant intra-abdominal scarring, with contracture of the transverse colon into the inflamed pancreatic bed.
On postoperative day 5, the patient developed a high-grade fever, increasing abdominal pain, and leukocytosis. A contrast-enhanced CT scan (**Figure 1**) revealed free air under the diaphragm and a fluid collection in the left upper quadrant, highly suggestive of a surgical site infection (SSI) and possible visceral perforation. The decision was made to return the patient to the operating room for emergent source control and further exploration.

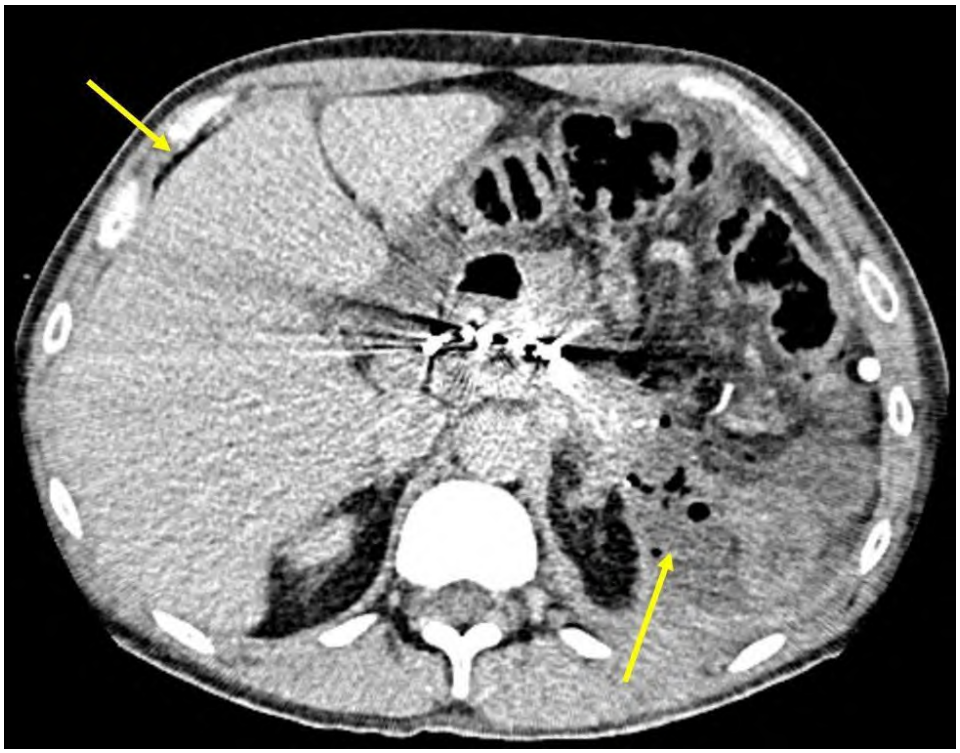

Figure 1. Abdominal CT scan shows pneumoperitoneum secondary to perforated viscus (left yellow arrow) and left subdiaphragmatic free fluid in the bed of spleen with sub-capsular liver collection (right yellow arrow).

Intraoperatively, an abscess was drained from the LUQ, and a colonic perforation was identified at the splenic flexure, where the transverse colon had contracted into the inflamed pancreatic bed. Immediate surgical source control was achieved through a segmental colon resection, colostomy creation, and construction of a Hartmann's pouch. The patient recovered uneventfully.

This case highlights the critical importance of source control in managing intra-abdominal infections, particularly when complicated by visceral perforation. The prompt identification of the infection source, followed by immediate surgical intervention, was essential in preventing the further spread of infection and mitigating the risk of sepsis.
These infections occur at or near the surgical incision within 30 days of the procedure or within one year if an implant is involved.

Pathophysiology and pathogenesis of surgical site infections (SSIs)

Surgical site infections (SSIs) are predominantly caused by bacterial contamination during or after a surgical procedure. The development and severity of SSIs are influenced by a complex interplay between the pathogen, the surgical site, and the host's immune response.
Microbial contamination and biofilms. The level of microbial load introduced during surgery is a critical determinant of infection risk. This contamination can occur due to the patient's own flora, the operating environment, or surgical instruments. Common pathogens include *Staphylococcus aureus*, *Escherichia coli*, and various anaerobic bacteria. Wounds are classified based on the anticipated degree of contamination:

- Clean (Class I): No infection and minimal contamination.
- Clean/Contaminated (Class II): Controlled entry into a hollow viscus with indigenous flora.
- Contaminated (Class III): Open, accidental wounds or significant breaches in sterility.
- Dirty (Class IV): Infected or necrotic wounds with substantial microbial presence.

Recent evidence highlights the role of biofilms in SSIs, where bacteria form protective communities that enhance resistance to antibiotics and immune responses. These biofilms allow pathogens to persist in host tissues and evade treatment, complicating the infection dynamics.
Immune evasion and host factors. Pathogens express virulence factors, such as toxins and adhesion molecules, facilitating their persistence and invasion in host tissues. Additionally, immune evasion mechanisms, including modulation of host immune signaling pathways and inhibition of phagocytosis, further complicate the infection dynamics. Host factors like diabetes, obesity, malnutrition, immunosuppression, and other comorbidities impair immune response and wound healing, significantly elevating the risk of infection.
Procedure duration and surgical technique. Longer surgeries increase the risk of SSIs due to prolonged exposure to potential contaminants. The method of wound closure and postoperative wound management are also crucial. Primary closure of wounds is typical in Class I and II wounds, whereas Class III and IV wounds may require open management to minimize infection risk. Advanced techniques, such as vacuum-assisted closure, can be beneficial in specific scenarios.
Advanced diagnostics and personalized approaches. The integration of advanced diagnostic tools, such as next-generation sequencing and proteomics, has enhanced the identification of specific microbial signatures and host responses. These tools enable more targeted and effective interventions, emphasizing the importance of personalized medicine approaches in managing SSIs. Genetic variations in both pathogens and hosts can influence susceptibility to infections, further underscoring the need for individualized treatment strategies.
By understanding the multifaceted nature of SSIs—ranging from microbial contamination to host factors and surgical techniques—healthcare professionals can better devise prevention and treatment strategies to reduce the incidence and severity of these infections.

Surveillance and reporting

In the United States, hospitals are mandated to monitor and report SSIs for 30 days post-surgery, a practice linked to increased adherence to preventive measures and reduced SSI rates. The National Healthcare Safety Network (NHSN) uses data from numerous hospitals to refine risk indices and guide quality improvement initiatives.

Clinical outcomes and healthcare implications

SSIs lead to considerable morbidity, extended hospital stays, increased healthcare costs, and patient dissatisfaction. The prevention and management of SSIs are critical aspects of surgical care, with significant implications for patient outcomes and healthcare resource utilization. This comprehensive understanding of SSIs underscores the importance of adhering to evidence-based practices and guidelines to minimize infection risks and enhance patient safety.

The latest definition of SSI according to the Centers for Disease Control and Prevention (CDC) categorizes SSIs into three main types based on the depth and location of the infection:

Superficial incisional SSI. This occurs within 30 days after the surgery and involves only the skin and subcutaneous tissue around the incision. Key indicators include purulent drainage from the incision, organisms isolated from the incision, or symptoms like pain, swelling, or redness that lead to the deliberate opening of the incision by a healthcare provider.

Deep incisional SSI. This type of SSI occurs within 30 days (or up to 90 days for surgeries involving implants) and involves deeper soft tissues, such as fascia and muscle. Indicators include purulent drainage from the deeper incision, spontaneous dehiscence (splitting or bursting open of a wound), or signs of infection such as fever and localized pain.

Organ/space SSI. This occurs within 30 days (or 90 days for implant surgeries) and involves any part of the anatomy that was opened or manipulated during the procedure, excluding the incision, fascia, or muscle layers. Indicators include purulent drainage from a drain placed in the organ/space, organisms isolated from the fluid or tissue in the organ/space, or an abscess detected during an examination.

These definitions help standardize the identification and reporting of SSIs, ensuring consistent surveillance and management across healthcare settings. For more detailed criteria and examples, refer to the CDC's SSI guidelines.

Evidence-based approaches for the prevention of surgical site infections

To effectively combat surgical site infections, it is essential to adopt a comprehensive, evidence-based approach. The following measures encompass preoperative, intraoperative, and postoperative strategies that have been demonstrated to significantly reduce the incidence of SSIs. **Table 1** presents a structured framework for preventing surgical site infections (SSIs) through a series of measures taken before, during, and after surgery. It divides the interventions into four categories. By integrating these evidence-based strategies into clinical practice, healthcare providers can significantly reduce the incidence of surgical site infections, ultimately enhancing patient safety and outcomes.

Table 1. Preoperative, intraoperative, and postoperative measures.

Measure	Specific actions
Preoperative measures	● **Patient screening and optimization.** Identify and manage comorbid conditions (e.g., diabetes, obesity) that increase infection risk. ● **Antiseptic showering.** Use chlorhexidine gluconate for preoperative showers to reduce skin microbial load. ● **Antibiotic prophylaxis.** Administer appropriate antibiotics within one hour before incision to ensure adequate tissue levels.
Intraoperative measures	● **Aseptic techniques.** Strict adherence to aseptic protocols (hand hygiene, sterile instruments, proper draping). ● **Surgical technique.** Use minimally invasive surgical techniques when possible to reduce tissue trauma. ● **Normothermia.** Maintain patient's core body temperature to prevent hypothermia-induced immune suppression. ● **Oxygenation.** Ensure adequate oxygenation throughout the procedure to enhance tissue oxygen levels and reduce infection risk.
Postoperative measures	● **Wound care.** Implement evidence-based wound care practices, including regular inspection and timely dressing changes. ● **Early mobilization.** Encourage early postoperative mobilization to improve circulation and immune function. ● **Monitoring and surveillance.** Establish protocols for continuous patient monitoring and rapid response to infection.
Education and training	● **Staff training.** Regularly train surgical and nursing staff on updated infection prevention guidelines and protocols. ● **Patient education.** Educate patients on following pre-and postoperative care instructions to reduce infection risk.

Diagnostic challenges

Diagnosing surgical infections can be challenging due to the variability in clinical presentation. Common signs include fever, erythema, and purulent discharge at the surgical site. However, these symptoms can be non-specific and may overlap with non-infectious postoperative complications. Advanced diagnostic tools, such as imaging techniques and molecular methods, have enhanced the accuracy of diagnosis. Clinical judgment remains paramount despite these advancements, particularly in distinguishing between infection and other postoperative complications. **Table 2** lists tools to aid in the diagnosis of SSI.

The treatment of surgical site infections typically involves a combination of surgical intervention and antimicrobial therapy. Surgical management typically includes simple wound opening but may require debridement, drainage of abscesses, and removal of infected hardware. Antimicrobial therapy should be guided by culture results and sensitivity patterns, with careful consideration given to the potential for antimicrobial resistance. The duration and route of antibiotic therapy depend on the severity and type of infection, with a preference for targeted therapy based on the identified pathogen.

Table 2. Practical ways to recognize SSIs (Adapted from Ban KA, *et al.* 2017; Owens CD, et al. 2008).

Category	Practical ways to recognize SSIs
Clinical signs & symptoms	● **Redness**, swelling, and increased pain at the surgical site. ● **Purulent drainage** or discharge from the wound. ● **Fever** or elevated body temperature. ● **Delayed healing** or separation of wound edges.
Laboratory tests	● **Elevated white blood cell count** and inflammatory markers (e.g., C-reactive protein, erythrocyte sedimentation rate). ● **Microbiological cultures** from wound exudates to identify causative pathogens.
Imaging techniques	● **Ultrasound, MRI, or CT scans** to detect deep infections and abscesses. ● **Radiographic evidence** of gas in tissues or fluid collections around the surgical site.
Advanced molecular diagnostics	● **Polymerase chain reaction (PCR)** for rapid identification of bacterial DNA. ● **Next-generation sequencing** for comprehensive microbial profiling. ● **Proteomic and metabolomic analyses** to detect specific infection-related biomarkers.

Abbreviations. CT: computed tomography, MRI: magnetic resonance imaging, SSIs: surgical site infections.

Infections requiring surgical intervention

Surgical intervention becomes a necessity in managing certain infections when conservative treatments, such as antibiotics, fail to control the infection when the infection leads to complications that pose significant risks to the patient, or when surgery remains the best option such as complicated diverticulitis. These conditions often involve complex pathophysiology and require prompt surgical action to prevent further deterioration of the patient's health. Below, we delve deeper into common infections that typically require surgical management, emphasizing the importance of a multidisciplinary approach.

Intra-abdominal infections

Infected pancreatic necrosis. In cases of severe acute pancreatitis, necrosis of pancreatic tissue can occur, leading to secondary bacterial infection. This condition is highly morbid, and intervention often requires a step-up approach starting with less invasive procedures like percutaneous drainage, followed by necrosectomy endoscopically or surgical (preferably through a minimally invasive approach) if needed. Early recognition and intervention are critical, as untreated infected pancreatic necrosis can lead to sepsis and multi-organ failure. The advent of endoscopic and minimally invasive surgical techniques has revolutionized the management of this condition, reducing morbidity and improving outcomes.

Diverticulitis. Diverticulitis occurs when the diverticula in the colon become inflamed or infected, leading to complications such as abscess formation, fistulae, or perforation. While uncomplicated diverticulitis can often be managed with antibiotics, complicated cases typically necessitate surgical intervention. The choice between laparoscopic *versus* open surgery, and whether to perform a primary resection with anastomosis or a Hartmann's procedure depends on the severity of the infection and the patient's condition at the time of surgery. Advances in imaging and surgical techniques have improved the management and outcomes of complicated diverticulitis.

Cholecystitis. Acute cholecystitis, often due to gallstone obstruction, can progress to gangrene or perforation of the gallbladder if not treated promptly. Cholecystectomy is the standard treatment, with laparoscopic cholecystectomy being the preferred method due to its minimally invasive nature, which reduces recovery time and complication rates. Early cholecystectomy, ideally within 72 hours of symptom onset, is associated with better outcomes compared to delayed surgery.

Appendicitis. Appendicitis is the inflammation of the appendix, typically resulting from obstruction by a fecalith or lymphoid hyperplasia. If untreated, it can lead to perforation, peritonitis, and sepsis. An appendectomy, either open or laparoscopic, remains the definitive treatment. The shift towards laparoscopic appendectomy has led to reduced postoperative pain, shorter hospital stays, and quicker recovery.

Soft tissue infections

Necrotizing fasciitis. This life-threatening infection involves the rapid spread of bacteria through the fascial planes, leading to extensive tissue necrosis. Group A *Streptococcus*, *Clostridium* species, and mixed anaerobic infections are common culprits. Necrotizing fasciitis requires urgent surgical debridement to remove all necrotic tissue, commonly necessitating multiple surgeries. Delay in treatment increases mortality, highlighting the importance of early diagnosis and intervention. Hyperbaric oxygen therapy is sometimes used as an adjunct treatment to enhance oxygen delivery to ischemic tissues and inhibit anaerobic bacteria.

Diabetic Foot Infections. Diabetic foot infections are a common and severe complication of diabetes, often leading to amputation if not managed effectively. These infections can extend to deeper tissues and bones (osteomyelitis), requiring aggressive surgical debridement, drainage of abscesses, and sometimes partial or total amputation to control the infection. A multidisciplinary approach involving endocrinologists, infectious disease specialists, podiatrists, and vascular surgeons is essential to optimize outcomes. Recent advances in wound care, such as the use of negative pressure wound therapy and bioengineered tissue, have shown promise in improving healing rates and reducing the need for amputation.

Pressure ulcers (decubitus ulcers). Pressure ulcers, particularly stage III (full-thickness skin loss) and stage IV (full-thickness tissue loss with exposure of muscle, bone, or supporting structures), are susceptible to secondary infections that may require surgical intervention. Surgical debridement of necrotic tissue is often necessary to reduce the bacterial load and promote healing. In cases where large defects are present, flap surgery might be employed to close the wound, restore blood supply, and cover exposed bones or tendons. Preventing pressure ulcers through regular repositioning, skincare, and the use of pressure-relieving devices is key to reducing the incidence of these infections.

Other severe infections

Empyema. Pleural empyema, characterized by the accumulation of pus in the pleural space, often arises as a complication of pneumonia, thoracic surgery, or trauma. Initial management includes chest tube drainage and antibiotics, but when these measures are insufficient, surgical intervention such as video-assisted thoracoscopic surgery (VATS) or open thoracotomy is required. These procedures aim to drain the infected pleural space and remove the thickened pleura (decortication) to allow lung re-expansion. Early intervention is associated with better outcomes and lower morbidity.

Osteomyelitis. Osteomyelitis, or infection of the bone, can occur due to direct inoculation during trauma or surgery, or from hematogenous spread of bacteria. Chronic osteomyelitis, particularly in the presence of necrotic bone (sequestrum), often requires surgical debridement to remove infected and dead bone tissue. This may be followed by reconstructive procedures to restore bone integrity, such as bone grafting or the use of antibiotic-impregnated beads. Long-term antibiotic therapy is usually necessary to eradicate the infection.

Role of advanced techniques and multidisciplinary care

The management of infections requiring surgical intervention has evolved significantly with the introduction of advanced surgical techniques and a better understanding of infection dynamics. Minimally invasive

procedures, including laparoscopic and endoscopic approaches, have become the gold standard for many conditions due to their association with reduced morbidity and faster recovery times. The use of advanced imaging techniques, such as CT and MRI, allows for more precise preoperative planning and better outcomes. Moreover, the importance of a multidisciplinary approach cannot be overstated. Collaborative care involving surgeons, infectious disease specialists, microbiologists, radiologists, and other healthcare professionals ensures comprehensive management of the patient's condition. This team-based approach facilitates early diagnosis, timely surgical intervention, appropriate antibiotic stewardship, and postoperative care, all of which are critical in reducing morbidity and improving patient outcomes.

Advancements in surgical infection management

The management of surgical infections has seen significant advancements, driven by both technological innovation and a deeper understanding of the complex pathophysiology of infections. These advancements aim to enhance treatment efficacy, reduce complications, and improve patient outcomes. Some of the most promising developments include:

Novel antimicrobial agents. With the increasing threat of antibiotic-resistant bacteria, the development of new antimicrobial agents has become critical. These include next-generation antibiotics that target bacterial cell membranes or essential enzymes, and bacteriophage therapy, which uses viruses to specifically target and kill bacteria. Additionally, the exploration of antimicrobial peptides and synthetic compounds offers the potential to address resistant pathogens.

Antibiotic-impregnated materials. Incorporating antibiotics into surgical materials, such as sutures, meshes, and implants, provides localized protection against bacterial colonization. These materials are particularly useful in surgeries with a high risk of infection, such as joint replacements, where infection can lead to severe complications.

Negative Pressure Wound Therapy (NPWT). NPWT has become a widely adopted method for managing complex and infected wounds. It involves applying controlled negative pressure to a wound, which helps reduce edema, increase blood flow, and promote granulation tissue formation. This technique not only facilitates wound closure but also decreases bacterial load and the need for repeat surgeries.

Microbiome and immunomodulatory therapies. The microbiome plays a significant role in modulating immune responses and influencing infection outcomes. Therapies that modulate the microbiome, such as probiotics or fecal microbiota transplantation, are being investigated as adjuncts to traditional antimicrobial treatments. Immunomodulatory therapies that enhance the host's immune response, including the use of cytokines and monoclonal antibodies, are also showing promise in improving infection management.

Ongoing research and clinical trials. The dynamic nature of surgical infection management is reflected in numerous ongoing clinical trials. These trials are essential for validating new therapies and integrating them into standard practice, ensuring that innovations in infection control and treatment are both effective and safe for widespread clinical use.

Infections of concern to the surgeon and occupational risks for surgeons

Surgeons are at heightened risk of acquiring and transmitting infections due to their direct contact with blood and bodily fluids. This occupational hazard necessitates strict adherence to infection control protocols,

particularly in the context of surgeries involving patients with infectious diseases. Key infections of concern include:

Human Immunodeficiency Virus. The risk of HIV transmission in surgical settings, though low, is primarily through needlestick injuries. The risk of seroconversion following exposure is approximately 0.3%. Post-exposure prophylaxis (PEP), involving antiretroviral medications, significantly reduces the risk of infection if administered within 72 hours of exposure.

Hepatitis B (HBV). HBV is highly infectious, with a transmission rate of up to 30% following a needlestick injury from an infected source. Vaccination is the most effective prevention strategy. For unvaccinated or incompletely vaccinated healthcare workers, post-exposure prophylaxis, including hepatitis B immunoglobulin (HBIG) and the hepatitis B vaccine series, is crucial.

Hepatitis C. HCV transmission risk is about 1.8% after percutaneous exposure. Unlike HBV, there is no vaccine for HCV, making prevention strategies focused on avoiding exposure and using antiviral therapy when indicated. Direct-acting antivirals (DAAs) have revolutionized HCV treatment, offering high cure rates, but the emphasis remains on preventing exposure through safe surgical practices.

Prion diseases. While rare, prion diseases represent a significant occupational hazard due to their resistance to decontamination. Surgeons must be aware of and follow strict protocols when dealing with potential prion disease cases, ensuring that instruments are properly decontaminated or safely disposed of to prevent transmission. The insidious nature of prion diseases, combined with their fatal outcomes, underscores the need for vigilance and adherence to specialized sterilization procedures. Prion diseases, such as Creutzfeldt-Jakob disease (CJD), present unique challenges in surgical settings due to their transmissibility and resistance to standard sterilization techniques. Prions are misfolded proteins that can induce other proteins to misfold, leading to neurodegenerative disorders. These diseases require rigorous decontamination protocols, as prions can survive conventional sterilization processes. Surgical instruments used on patients with prion diseases must be subjected to specialized protocols involving extended autoclave cycles or chemical decontaminants like sodium hydroxide. The management of prion disease-related surgical cases demands strict adherence to these protocols to prevent iatrogenic transmission.

Other infections. Surgeons must also be vigilant against infections such as methicillin-resistant *Staphylococcus aureus* (MRSA), *Clostridium difficile*, and tuberculosis. Comprehensive infection control protocols, including environmental cleaning, antimicrobial stewardship, and patient screening, are critical in preventing these infections.

Risk mitigation

Instituting rigorous infection control measures, ensuring vaccination compliance, utilizing safety-engineered devices, and providing timely PEP and follow-up care are essential strategies to protect surgeons and patients alike. This includes using needleless systems and blunt suture needles and adhering to protocols for the safe handling and disposal of sharp instruments. Additionally, ongoing education and training on infection prevention and control practices are vital in maintaining a safe surgical environment. Regular training sessions and updates on the latest guidelines and best practices help ensure that all surgical team members are aware of and adhere to protocols designed to minimize infection risks.

Continuous improvement. By maintaining a high standard of infection control practices and staying updated with the latest guidelines, surgeons can effectively manage the risks associated with these infections, ensuring both their safety and that of their patients. Continuous improvement efforts, such as participating in quality improvement programs and infection control committees, play a crucial role in identifying areas for

improvement and implementing evidence-based practices to enhance patient care. Surgeons should advocate for institutional support for infection control measures and should work collaboratively with other healthcare professionals to develop and enforce policies that protect both healthcare workers and patients from infectious risks.

Through these combined efforts, the surgical community can significantly reduce the incidence of occupational infections, thereby promoting a safer environment for both healthcare providers and patients.

Conclusion

The management of surgical infections necessitates a comprehensive, multidisciplinary approach that integrates meticulous surgical techniques, robust prevention strategies, accurate diagnosis, and appropriate treatment. Despite significant advancements in the field, surgical infections remain a formidable challenge, impacting patient outcomes and healthcare costs. Continuous research and innovation are essential to developing new strategies and refining existing protocols. By understanding the complexities of surgical infections and consistently applying evidence-based practices, healthcare professionals can enhance patient care and outcomes, ultimately reducing the burden of these infections on the healthcare system. To effectively combat surgical site infections, it is imperative to adopt a holistic approach that combines cutting-edge research with practical applications. Enhanced infection control measures, early and precise diagnostic techniques, and personalized treatment plans tailored to individual patient profiles are vital components of this strategy. Additionally, fostering collaboration among healthcare providers, researchers, and policymakers will ensure the continuous evolution and implementation of best practices in surgical infection management. Through these concerted efforts, the medical community can make significant strides in mitigating the impact of surgical infections, thereby improving the overall quality of surgical care and patient safety.

Competing interests

The authors have no financial and non-financial competing interests to declare.

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Chapter 105

Perspectives in surgical infections: what will the future hold?

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Introduction

Despite progress and efforts in reducing hospital-acquired infections, the number of surgical site infections remains consistent and contributes to substantial cost and length of stay. The focus of ongoing initiatives to decrease these rates of surgical site infections includes a multifaceted approach to remaining research questions as outlined by the Surgical Infection Society. Several themes persist through these research questions, which we will focus on here. The first theme focuses on limiting the duration of antibiotic therapy or avoiding antimicrobial agents altogether in specific contexts, given the prevalence of multidrug-resistant organisms. The second theme is the advancement in artificial intelligence and data analytics; this could lead to earlier detection of surgical site infections and the prediction of infection risk. The final theme is the development of personalized medicine to tailor prophylactic antibiotics based on specific risk factors. The overall focus of the future of surgical infections includes utilizing and integrating technological advancements to improve the prevention and more effective management of surgical site infections.

Strategic use of antibiotic prophylaxis

The appropriate duration and use of antibiotics for prevention and treatment in surgical patients are crucial for optimizing patient outcomes and preventing antibiotic resistance. Resistant bacteria pose a significant threat, so it's essential to carefully consider antibiotic usage. Prophylactic antibiotics are commonly used by surgeons daily and play a key role in preventing surgical site infections. In 2016, the American College of Surgeons and Surgical Infection Society published comprehensive guidelines for antibiotic prophylaxis. These guidelines emphasize the importance of administering antibiotics only when necessary and tailoring them to the specific procedure and likely pathogens involved. While these guidelines are helpful, further research is needed to provide more specific recommendations on when antibiotics are indicated.
There is no evidence to suggest that administering antibiotics after incision closure further reduces the risk of surgical site infections. It is recommended to discontinue antibiotics at the time of incision closure. Studies

have shown that limiting prophylactic antibiotic duration to a single preoperative dose can reduce the risk of postoperative *C. difficile* infections compared to prolonged antibiotic use exceeding 48 hours. Prolonged perioperative antibiotic use has been linked to higher rates of antibiotic-resistant bacteria, as demonstrated in a cohort of 2600 patients who underwent coronary artery bypass. Despite this evidence, inappropriate prescribing practices persist, as shown by a study in a vascular surgery population where only 37% adherence to all five categories of correct antibiotic choice, dose, interval, timing, and duration was observed.
Barriers to proper antibiotic use likely include a need for more awareness among practicing surgeons regarding relevant studies and guidelines and difficulty adapting to new practices. More research is needed to guide clinicians on appropriate antibiotic prophylaxis and duration.

Artificial intelligence in infection risk management

Artificial intelligence (AI) has a role in infection risk management through preventing, diagnosing, and treating infections. A systematic review of AI-based tools regarding healthcare-associated infections notes that the current adoption level mainly focuses on the development and testing of models. Risk prediction models are working to utilize large-scale patient data, medical history, and environmental factors to predict the risk of infection in the hospital. While there is moderate evidence that AI-based models perform equally or better compared to clinical scores or traditional statistical analyses, there is a high heterogeneity among studies and minimal evidence of direct application. One study that successfully utilized AI in a clinical database was predicting surgical site infections in posterior spinal fusions. A model was trained using 4046 patients and ultimately had a positive predictive value of 92.56% and a negative predictive value of 98.45%. Despite these findings, the implications of this model to guide clinical decisions are unclear. There still is significant work to do to adopt and utilize these AI-based programs in clinical practice to affect patient care, and this space will likely transform in the coming years as AI technology becomes more widely adopted.

Personalized antibiotic therapy: customizing antibiotic therapy

Personalized antibiotic therapy allows the tailoring of antibiotic therapy to individual patient characteristics to optimize their effectiveness while limiting downsides such as resistance patterns and side effects, as antibiotic stewardship is crucial. Therapeutic drug monitoring measures drugs' pharmacokinetic or pharmacodynamic breakdown within individual patient’s bodies through different modalities. Patient factors that are critical to consider include patient immune status, organ system functions, and critically ill patient status, as these can alter antibiotic therapeutic levels. To personalize antibiotics further, studies have worked to utilize machine learning to determine personalized antibiograms to decrease resistance patterns and develop algorithms to find the best antibiotic for specific circumstances. One particular study utilized electronic health data to compare the utilization of personalized antibiograms using linear programming *versus* broad-spectrum antibiotic therapy. This study found that customized antibiograms developed using machine learning classifiers maintained adequate coverage but narrowed antibiotics at an earlier rate than the standard treatment. A second study examined a large dataset for antibiotic resistance results of bacteria cultures from hospitalized patients across five antibiotics. They used an ensemble model to train competitive models with the area under the receiver operator characteristic (auROC) scores in the range of 0.73-0.79 even when bacterial species were not known. Similarly, machine learning models were also trained to predict antibiotic therapy

choices for uncomplicated urinary tract infections. Using a cohort of 3629 patients, the model achieved an 18% reduction in inappropriate antibiotic therapy and led to a 67% reduction in choosing second-line antibiotics compared to clinicians. Overall, there is room for personalized antibiotic therapy, using both patient characteristics and machine learning technology, to improve antibiotic stewardship.

Conclusion

In summary, the future directions of surgical infection prevention include adopting new technology to utilize personalized medicine for antibiotic therapy, using artificial intelligence in infection risk models, and optimizing antibiotic therapy duration guidelines to promote antibiotic stewardship and work towards a future with fewer surgical infections.

Competing interests

The authors have no financial and non-financial competing interests to declare.

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Chapter 106

Educating surgeons in antimicrobial stewardship practice

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Introduction

Many drivers for inappropriate antibiotic use have been identified in surgery. These include unclear surgical infection guidelines, non-compliance with guidelines, suboptimal cooperation of surgical and AMS teams, underuse of laboratory resources by surgeons often exacerbated by inadequate lab services, rigid hierarchy of surgical teams, increased sense of clinical autonomy, antibiotic prescribing delegated to junior surgeons and lower awareness of the magnitude of the AMR problem globally and locally.
These drivers provide a background for the stewardship challenges and solutions required in modern surgical practice.

Challenges

- Healthcare-associated infections (HAI) affect 5-15% of hospitalized patients, leading to increased vulnerability to infections due to multi-drug-resistant organisms (MDRO).
- Surgical site infections (SSI) occur in 1-3% of inpatient surgeries, contributing to patient harm, mortality, and increased healthcare costs.
- Optimal antibiotic use in surgery faces challenges such as unclear indications for empirical treatment, lack of adherence to guidelines and culture around overuse of antibiotics.

Solutions

- Effective AMS programmes (ASP) are key to tackling AMR, reducing HAI and achieving optimal clinical outcomes for patients.

- ASP objectives include optimal choice, duration and dose of antimicrobial prophylaxis, empirical therapy recommendations and review to support de-escalation, IV to oral switch, and discontinuation of treatment when no evidence of infection.
- The development of evidence-based guidelines supported by education is essential for effective AMS and guideline implementation should include audit of compliance with guidelines.
- AMS in surgical wards should focus specifically on the prevention of surgical site infection (SSI) via robust guidelines for surgical antibiotic prophylaxis (SAP).
- Education plays a vital role in ASP, including ongoing sessions tailored to clinical team needs.
- AMS interventions should be tailored to local conditions and implemented through behaviour-changing techniques to embed good practice.
- AMS should be supported by diagnostic Stewardship (DS) to ensure the right test for the right patient at the right time, utilizing rapid diagnostics and biomarkers for prompt pathogen identification.

Increased awareness, knowledge and understanding of AMR and how AMS can support best practices in the prevention and management of infection in surgical patients are therefore important to overcome these challenges with education underpinning prescribing behaviours required by surgical teams to optimise care.

Education within standards for AMS

To promote better antimicrobial prescribing a set of ten generic clinical “golden rules” for hospital practice have been proposed. These rules encompass good infection prevention and control practice, good antimicrobial prescribing habits, good stewardship, good surgical practice and the critical role of teamwork and education. Furthermore, education-based stewardship delivered through a collaborative inter-professional team-based model is an effective intervention, even in lower resource settings. Many of these clinical rules have been condensed into simple clinical care standards or care pathways, that can be used to support everyday practice. For example, fact sheets have been created that can be used by clinicians to support the use and implementation of AMS at the bedside including advice for surgical settings.

Impact of education on AMS

One of the common themes to support an improvement in practice and ultimately outcomes is education. A recent global systematic review and meta-analysis revealed that many ASP interventions appear to be effective in reducing antibiotic consumption in both hospital and non-hospital settings. Education and training along with guidelines (a combination of training health workers on treatment practices, updating guidelines and use of decision support tools) usually as a part of other AMS interventions, was a key success factor. This is consistent with the findings of a previous Cochrane review which also confirmed that educationimproved practice and led to reduced antibiotic use, improved quality of use and reduced length of hospital stay without an adverse impact on mortality. Finally, to add further weight to the growing and compelling evidence to support education-based AMS interventions it is important to consider a study by Tamma *et al.* that reports on the success of the largest pragmatic quality improvement antimicrobial stewardship program initiative in the US. In this large study, the investigators supported a cohort of 402 hospitals in developing sustainable antimicrobial stewardship programs and educating frontline clinical staff on incorporating antimicrobial

stewardship into routine clinical care. Through basic implementation strategies, including web-based and durable educational content, external facilitation from trained AMS and quality improvement experts, team-based review of antibiotic prescribing, and quarterly feedback on antibiotic use data, the program demonstrated significant reductions in overall antibiotic use. Reductions specifically in fluoroquinolone use and hospital-onset *C. difficile* rates were also observed. In a nutshell, ASP with an education focus impacts favourably on a range of key clinical, microbiological and economic outcomes.

A specific example of the benefits of an ASP in a surgical setting is demonstrated in a systematic review focused on AMS in surgical prophylaxis and treatment. In this review AMS interventions such as audit, feedback, education, implementation of a protocol, and a computer-assisted decision support methodology, appeared to be effective in promoting adherence to surgical antibiotic prophylaxis protocols, reducing surgical site infection rate and had a positive economic impact.

Competencies for AMS education

In modern healthcare across the world surgeons in training and those partaking in continuous professional development are required to fulfil competency requirements across a range of skills either as part of their ongoing regulatory requirements and or professional development. Currently, no internationally agreed global surgical competencies and curricula exist. Most are created specifically for national use or by healthcare facilities. Recently nine global competencies developed through a Delphi consensus have been recommended to support the development of specific curricula. One key competency identified is to understand public health concepts including epidemiology, measures of morbidity and mortality, and multiple determinants of health in relation to the global burden of surgical disease (GBSD) within and across various geographical areas. This and other clinically focused surgical competencies would support the integration of concepts in relation to antimicrobial resistance, infection prevention and management and antimicrobial and diagnostic stewardship. Specific AMS competencies and curricula have been developed for prescribing and non-prescribing healthcare professionals. How these could be adapted and adopted within specific surgical training and practice requirements is a challenge. One must recognise that the learning needs of surgeons will change over time and will be dependent on context amongst many other factors. Therefore, adopting an incremental, local and flexible approach to content development and delivery will be critical to the success of the educational programme.

The World Health Organisation (WHO) has proposed a general AMR competency framework and associated curriculum guide that can be used by countries, academic and healthcare facilities to inform the development of local competencies and curricula. Another example, by the European Society for Microbiology and Infectious Diseases (ESCMID), through a Delphi consensus process, has created generic competencies in antimicrobial prescribing and stewardship specific to the European setting. While we recognise that not all these may necessarily be relevant to a surgeon it is important to also consider the broader multi-professional-disciplinary team which often delivers care at the bedside, and thereby represents an opportunity for interprofessional training & learning.

To address the growing need for dedicated stewardship training in undergraduate medical education, Wang and colleagues developed an antimicrobial stewardship curriculum for medical students with the objectives of increasing expertise in antimicrobial prescribing, introducing antimicrobial stewardship fundamentals, and enhancing comfort with engagement in interprofessional antimicrobial stewardship activities. This ASSURE (Antibiotic Stewardship, Safety, Utilization, Resistance and Evaluation Elective) programme provides a

pragmatic and adaptable approach to curricular and competency-based training and in our view has a broad appeal and a potential value for training surgeons and other clinicians.

Education planning

When embarking upon developing, delivering and evaluating an AMR/AMS education programme for surgeons it is important to recognise and consider the following:

- Core AMR and AMS competencies for healthcare professionals working in hospitals.
- Different education and training models for delivery of AMS training.
- Documentation of a basic education and training delivery plan to ensure effective implementation.
- The most feasible methods for educational delivery in your own setting.
- The increasing role of e-learning in delivering education and the potential resources available that could be utilised or promoted.

The following steps will support the development of the implementation plan.

1. Assess learning needs – what is current awareness/knowledge? Which topics are required, Which staff groups? How many learners?
2. Review learning needs versus capacity for training - what are the priorities for education delivery?
3. Consider logistics to set goals and objectives - When will it be done? Where will it be done? Who will do it (establish a faculty)? Timescale for delivery?
4. Develop a plan - What educational content and resources are required?
5. Implementation – education delivery.
6. Evaluation - How are we doing? Important to monitor uptake, evaluate impact, invite feedback and review information gathered to inform ongoing education delivery.

In summary, when delivering education, one must adopt a flexible and pragmatic approach utilising the competencies required for different staff groups to develop a training delivery plan with timescales, including details of an education leader, teachers and participants. The opportunity to use real-world clinical opportunities for training (e.g. ward rounds, clinical case discussions) cannot be over-emphasized as an approach to embed AMS knowledge. In addition, participants should be encouraged to access supplementary external training opportunities, including available e-learning options.

Methods of delivering education

To equip a surgeon with sufficient and appropriate AMR-AMS skill sets or competencies education and training can be delivered at numerous points along the education pathway: pre-service (i.e. University Undergraduate education) and in-service training through attending face-to-face workshops/conferences held by professional organisations, face to face internal facility training events, external solicited and unsolicited continuing medical education opportunities, e-learning, on the job training amongst others. Using existing or routine facility structures and meetings where training could be provided include morbidity and mortality meetings, audit meetings, quality improvement and safety briefs, significant event analysis, risk management meetings and journal clubs. Where possible and relevant, using team-based or multidisciplinary teaching and

training events also provides an excellent opportunity for interprofessional learning. The WHO has developed an excellent practical toolkit that includes in-service AMS training to support the development of ASP with a focus on low- and middle-income countries (LMICs).

The organizational, resource-related and fiscal benefits of e-learning for healthcare professionals have been outlined in an excellent systematic review. This complementary approach to formal teaching and on-the-job training has relevance for optimal patient management and can be instructive, valued and lead to knowledge being retained.

The importance of directing participants to local, national and international e-learning resources is important in ensuring the long-term sustainability of educational activities, and various resources already exist. Indeed, e-learning has been commended as one important form of effectively delivering education in AMS, but e-learning is a means to an end, rather than the end in itself. Using e-learning can result in greater educational opportunities for students while simultaneously enhancing faculty effectiveness and efficiency. However, this potential of e-learning assumes a certain level of institutional readiness in human and infrastructural resources that is not always present in LMICs. Institutional readiness for e-learning adoption ensures the alignment of new tools to the educational and economic context.

While face-to-face training methods are the norm in most facilities, different types of e-learning are increasingly used and becoming more popular, often complementing or augmenting face-to-face learning, the so-called hybrid or blended learning model. There is evidence that the use of online and mobile digital education in the management of antibiotics for post-registration healthcare professionals is associated with increased professional knowledge compared with traditional education. E-learning approaches have been shown to provide flexible, low-cost, user-centred and easily updated learning. However, the effectiveness of e-learning varies from context to context and has been shown to make considerable demands on users' motivation levels. **Table 1** summarises the potential advantages and disadvantages of e-learning.

Table 1. E-learning potential advantages and disadvantages (Adapted from Rocha-Pereira, *et al.* 2015).

Advantages	**Disadvantages**
• Wide availability, breaking down of geographical and temporal limits • Reduce costs of educational content delivery • Flexibility of schedules • Portability of educational content • Access to experts and curricula otherwise inaccessible • Easier development and update of educational resources and activities • Self-paced learning • Potential for improved student–teacher and student-student contact and discussions • Access to national and international experts • Potential to connect with other learners worldwide and develop personal learning networks • Potential to learn in teams that may replicate the workplace	• Laborious preparation of educational contents • More time-consuming for students • Lack of student-teacher interaction and tutor support • Possibility of isolation • Inability to clarify doubts properly • Lack of in-depth group discussion • Difficulty in delivering some educational contents without human interaction • Learners may feel isolated • Lack of local technical infrastructure and resources may limit access to online resources and learning opportunities • Language translation and cultural context

Access to education resources

An increasing number of e-learning resources are available to support AMS practice. These resources are housed on a great variety of sites, some of them requiring payment for access, some are of variable quality and lacking in transparency, many are inaccessible to those working in LMICs and many are only available in English. The Global Antimicrobial Stewardship Partnership Hub (GASPH) (https://global-asp-hub.com/), hosted by the British Society for Antimicrobial Chemotherapy (BSAC), aims to establish a truly cooperative global community dedicated to addressing the challenges of AMR through shared education, training and tacit learning. The mission of GASPH is to accelerate the PACE of action on AMR through Partnership, Advocacy, Commerce and investment, and Education. Representatives from over 40 partner organizations have joined the GASPH. The provision of an open-access e-learning, knowledge-sharing platform will amplify, promote and enhance the work undertaken by a range of stakeholders now and in the future. Regular virtual meetings will support sharing of outputs from collaboration and stimulate discussion of key issues, exploration of further areas for collaborative working and development of new relationships. Partners organizations are multi-professional ranging from professional societies, non-governmental organizations (NGOs) and others. Their primary focus is to actively promote or champion sharing and curation of digital learning within their own and the broader communities and create a global knowledge network focused on education and 'real world' implementation of AMS and broader AMR interventions. This focus on open access to digital training resources, thereby reducing costs and fostering greater buy-in from professional societies will help to overcome barriers identified to participating in AMS training. The combination of online learning, with face-to-face training where required and remote expert coaching may prove to be most useful to develop and embed AMS practice. The key benefit of joining GASPH is shared learning with free membership for partner organizations wishing to share resources including good practice examples and importantly also for individual learners seeking access to education and training. To date, the GASPH e-learning repository has 829 resources (https://global-asp-hub.com/ams-amr-repository/) from 38 countries across six continents (most are peer-reviewed) and includes 32 online courses. We acknowledge the potential challenges of digital resources in some settings and the language requirements of learners. Most resources are in English, but we are exploring how to increase access to content in other languages. Links to enable access to a variety of resources on AMS in general and those pertinent to surgical teams are provided at the end of this chapter.

Conclusion

- Globally there is widespread evidence of misuse and excessive use of antimicrobials in the prevention and treatment of surgical infections.
- Embedding core principles of good antimicrobial prescribing and AMS practice in all surgical settings (clinics, theatres, wards, ICU) is critical to improve prescribing and clinical, microbiological and economic outcomes.
- Education, usually in combination with other AMS interventions, is a core element of successful AMS programmes.
- Creating, delivering, monitoring and evaluating education and training to healthcare professionals (and patients where appropriate) requires a robust education delivery plan.
- The delivery of education and training requires an assessment of learning needs and required competencies combined with a curriculum that supports the necessary content.

- Ensuring that education is language, context and resource setting specific and using a blended approach is another key factor for success.
- E-learning, combined with traditional face-to-face learning, is emerging as a highly efficacious and cost-effective method of providing training. E-learning resources for AMS are being widely developed although there is clearly a demand for creating and sharing those specific to surgical practice. GASPH is a knowledge-sharing learning platform that can support the latter.

Competing interests

The authors have no financial and non-financial competing interests to declare.

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Links to education resources

Specific surgical resources

Open on line BSAC-ICARS course on how to set up an antimicrobial stewardship programme and case study of AMS principles applied to real world AMS interventions to improve surgical antibiotic prophylaxis practice in Georgia (https://icars-global.org/knowledge/icars-and-bsac-courses-on-amr-and-ams-in-georgia/).

AMS for surgical antibiotic prophylaxis – YouTube video of seminars (https://www.youtube.com/watch?v=s51iyglimug).

Global Alliance for Infections in Surgery (https://infectionsinsurgery.org/improve-antibiotic-prescribing-practices-among-surgeons/, https://infectionsinsurgery.org/wp-content/uploads/2019/01/antibiotic-prescribing-practices-in-surgery-definitive-1.pdf).

Surgical antibiotic prophylaxis – global care bundle (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10812782/).

Antimicrobials: surgical prophylaxis, an on-line course hosted by the Australian Commission on Safety and Quality in Health Care Antibiotic prophylaxis & surgery (nps.org.au)

WHO infographic – Handle antibiotics with care in surgery https://www.who.int/multi-media/details/handle-antibiotics-with-care-in-surgery)

Commonwealth Pharmacists Association. Surgical prophylaxis short video discussion (Uganda) https://www.youtube.com/watch?v=WGunz6Riiiw&feature=youtu.be.

General AMR/AMS resources

WHO AwaRe Antibiotic prescribing handbook – excellent global resource for infection management of common community and healthcare acquired infections- supports essential medicines list of antibiotics and informing local infection “syndrome” management guidance (https://www.who.int/publications/i/item/9789240062382)

WHO policy guidance on integrated antimicrobial stewardship activities – open on-line course that supports WHO policy guidance on how to facilitate the implementation of national AMS activities in an integrated and programmatic approach (https://open-who.org/courses/policy-guidance-on-AMS).

Antimicrobial stewardship programmes in healthcare facilities in low- and middle-income countries - a practical toolkit. This open online course (https://openwho.org/courses/practical-toolkit-for-AMS) supports the toolkit (https://www.who.int/publications/i/item/9789241515481) and provides guidance on where to get started, including the structures and resources that should be put in place at the national and health-care facility level, through a stepwise approach in low-resource settings. The toolkit also provides detailed guidance on how to plan, perform and assess AMS interventions as well as an overview of the competencies an AMS team needs to guide health-care professionals in changing their antibiotic prescribing behaviours.

Antimicrobial stewardship - a competency based approach (https://openwho.org/courses/AMR-competency). This course will equip clinicians who frequently prescribe antimicrobials with knowledge and tools to improve their use of these essential medications in daily clinical practice. Through case-based examples, the course will highlight how antimicrobial stewardship principles can be applied to common clinical scenarios.

AMS – From principles to practice e-book

https://bsac.org.uk/antimicrobial-stewardship-from-principles-to-practice-e-book/.

The Antibiotic Review Kit (https://infectionlearninghub.co.uk/ark-the-antibiotic-review-kit/). ARK is an antimicrobial stewardship initiative that aims to safely reduce unnecessary antibiotic use in hospitals by helping staff stop unnecessary antibiotic treatments. This protects patients from drug side-effects and harms like *C. difficile* and antibiotic resistant infections.
Utilising Social Science and Behaviour Change in Antimicrobial Stewardship Programmes: Improving Healthcare- on line course (https://www.futurelearn.com/courses/behaviour-change) How can social science and behaviour change techniques be used within antimicrobial stewardship projects to bring about change.

Chapter 107

How to involve surgeons in infection prevention and management

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Introduction

Modern surgery relies on safe and effective antimicrobial prophylaxis and requires a careful balance between optimal prophylaxis or treatment while also avoiding inappropriate antimicrobial use that may promote the development of antimicrobial resistance (AMR). Given the complexity of these issues, many hospitals and health systems employ multidisciplinary teams dedicated to infection prevention and control that include clinical microbiologists, nurse specialists, clinical engineers, laboratory and technical staff, doctors in training and administrators. Each has a valuable role to play in improving care. Similarly, surgeons play a central role in the treatment and prevention of infection, given their direct patient-facing roles. As a result, the participation of surgeons in initiatives that aim to improve infection prevention and management is critical.
In this chapter, the need for inclusion of surgeons in efforts to improve infection prevention and management is highlighted and areas of mutual interest are outlined. Guidance on how best to achieve impact is provided with a specific focus on methodologies that support quality improvement and implementation in the surgical context.

Why involve surgeons?

A wide range of areas relevant to infection prevention and control (IPC) fall within the surgical ecosystem (**Table 1**). As a result of the degree of influence that surgeons hold within this ecosystem, their participation can be a powerful lever for change. Adequate source control is a central component of managing infection. While the introduction of the so-called “sepsis six” (a set of six tasks including administration of oxygen, sampling of blood cultures, administration of antibiotics, administration of intravenous fluid supplementation, lactate measurement and urine output monitoring) is an important aide-memoire for non-specialists in management of sepsis, early access to senior decision-makers is identified as important in all implementation guidelines. Optimal management of patients with many forms of infection requires both timely access to and a good working relationship with surgeons.

Table 1. Identifying potential areas of influence in the surgical ecosystem.

Aseptic techniques, theatre etiquette and hygiene standards
Surgical techniques, perioperative care and risk mitigation strategies
Early identification of infection and sepsis
Early source control for diagnosed infections
Early identification of symptoms related to HCAI
Selection of antimicrobial therapies “Choosing wisely the first time”
Selection and administration of antimicrobial prophylaxis
Participation in a range of multidisciplinary teams
Surgical audit and outcome measurement
Educator, trainer and role model to health services staff and students
Public education and advocacy of the hazards of antimicrobial resistance

While clearly operative interventions mandate surgical participation, the wider surgical skillset encompassing clinical evaluation, interpretation of imaging and decision-making is indispensable. This is increasingly the case given the complex range of options now available for source control, including percutaneous, endoscopic, laparoscopic, robotic and open approaches. Surgeons are trained to balance and mitigate clinical risks. While surgical training emphasises the importance of evidence-based and standardised approaches, especially in perioperative and post-operative care, experienced surgeons become proficient in individualised decision-making in the complex clinical scenarios encountered in surgical infections. In the realm of infection prevention, surgeons play a central role in the prescription and administration of surgical antimicrobial prophylaxis, in the maintenance of standards of hygiene and asepsis in the operating theatre environment and as role models in their hospitals and wider health system.

Surgeons are highly motivated to collaborate with IPC teams, especially when there is a focus on improving surgical outcomes, most notably morbidity and mortality. Perioperative infectious complications reduce patient well-being and satisfaction and place patients at increased risk of harm. Long-term surgical outcomes are demonstrably worse in patients who experience postoperative infection, with infections occurring in the 30 days after surgery being associated with a 1.9-fold higher risk of death in the year after surgery when compared to similar patients who do not experience an infection. Likewise, there is evidence that long-term oncologic outcomes are compromised in people undergoing cancer surgery who experience a postoperative SSI. The discipline of surgery has been revolutionised by the safe use of surgical implants and other devices. Bone and joint infection can have a catastrophic impact on function and lead to prolonged morbidity. Safe use of mesh requires meticulous asepsis and appropriate antimicrobials. There is increasing evidence that anastomotic integrity is closely associated with the constituents of an individual’s microbiome. Aside from the profound effects of SSI on patients, infection-related complications, especially if avoidable, carry considerable medicolegal risk. Undoubtedly, the emergence of multi-drug-resistant organisms mandates improvement in standard practice to avoid catastrophic healthcare and societal consequences. For all of these reasons, surgeons have a compelling responsibility to collaborate IPC teams.

Optimal IPC work practices can be significantly affected by surgical care pathways. The move towards ambulatory surgery and reductions in the length of hospital stay following scheduled surgery substantially alters the optimal surveillance for surgical site infection, now largely an ~~out -~~out-of-hospital event, with substantial implications for resourcing. Infection prevention and control teams that actively collaborate with surgical counterparts can co-create cost-effective solutions to address the challenges that changed models of care can

present. There are similar opportunities to improve theatre efficiency and reduce costs, including environmental costs. Rituals and behaviours in the operating theatre that aim to reduce the risk of nosocomial infection are sometimes not evidence-based and warrant scrutiny.

Clearly surgeons and infection prevention and control teams have a large number of aligned interests. Nonetheless, introducing change in clinical practice, even when carefully considered and evidence-based, is challenging, time-consuming and carries potential risks. It is especially easy to underestimate the importance of context in implementing evidence-based practice as processes that work in one context may be harmful in another. Likewise, the willingness and ability of individuals and organisations to change can vary and, even among the willing, sustaining change is a challenge. The nature of surgical practice requires that surgeons spend prolonged periods engaged in one-to-one direct patient care so that non-operative aspects of care are often compressed into short parts of the day, resulting in sometimes limited time and bandwidth to devote to making change happen. Given the diverse domains of surgical responsibility, unsuccessful change efforts can lead to frustration and a lack of willingness to remain engaged. Understanding how IPC teams can support surgeons to successfully implement and sustain change is critical to maintaining surgical involvement in infection prevention and management initiatives.

Making change happen in the surgical environment

Interventions to improve infection prevention and management can consume scarce healthcare resources, including financial impacts, workforce time and environmental costs. In constrained environments, trade-offs are sometimes required to make the best use of healthcare's scarce resources. This is especially the case when a proposed change results in altered workflow, leading to the omission of other patient care activities. There are a number of methodologies by which change can be introduced. The use of a theory of change can assist in ensuring that the proposed change is having the desired effect and can help to build a case to persuade surgeons and other clinicians of the value of the proposed change. A theory of change defines in advance the proposed change, hypothesis, and the methodology by which the change will be implemented, enabling rigorous evaluation of new practices. This is important because not all change leads to improvement; sometimes solutions that appear 'obvious' do not work. Quality improvement methodology, especially the use of methodologies incorporating rapid cycles of change, supports successful change initiatives.

How to use improvement science to support surgical involvement in infection prevention and management

Improvement science is a problem-solving approach based that assists in process design. There are a number of well-described improvement science methodologies including lean Six Sigma, IHI and microsystems, among others. Most healthcare improvement methodologies are characterised by the use of improvement cycles, known as plan-do-study-act (PDSA) cycles, that encourage rapid cycles of change and continuous learning by front-line staff. Quality improvement commences with an exploration of the nature of the problem to be addressed, the existing processes and the determination of measures that can evaluate the baseline state. Recognising that not all change represents improvement is central to the methodology, so measurement is critical. Exploration of a possible future state encompasses the identification of interventions or changes that might lead to improvement and the planning and execution of a series of tests to evaluate

proposed changes. A series of cycles of change followed by evaluation of outcomes, modifications and further tests then take place until a sustainable solution is identified.

Quality improvement initiatives target the reduction of unnecessary variation by a focus on measures, especially process measures and to a lesser extent structural and outcome measures. Care should be taken in the design of metrics to ensure transparency and the avoidance of duplication of effort; whenever possible data should be integrated into standard data capture systems instead of bespoke additional activities that are time-consuming to maintain. While sometimes criticised for its focus on "quick wins", successful QI initiatives often rely on a deep understanding of human factors and organisational psychology to achieve results. A central principle of quality improvement is "nothing about me, without me". Infection prevention and control teams that are experienced in quality improvement in the surgical arena routinely involve members of the extended surgical team including but not limited to surgeons, anaesthesiologists, surgical nurses and members of the theatre team in their improvement activities. In addition to the inclusion of team members, careful consideration of their working patterns and place of work is necessary to facilitate their involvement in the change initiative.

The bias towards action that characterises QI methodologies is often a good fit with the surgical mindset, as is the reliance on data for improvement but sustainability of change is often a challenge in front-line change initiatives. Successful QI initiatives facilitate change by integrating best practices into existing processes, with the design of forcing functions and the elimination of unnecessary or low-value care (de-innovation) being important sustainability factors. Health systems that incentivise good practice are more likely to be successful.

How to use implementation science to support surgical involvement in infection prevention and management

Implementation science (IS) is the study of methods that promote the integration of research findings and evidence into healthcare policy and practice. The discipline has defined a number of conceptual models that explore different aspects of a proposed innovation or change. Implementation science includes theories, models and frameworks that enable insights into the mechanisms by which implementation is more likely to succeed. A key strength of the implementation science approach is that it recognises that the job of implementation is a specific skill set, distinct from the delivery of care. As a result of this concept, an implementation team is charged with supporting the clinical team to successfully implement and sustain evidence-based practice. In the area of infection prevention and management in a surgical context, the IPC team can play an important role by bringing the skills of IS to their work. The purposeful use of IS methodologies can foster better collaborations between surgeons and colleagues throughout the IPC community. The addition of implementation science to the standard QI approach has the potential to increase the sustainment of evidence-based practice after the rapid cycle change phase has been completed.

Implementation frameworks can be classified as process models, determinant frameworks and evaluation frameworks. Process models focus on the mechanisms by which a change is implemented, whereas determinant frameworks prioritise the context and environment in which change happens. In contrast, evaluation frameworks can assist in developing a greater understanding of the components that contributed to the successes and failures of a change initiative. A characteristic of the implementation science approach is its focus on measurement, especially in two important domains. First, the success of the innovation is measured by means of intervention outcomes, in other words, the extent to which the new change is delivering the expected improvement in patient care. Equally importantly, however, the change effort itself is evaluated, using

implementation outcomes that assess whether the proposed innovation was reproducibly delivered in the same way to every patient, every time. Evaluation of both measures is critical in complex processes that involve behavioural change where implementation can be variable and may not always happen in the way originally envisaged. Implementation has a number of stages (**Table 2**).

Table 2. Actions that support successful implementation vary by stage of implementation.

Stage of implementation	Actions to support successful implementation
Exploration	Explicit evaluation of context to determine factors that might support or inhibit the adoption of an innovation.
Installation	Put in place required precursors to change, including organisational changes, accountability, resources and necessary staff education
Initial implementation	Commence use of innovation and develop data systems to measure progress, with the use of improvement cycles to drive change
Full implementation	Use the new innovation as standard practice with systematic measurement of implementation and intervention outcomes
Sustainability	Adjust internal and external factors to embed change, including security of future funding and plans to mitigate risks arising from staff turnover.
Innovation	Develop a mechanism to embed the new practice in organisational memory, to learn from positive innovations and avoid undesirable program drift

In general terms, each implementation framework evaluates a different aspect of successful implementation based on the stage of implementation. For example, prior to the implementation of a new innovation or intervention (during the *exploration phase*), an explicit evaluation of the need, fit and feasibility of the proposed innovation should take place. The context and organisational readiness to change should be carefully considered and optimised prior to beginning installation to reduce the risk of an unsuccessful change effort. In the dynamic healthcare environment, the exploration stage is often omitted due to a bias towards action. This is a missed opportunity that increases the risk of failure of the change effort, leading to wasted staff time, disillusionment and unnecessary costs. Time spent carefully defining the core components of a proposed innovation, and addressing challenges in the implementation context, increase the likelihood of successful implementation. This is especially important when managing reluctant adopters of change.

Later stages of implementation are characterised by action to a greater extent. Special consideration is given to key factors that drive successful implementation, the so-called *implementation drivers* of competence, organisation and leadership. The development of competence in the use of a novel innovation may require recruitment and selection of appropriate staff, bespoke training or focused coaching of individuals in the use of the innovation, or a combination of all of these. Organisational drivers that require attention include the development of appropriate systems, governance and administration that support the innovation, as well as mechanisms to capture the data necessary to measure and evaluate progress. Underpinning successful implementation is leadership that includes both subject matter experts and change management experts, working in tandem. Adequate consideration of the differing roles that surgeons and IPC teams can play in delivering change increases the likelihood of successful collaboration.

Conclusion

Improvement of infection prevention, control and management for surgical patients is necessary to maintain the considerable advances in health that are enabled by modern surgical practice, especially in the context of emerging multi-drug-resistant organisms. Close collaboration with surgeons is facilitated by mutual respect, understanding of the surgical ecosystem and areas of influence, and targeted efforts to enable surgical participation in change initiatives. The use of a theory for change and measurement of outcomes is necessary. Improvement and implementation science methodologies have much to offer in the design, delivery and sustainment of healthcare improvement.

Competing interests

The author has no financial and non-financial competing interests to declare.

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Chapter 108

Patient understanding of and participation in infection care across surgical specialties

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Introduction

Surgical site infections (SSI) are one of the most common healthcare-associated infections, especially in low- and middle-income countries where their rates are higher than in high-income countries. While preventable, they do occur, contributing to healthcare costs, longer hospital stays, and disrupting and compromising surgical recovery and outcomes. Patients are affected, and by extension, patient carers and families.

Traditionally, the goal of preventing infections in the healthcare setting has been viewed as that of the healthcare providers who provide patient care, and who can provide further instructions for care to the patient at discharge, if needed. Patient engagement in care, including surgical and infection care, while not initially a key aspect of healthcare, has recently gained traction, highlighting the vital role that patients and their carers or families play in infection prevention and management, in surgical and non-surgical specialties. Across all specialties of care, patient engagement is increasingly seen as a major key to improved health outcomes and experiences. As the subject of care, the patient is positioned to participate in own care, to help prevent SSI or manage SSI when it develops. Of course, some components of SSI care are beyond the patient's control and depend on a functional, competent and infection-conscious healthcare system and team. For those where the patient can participate, a few factors can influence such participation.

This chapter explores (1) the dynamics of and necessary considerations, (2) facilitators, and (3) barriers, to patient engagement in infection care across surgical specialties. It explores strategies that can be employed by patients and their carers to prevent or manage infections in the surgical pathway and highlights the importance of patient education, communication, and shared decision-making in the patient's surgical journey.

Infection prevention and management as a key surgical strategy

By its very nature, surgical procedures are invasive and so present inherent risks for infections. Infections in the surgical patient can be introduced through various sources during the surgical and recovery process. Such infection sources can be the skin flora of the patient or surgical team, and the surgical environment including the theatre environment and instruments used in surgery and post-surgical care.

The risk of infections is higher when the patient is exposed to some factors that serve as co-morbidities for surgical infections. Factors such as smoking, high body mass index, and uncontrolled hyperglycaemia, are examples of risks that can predispose the patient to infections. These factors can be modified by the patient to lower the risk of surgical site infections (SSIs) and other related infections following surgery. SSI rates range from 2 to over 30% depending on several factors, and are generally higher in low- and middle-income countries (LMICs) compared to high-income countries. In LMICs, a considerable number of surgery-related infections are also resistant to antibiotics, further complicating care and recovery.

Engaging the patient to address SSI risks pre-operatively and in the post-operative phase is one of the key aspects that can be employed to reduce SSI and other surgery-related infection risks and improve patient participation in surgical and infection care. To participate in infection prevention, control and management strategies in the surgical pathway, the patient needs to understand infection risks – including risks of antimicrobial-resistant infections, and the basics of infection prevention and control. Patient understanding of these concepts can be strengthened by appropriate engagement – by members of the healthcare team – with due consideration of factors that can influence such engagement. This can help ensure that the primary purpose of surgery to improve patient health through operative procedures is achieved with minimal or no surgery-related infections or complications.

The surgical patient's involvement in infection prevention and management

The risk of surgical site infections (SSIs) in the surgical pathway begins well before surgery. While these risks are present, they can be minimised by some actions that take place from the pre-surgical to the post-discharge continuum of care. Prevention of infections is a critical component of surgical care, to ensure recovery proceeds smoothly, as SSIs can complicate care and increase morbidity, prolong hospitalisation, and increase healthcare costs. While patient engagement and participation are important for improved infection care outcomes in the surgical pathway, infection care initiatives in healthcare pathways have predominantly targeted healthcare professionals directly involved in patient care such as doctors/surgeons and nurses. The patient's position in the surgical pathway presents an opportunity to involve another stakeholder – whose care is being undertaken – to ensure surgical care and recovery proceed without minimal complications. The reasons for patient involvement in surgical infection care provide further support.

Why should patients be engaged in surgical infection care?

Patient engagement in infection prevention and control is crucial in all healthcare settings, especially in surgical settings where the patient may be at risk of SSIs and other healthcare-associated infections. It is crucial for patients to understand infection risks and be actively involved in their care for several reasons.

Infection risks to patients and the public

Infections and infection risks do not discriminate and can affect both patients and non-patients in communities and other spaces. Community-acquired infections, which may be resistant to antibiotics, can spread in healthcare facilities, affecting patients and staff. Similarly, healthcare-associated infections can spread to the patient's contacts after discharge. This underscores the need for patients to be involved as co-stakeholders in infection prevention and management initiatives. By protecting themselves from infection risks, patients also protect their communities.

Patients as care recipients and consumers of antimicrobials

As recipients of healthcare, patients – and, by extension, their careers and families – are subjects of care, which makes them key stakeholders in infection care. Patients also consume antimicrobials for their care – to prevent or manage SSIs. The risks of SSIs and other infections, especially antimicrobial-resistant ones related to surgery, can increase with patient exposure to antibiotics. Despite this, evidence highlights that knowledge about antimicrobials and the scale of antimicrobial resistance (AMR) is poor and not well appreciated among the patient and public populations.

The risk of antimicrobial overuse which can predispose to resistant infections, thought to be more in settings where antimicrobials can be accessed without prescription, has also been noted to be equally high in settings where antimicrobial access requires a prescription. This is sometimes motivated by the prescriber's need to satisfy patient expectations for antibiotics. As such, patients and carers have key roles in antimicrobial stewardship, as the way in which an antibiotic is used or misused by a patient can make the difference between recovery from surgery-related antibiotic-susceptible infection and development of an antibiotic-resistant infection.

Patient understanding of and involvement in stewardship principles can therefore help to teach patients and their carers about the risks of antibiotic-resistant infections with increased exposure to and unnecessary use of antibiotics. This can foster a sense of responsibility in antibiotic care and preservation and help ensure that the patient actively participates in appropriate antibiotic use by minimizing unnecessary antibiotic expectations, which can drive inappropriate prescribing.

Patient engagement and health equity

The limited awareness of AMR risks among patients and the public contributes to creating knowledge gradients between the patient and healthcare worker, disabling the patient from participating in own infection care. Patient involvement in care routines and understanding of infection risks can help bridge the gap between care recipients and providers, contributing to improved communication and health equity. By actively engaging in infection care, patients can gain agency and contribute to better communication with their surgical care teams.

Below are some factors to consider – to help facilitate patient engagement in surgical infection care.

Considerations for patient engagement in infection care

Effective patient engagement in infection care, especially in the surgical pathway, depends on some key factors. Careful consideration of these factors in engagement initiatives is important to ensure the patient can participate as a co-stakeholder in own healthcare journey. Patient engagement is generally initiated by healthcare providers, highlighting their relevance and roles in patient engagement.

In the surgical pathway, infection care and management – including the choice of appropriate antibiotics for infections when these are not prevented – relies on surgical teams, who will engage with the patient in these

concepts. As a specialty that has been noted as challenging to reach for stewardship interventions, surgical teams have also been noted to be less intensive and proactive in SSI prevention strategies in cases where they feel infection risks are high and unavoidable.

Since patient engagement relies a lot on the healthcare team to initiate such engagement, surgical teams can benefit from infection and stewardship champions who can regularly communicate the preventive nature of surgical infections to the patient and healthcare team. This can increase patient understanding, enhancing adherence to care protocols and empowering the patient to proactively participate in infection management measures. Some of these considerations highlight the value of patient education and awareness, collaborative care, and infection prevention strategies in patient engagement.

Patient awareness of infection risks

Patient education

Patients undergoing surgery and thus needing anaesthesia may not fully understand the infection risks associated with both the anaesthetic procedure itself and the broader surgical context. A patient who is not aware of infection risks would not be able to pre-empt and avoid such risks. Education plays a considerable and foundational role in patient engagement and involvement in infection prevention. Education of patients is recommended as an essential component of Enhanced Recovery after Surgery (ERAS) protocols. Effective preoperative education is essential for empowering patients to participate in infection prevention efforts, such as adhering to preoperative fasting and skin preparation protocols. Research shows that preoperative education can significantly impact patient adherence to infection control practices. Such education can be provided on various infection risks in the surgical pathway and can be initiated before surgery and continued along the surgical pathway – even after discharge.

Patient education can be helpful when it involves other people such as the carers and family members involved in the patient's care, with the patient's permission. Education topics should emphasise the importance of infection care measures and when such are needed. Evidence has shown that patients are very likely to adhere to infection control measures when they understand the rationale for these. Concepts such as hand hygiene, smoking cessation, glycaemic control, the importance of pre-operative scrubbing, etc, can be introduced and made relevant by making it relatable to the patient's context. The patient can be encouraged to practice infection care measures needed in the pre-op phase, as well as those needed across all phases such as hand hygiene practices.

Timing, style and platforms for patient education

Patient education on surgical infection care should commence well before the surgery, to ensure that the patient optimises his/her surgical recovery. Education should be provided at a time that is conducive for the patient, which may not necessarily be the same for all patients. It is helpful to involve the patient's carer and support system in the education programmes, as carers may be able to remember care advice and instructions if the patient does not. Patient education also needs to consider the appropriate presentation of care information, tailored to the needs of the patient, through consideration of language, health literacy, culture and context including the history of previous care, if relevant. Literature has highlighted that a multi-pronged approach to patient education, that presents the same information in different formats and across different platforms, is more effective than a single patient education method.

Communication and feedback

Communication and dialogue channels

As recipients of care, patients should be engaged through effective communication. Open communication and dialogue channels between patients (and their carers/families) and healthcare providers empower patients to ask questions, discuss care concerns and receive responses to these. These make the patient feel more involved in care. Check-ins and appointments in the surgical pathway, between the doctor and patient when needed, in person or virtually through technological and mobile health applications, can facilitate timely interventions based on the patient's and carer's feedback, when needed. Such check-ins are not only needed post-discharge but should be incorporated along the entire surgical pathway, and can serve to increase the patient's understanding of infection risks and actions that can prevent these.

Patient feedback mechanisms

Patient engagement can benefit from patient and carer feedback on care received, which can be used to improve care for successive sets of patients and carers. Such feedback cycles can improve on care received – from patient and carer insights and experiences – and be used to inform policies as needed for better patient education, care and experiences.

Shared and synergistic patient care plans

Patient and carer involvement

In many cases, patient care following surgery involves some component of care by another person in the patient's community, in the post-discharge continuum of care. Patients come from this community of support before surgery and return to this community after surgery. Involving individuals who care for the patient in the post-discharge phase, is a key aspect of patient engagement in infection care plans. Such engagement can be initiated from the time surgery is contemplated, and continued as needed until the patient has fully recovered. This ensures that everyone (patient, carer, healthcare provider) understands the care techniques to be provided to the patient, and gives opportunities for carers to be involved in care discussions. It also contributes to a sense of responsibility and ownership for health and surgical outcomes, on the part of the patient and the carer. In addition, it strengthens the patient's support system and improves adherence to infection prevention and management practices. This involvement of people within the patient's care circle in care plans provides opportunities for better articulation and insight into patient care needs and the home environment, and how these will influence care and recovery, allowing for contextually fit infection prevention and management strategies.

Shared decision-making

In shared decision-making spaces, patients make decisions for their care following a co-engagement process between them and their families or carers on the one hand, and the healthcare provider on the other. This also serves to improve engagement as the patient is more likely to follow co-developed recommendations rather than those trust on the patient without patient input.

Practical infection prevention practices

Infection prevention practices are key to preventing infection complications in the surgical pathway. While some of these are driven by members of the healthcare team, there are also others that can be driven by the patient – to improve infection prevention and health outcomes in the surgical pathway. Antibiotic prophylaxis is a common practice in surgical anaesthesia to prevent postoperative infections. However, patients often have limited understanding of the role and timing of antibiotics. Educating patients on the rationale for

antibiotic prophylaxis, the timing of administration, and potential side effects helps foster informed consent and adherence to postoperative antibiotic regimens, reducing the risk of infection and resistance. In addition, patient understanding of infection care risks can facilitate their participation in strategies that can be patient-driven such as hand hygiene, pre-operative scrubbing, post-discharge wound care, adherence to prescribed medicines, and adequate nutrition and hydration. As one of the simplest methods of infection prevention, and yet one that presents a challenge to adopting in terms of care behaviours, the effectiveness of hand hygiene in infection prevention should be effectively communicated to the patient. This includes education on proper hand washing techniques, as well as information on critical times for hand hygiene. The 5 moments for hand hygiene is a key concept that can be explained and made relatable to the patient and the patient's care support team.

Pre-operative scrubbing can help minimise infectious colonies on the patient's body – prior to surgery. Patients need to understand the importance of preparing the skin prior to surgery by scrubbing with recommended agents such as chlorhexidine (where recommended). Following surgery, surgical wounds need to be cared for appropriately to prevent infections. For procedures such as subarachnoid block (spinal anaesthesia) or epidural anaesthesia, maintaining a sterile environment is critical to prevent infections like meningitis or epidural abscesses. Educating patients about the aseptic techniques employed during these procedures can enhance trust and understanding, as well as encourage them to report any breach in sterility they might observe. Anaesthesia equipment such as ventilators, endotracheal tubes, and laryngoscopes can serve as vectors for infections if not properly sterilized. Educating patients about the steps taken to sterilize and maintain anaesthesia equipment helps build transparency and trust. Moreover, patients can be encouraged to inquire about infection control practices, thus becoming more active participants in ensuring a sterile environment.

Patient education should involve clear, relatable advice on how to care for surgical wounds in the discharge phase. Components of basic wound dressing – including which agents to use, how to keep the wound clean and dry, and signs to look out for which may indicate SSI – should be communicated. The use of central lines, arterial lines, and urinary catheters in anaesthesia practice increases the risk of catheter-associated infections. Patients should be informed about these risks and the measures taken to minimize them, including the importance of line maintenance and timely removal. By involving patients in monitoring these devices, such as reporting any discomfort or signs of infection, anaesthetists can engage them as active participants in infection prevention. It is also important for the patient to understand the medicines provided which can help in infection prevention and management. In some cases, this does not only include the patient's post-discharge antibiotics but other agents that can help optimise the body for infection prevention and management such as the patient's antidiabetic agents for glycaemic control.

After surgery and anaesthesia, patients can play a role in monitoring for infection signs, such as fever, redness, or swelling at the surgical site. Educating patients about what symptoms to watch for and when to report them to their healthcare provider is essential for early infection detection and treatment. Involving patients in post-anaesthesia infection surveillance encourages self-advocacy and enhances outcomes. Carer support is important here, as in other aspects too, to ensure patient adherence to prescribed medicines and care routines. Carer support is also important in providing nutrition and hydration for the patient. Patient education should include components of balanced and nutritious meals, and hydration, in the patient's surgical journey.

Facilitators to patient engagement

While barriers exist to the engagement of the surgical patient, some factors can help address such barriers to improve patient engagement and participation. These include effective communication, education and engagement of the patient's support system (carers and family). A patient's engagement in infection care can be enhanced by various factors.

Communication

Healthcare provider communication is one of the biggest factors that can influence patient engagement. When communication is presented in words that the patient can relate to, the patient is more likely to understand and be able to participate in care. The same can also be obtained when communication is directed at the patient specifically, and not to a general group. When communication with the patient is intentional and the patient can relate to what is presented or communicated, such communication can empower the patient to ask questions to better understand what is being presented and to better participate in care. Healthcare workers who are more intentional in their communications with patients and who make the information communicated relatable to the patient are more likely to have more engaged patients. Conversely, when communication is not intentionally delivered to the patient, is one-sided, does not invite the patient to contribute to the discussion, or is not relatable to the patient, the chances of the patient understanding and following with the discussion is much less, which limits participation in care.

Patient education

Patient education can improve patient engagement, especially when delivered in an accessible format, using a multi-pronged approach that employs different resources such as brochures, videos, online information platforms, graphics in online platforms, etc. All these can facilitate the patient's understanding of what is being communicated, improving the patient's engagement and participation in care.

Patient education does not need to start only when the patient is admitted for surgery; such participation can start in the preoperative phase when the patient is counselled on the surgical procedure to be conducted. Information on infection risks, especially healthcare-associated infection risks, can be communicated to the patient and the patient's carer in the pre-operative phase, allowing better communication and facilitating the patient's engagement in care. Such engagement can also continue outside the hospital when the patient's care can be supported by an informal carer in the patient's support group.

Models of shared decision making

Patient involvement in discussions related to their care – for instance, by asking how a particular care routine fits their daily routine, how they can participate in a specific course of action, and how often they can practice an activity that will improve their care – provides opportunities for the patient to present what they think fits their setting, which can facilitate their engagement and participation in own care. This is different from when care instructions are provided to patients in a top-down approach, without asking for the patient's input or how the care being proposed fits the patient's life and lifestyle. Models of shared decision-making include the patient as a co-stakeholder in own care and care discussions, allowing them to contribute to discussions rather than being solely recipients of care instructions, which can facilitate engagement and participation in care.

Carer involvement

In many cases, patients need some level of support with their care, especially soon after discharge from the surgical specialty. In such cases, the patient's carer or immediate family is usually among those who participate in and contribute to nursing the patient back to care. Involvement of the patient's carer(s) and support system in discussions, with the patient's approval, has the potential to widen the sphere of service providers to the -patient. Such service providers are engaged and knowledgeable about the patient's condition, enabling them to better participate in providing care and improving care outcomes.

Follow-up care

Opportunities exist for engagement of the patient and carer in the post-discharge phase, after the patient has left the care facility. Such engagement can be initiated and planned while the patient is still in the facility (before discharge). Patients can be involved in discussions related to their options for follow-up care, including which facility close to them will be preferred for follow-up. Such conversations could be very helpful at the start of the engagement exercise, to enable patients present issues that they think may compromise participation – well before such issues come up. Discussing this follow-up care before discharge puts some perspectives in place for the patient, on how to navigate care outside the healthcare facility. Such follow-up discussions are important given the potential for gaps in the post-discharge surgical pathway, where patient infection issues may not be readily picked up. Follow-up care can be facilitated using technologies such as digital health tools which can enhance engagement and participation by providing information, allowing check-ins and remote consultations, and providing care and feedback, all in the comfort of the patient's home space.

Barriers to patient engagement

Gaps in education and awareness

One of the biggest challenges to patient engagement in surgical infection care stems from a lack of information on the subject. The concept of infection care, to reduce the risk of surgical site infection and other healthcare-associated infections, especially after discharge, may be one that patients struggle with. There is a need for a post-discharge check-in at a very accessible care facility for the patient, or for this care to be brought to the patient, especially in the post-discharge phase where the patient may need a lot of rest, may not be disposed to going out or may not even be able to afford care or transport to the facility. While it is important for patients to be mobilised and to show up for care post-discharge, doing so outside their homes may be challenging. Some models of care have begun to address this gap by taking post-discharge care to the patient where they are, or somewhere close by, rather than having them visit the care facility where they may wait long hours to receive care, especially in the public sector.

Sometimes, patients may not receive clear and comprehensive information about their care – preadmission and post-discharge. In some cases, this information may be provided but patients are unable to comprehend it, given their state of mind and other things happening in the care centre where they happen to be. In such cases, there may be confusion and disengagement, with the patient managing post-discharge infection care discretely and as they think it should be managed, without necessarily knowing if they are doing it the right way.

Low health literacy, where patients know little about their health and the care they are receiving, can make it very difficult and challenging for patients to participate in care. In such cases, patients may be incapacitated by their inability to comprehend the message they receive – which can compromise care. Such challenge highlights the importance of language in the communication of surgical care and the patient's understanding of communicated information.

Communication gaps

The use of medical and clinical terminology, without making these relatable to and for the patient, especially in low-income settings where socioeconomic and socio-demographic factors may affect engagement, is a challenge to patient engagement in surgical infection care. Surgery, in and of itself, is a challenging concept for the patient, given its risks and dangers, especially in Africa. In such a setting, information provided may be lost in translation, especially when it is not clearly communicated to the patient or clearly received by the patient. There are cases where patients have had to check online for the meaning of terms used by the surgical team, to better understand their care. In situations where information is effectively communicated to the patient, such would not be the case.

Cultural norms

Culture, the way of life of a people, can influence how they perceive their role in decision making including decisions related to their health and surgery. In some cultures, a belief exists that women should be seen and not heard, which can greatly affect a woman's ability to engage in her healthcare, especially in surgical environments where male practitioners are often the norm. Furthermore, these cultural beliefs can intersect with a patient's socio-economic status, as those from lower socio-economic backgrounds may feel less empowered to take an active role in their care, particularly within the public healthcare system. Instead, they often wait for healthcare providers to begin discussions before engaging, and even then, their involvement tends to be more passive than active. Healthcare and surgical teams need to be aware of such norms which can make patients refrain from proactively initiating engagement and their participation in care, so that they can effectively address these to promote patient understanding of and participation in care.

System navigation

Following surgery, patients may need to follow up at the surgical facility or a different facility for their post-surgical care. For some patients, navigating the healthcare system is fraught with challenges and constraints, especially for those who need care from different specialties and must visit these different specialties. When the patients are at these facilities, these may provide opportunities for their engagement; however, the time for engagement may vary for different patients and even for the same patient, where engagement will depend on the patient's mood, condition, and openness to care and engagement discussions. Such time constraints may make navigating the healthcare setting a challenge, causing a barrier in patient engagement.

Conclusion

Patient understanding of and participation in infection care across surgical specialties could make a significant impact in reducing surgery-related infection. Comprehensive risk assessment can provide further details on risks that can be managed by the patient, to facilitate their participation in care. While there are various barriers to surgical patient engagement, effective communication, education, and support systems can serve as significant facilitators. Addressing engagement challenges can lead to improved patient outcomes and experiences following surgical care.

Competing interests

The authors have no financial and non-financial competing interests to declare.

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Chapter 109

Surgical site infections: principles of prevention and management

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Introduction

Surgical site infections (SSIs) are among the most common complications following surgical procedures, posing significant risks to patients' health outcomes and burdening healthcare systems with increased costs and resources. An SSI, as defined by the United States Centers for Disease Control and Prevention (CDC), is an infection linked to a surgical operation. It typically manifests at or close to the surgery within 30 days post-procedure, or during 90 days if prosthetic material was inserted. SSIs are classified as superficial incisional infection, deep incisional infection, and organ space infection.
Superficial incisional infections are the most common type of SSIs. Deep incisional and organ/space are the types of SSIs that cause the most morbidity. SSIs stand as the predominant hospital-acquired infection among surgical patients, constituting 38% of such cases. Approximately 3% to 5% of the over 40 million patients undergoing surgeries annually are estimated to encounter SSIs. Hence, in the United States, one out of every 24 inpatient surgery patients develops an SSI post-surgery. SSIs can lead to prolonged hospital stays, readmissions, and in severe cases, even mortality. However, with meticulous attention to preventive measures and effective management strategies, the incidence of SSIs can be substantially reduced.
This chapter explores the principles of prevention and management of SSIs, encompassing preoperative, intraoperative, and postoperative strategies.

Preoperative measures

Preparation is key in preventing SSIs. Preoperative optimization of the patient's condition is crucial. This involves identifying and addressing any underlying medical conditions that may increase the risk of infection, such as diabetes or immunosuppression. Preoperative screening for bacterial colonization, particularly with methicillin-resistant *Staphylococcus aureus* (MRSA), can guide targeted antimicrobial prophylaxis. An infection control program represents a crucial component of SSI prevention. A well-structured and executed program can slash the rate of SSI by about 40 percent. Alongside maintaining a sterile operating room (OR) environment, pivotal factors in preventing SSIs include administering effective antibiotics promptly before surgery and meticulously adhering to surgical techniques. The responsibility for cleaning and disinfecting the OR is shared among the OR staff, performed before the first procedure of the day, between subsequent procedures, and after the last one. Several additional perioperative infection control measures have been adopted to minimize the risk of SSIs. These encompass practices such as hand hygiene, the utilization of gloves and other barrier devices by OR staff, patient decontamination, skin cleansing, and preferring hair

clipping over shaving. These procedures aim to minimize patient exposure to microbial flora from hospital staff's hands, hair, scalp, nostrils, and oropharynx. Additionally, actively monitoring and reporting SSI rates to surgical practitioners can also contribute to reducing infection rates.

Timing of surgery – In relation to other treatments it may affect the likelihood of experiencing SSIs. Patients undergoing urgent or emergent surgical procedures are at an increased chance of negative results, including SSI. In certain status, interim measures may be employed to transform an emergency situation into a more elective one or to enhance patient physiology and tissue perfusion. For instance, an interim stent may be employed to address colonic obstruction.

Oncologic treatment – It has been demonstrated that neoadjuvant chemoradiotherapy treatments increase the risk of subsequent SSIs.

Remote infection — Patients who show signs of active infection at a distant site before elective surgery should finish their infection treatment before proceeding with the surgery particularly where implantation of prosthetic material is anticipated.

Malnutrition — Hypoalbuminemia, is linked to a sixfold elevated risk of SSI compared to normal albumin levels. A meta-analysis revealed a decrease in SSIs among patients who received an enteral diet supplemented with either glutamine, arginine, or both.

Medication varieties — Immunosuppressive therapies have been shown to impair wound healing, they are also considered to be closely associated with the emergence of SSIs. However, in specific surgical procedures such as joint arthroplasty, spine surgeries, and solid organ transplants, the effectiveness of immunosuppressive treatments may vary depending on the dosage and timing, which can significantly impact outcomes.

Smoking cessation — There is a correlation between smoking and an elevated likelihood of SSI and other postoperative complications. For those who have ceased smoking, the risk is situated between that of current smokers and that of individuals who have never smoked. It is advised that smokers cease smoking three to five weeks before planned surgery to minimize the likelihood of pulmonary complications. Furthermore, smoking cessation has been demonstrated to minimize the risk of wound complications, including SSI. It's essential to cease smoking before undergoing any surgical procedure involving flap creation like flap-based breast reconstruction following mastectomy and other reconstructive procedures. A thorough analysis of the American College of Surgeons National Surgical Quality Improvement Program database examined results from various plastic surgery procedures. The study revealed that smokers faced elevated risks of encountering wound complications (odds ratio [OR] 1.49, 95% CI 1.31-1.70), wound dehiscence (OR 1.84, 95% CI 1.41-2.41), and superficial incisional SSIs (OR 1.40, 95% CI 1.40-1.63).

Bowel preparation — Pre-surgery bowel preparation lowers the rates of SSIs in colon surgeries.

Hand hygiene — It is suggested that surgical hand hygiene include the cleansing of the hands and forearms with an antiseptic agent prior to surgical intervention. Employing an aqueous alcoholic solution could prove equally effective as the conventional method of hand brushing with antiseptic soap in averting healthcare-associated infections.

Skin antisepsis — Prior to surgical incision, it is recommended that a routine antiseptic application be performed to the skin to lessen the presence of skin bacteria. Nevertheless, it is important to note that bacteria are also present in hair follicles and sebaceous glands, and thus, no topical antiseptic agent can completely eliminate skin bacteria. It is advised to utilize skin antiseptics containing chlorhexidine and alcohol for pre-surgical skin preparation. It has been demonstrated that chlorhexidine is a superior antiseptic to iodine, as it is not inactivated by blood or serum. It is evident that certain interventions, such as the application of skin preparation agents in concentric rings (as opposed to a horizontal approach), the use of markers for surgical sites, and the utilisation of antimicrobial coatings for skin preparation before surgery, do not seem to decrease the probability of SSIs.

Hair removal — It is recommended that the shaving of hair at the planned surgical site be avoided. If hair removal is deemed required, it can be accomplished by involving hair clippers or depilatory substances. Pre-

surgery hair removal has been connected to a heightened risk of SSI. A meta-analysis of 19 studies demonstrated that no epilation was linked to a notably lower risk of SSI compared to shaving epilation (relative risk [RR] 0.56, 95% CI 0.34 to 0.96). The timing of epilation is also a crucial factor. The lowest SSI rates were observed when epilation was performed immediately before the surgical incision. Additionally, proper skin preparation plays a vital role in reducing SSIs. Hair removal should be done using clippers rather than razors to minimize the risk of skin abrasions and subsequent infections. Antiseptic solutions, such as chlorhexidine or povidone-iodine, should be applied to the surgical site before incision to decrease the microbial load on the skin.

Intraoperative measures

Maintaining a sterile surgical environment is essential during the intraoperative phase to prevent SSIs. Strict adherence to aseptic techniques, including proper hand hygiene, sterile draping, and use of sterile instruments and supplies, is paramount. Surgical teams should also minimize traffic in the OR and ensure proper ventilation to decrease the risk of airborne contamination. Limiting the number of people in the OR and restricting limiting entrances/exits to essential-only personnel is advised. Studies based on observation of cardiac and orthopaedic surgery have demonstrated that an increase in traffic through the OR is linked to an elevated risk of SSI. The presence of airborne particulates in the OR correlates with both the number of individuals present and the frequency of door openings. It has been demonstrated that microorganisms that can cause SSIs can be detected in the surrounding air while undergoing surgery.
Additional perioperative strategies, including maintaining normal body temperature, ensuring proper oxygen levels, controlling glucose levels, minimizing the necessity for red blood cell transfusions, reducing traffic in the OR, and potentially employing laminar flow in specific cases, can contribute to lowering surgical SSI rates. Enhanced recovery after surgery (ERAS) programs and adherence to surgical safety lists also play vital roles in reducing postoperative complications, including SSIs.
The innovative air barrier system channels ambient air through high-efficiency filters before directing this purified air across the surface of the wound. A study involving 294 patients demonstrated that this barrier system markedly decreased the likelihood of SSI following implant surgery. Furthermore, the trial demonstrated that the density of airborne microorganisms was four times greater in procedures that resulted in implant infections.

Appropriate antibiotic prophylaxis — This is another critical intraoperative measure to prevent SSIs. Administering antibiotics within one hour before surgical incision, based on the procedure type and local antimicrobial resistance patterns, can effectively reduce the risk of postoperative infections. However, antibiotic selection should be judicious to avoid promoting antibiotic resistance and unnecessary adverse effects.

Maintain normothermia — It is recommended that normothermia be maintained perioperatively, as hypothermia could potentially raise the risk of SSI by inducing vasoconstriction and lowering subcutaneous oxygen levels. On the contrary, there's a proposition suggesting that hypothermia could shield tissue from ischemia by lowering oxygen utilization during surgery. Nevertheless, the majority of surgeons, anesthesiologists, and hospital epidemiologists recognize the advantage of maintaining perioperative normothermia to decrease the likelihood of SSI.

Minimize red cell transfusion — It is recommended that the number of red cell transfusions be minimised, as these have been linked to a heightened risk of SSI among hospitalised patients. A restrictive transfusion

strategy, defined as transfusion at a lower haemoglobin level, has been demonstrated to decrease the likelihood of SSI compared with a more liberal transfusion approach.

Surgical technique — Furthermore, techniques such as tissue handling and hemostasis should be performed meticulously to minimize tissue trauma and reduce the risk of contamination. Although a good surgical technique may help to decrease the incidence of SSIs, there is currently a scarcity of evidence supporting a direct correlation between a particular surgical technique and the likelihood of an SSI. Surgery should include gentle traction, efficient hemostasis, extraction of necrotic tissues, minimizing the use of electrocautery to prevent thermal dissemination, addressing dead space, irrigating tissues with saline to prevent overly abundant drying, closing wounds without tension to prevent ischemia, and using closed-suction drains judiciously. Using antimicrobial-coated sutures might correlate with a decreased likelihood of developing SSI. Some evidence indicates that the utilization of wound protectors during surgical procedures may result in a reduction in the incidence of SSIs.
Wound protectors, which are devices used during surgical procedures to safeguard the edges of abdominal wounds due to trauma and contamination, are recommended for the prevention of SSIs in the context of biliary and abdominal surgeries. After making the incision, the wound protector is inserted into the wound to offer gentle tissue retraction and serve as a barrier to prevent the wound edges from desiccation. A systematic review analyzed 14 randomized studies involving 2,684 patients. The utilization of a wound protector was linked to a decreased likelihood of SSI contrasted to standard care (15% *versus* 21%; RR 0.70, 95% CI 0.51-0.96). Additionally, a dual-ring device was found to be increasingly efficient than a single-ring device (4.4% *versus* 17.8%; RR 0.31, 95% CI 0.15-0.58). These findings align with alternative meta-analyses and subsequent studies, endorsing the utilization of an abdominal wound protector in preventing abdominal SSIs.
The application of certain wound dressings, particularly negative pressure wound treatment, on specific closed surgical wounds has been demonstrated to reduce the occurrence of SSIs. Application of surgical drains should be limited to cases where necessary, as they can serve as a potential route for microbial entry into the surgical site.

Open *vs.* minimally invasive approach — Minimally invasive and laparoscopic-assisted techniques exhibit lower incidences of SSIs in contrast to conventional procedures. In cholecystectomy and colon surgery, the SSI rate in each risk category was significantly lower with laparoscopy. Conversely, in appendectomy and gastric surgery, the utilization of laparoscopy only altered SSI rates in the absence of other risk factors.
Surgical attire and barrier devices — Theoretically, replacing outer gloves and employing fresh instruments for closure is a logical approach, particularly in the context of contaminated and dirty procedures.

Postoperative measures

Vigilant postoperative monitoring and management are essential components of SSI prevention and management. Early recognition of signs and symptoms suggestive of infection, such as wound erythema, warmth, swelling, or purulent drainage, enables prompt intervention. Proper wound care, including regular dressing changes and wound assessment, helps prevent secondary infections and facilitates healing. Timely removal of surgical drains and other foreign bodies reduces the risk of persistent contamination and subsequent infections. Additionally, appropriate pain management is crucial as it promotes mobility and early ambulation, which are essential for preventing complications such as deep vein thrombosis and pneumonia.

Patient education also plays an important function in SSI prevention during the postoperative period. Patients should be educated on signs of infection, proper wound care techniques, and the importance of adhering to prescribed medications, including antibiotics, to prevent the development of resistant organisms.

Challenges and future directions

Even with progress in surgical methods and infection prevention strategies, SSIs remain a significant challenge in modern healthcare. Factors such as the emergence of antimicrobial resistance, the increasing complexity of surgical procedures, and the aging population pose ongoing challenges in SSI prevention and management.

Future directions in SSI prevention may involve the development of novel antimicrobial agents, implementation of enhanced surveillance systems, and further optimization of perioperative protocols. Multidisciplinary collaboration among surgeons, infectious disease specialists, microbiologists, and other healthcare professionals is essential to address the multifaceted nature of SSIs and implement comprehensive strategies for their prevention and management.

Conclusion

SSIs represent a significant clinical and economic burden, but they are largely preventable with adherence to evidence-based practices throughout the perioperative period. By implementing a combination of preoperative, intraoperative, and postoperative measures, healthcare providers can minimize the risk of SSIs and improve patient outcomes. Continued research, education, and collaboration are essential in the ongoing effort to combat SSIs and enhance the safety of surgical care.

Competing interests

The author has no financial and non-financial competing interests to declare.

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Chapter 110

Surgical wound care

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Introduction

Surgical wounds are acute wounds that heal by primary intention. A proper post-operative management can reduce the Surgical Site Infection (SSI) rate when pre-operative and intra-operative measures have been applied, even if patient-related risk factors, type of surgery and surgical technique are parts of a holistic assessment process. The aim of the surgical team should be to protect the surgical incision from external environment contamination, to remove any obstacle to the completion of the healing process and to identify precociously any sign of complications, according to patient comfort and a good aesthetic result.
A Surgical Wound Complication (SWC) has a considerable impact on patient quality of life and the wider healthcare setting and remains a significant challenge for clinicians, as one of the leading causes of morbidity. Many different types of dressing are available, but it is still unclear whether one type is better than the others. There is a rapidly emerging literature on the effect of incisional-Negative Pressure Wound Therapy (iNPWT), on closed clean/clean-contaminated surgical wounds to prevent SWCs, such as infection, dehiscence, seroma, hematoma and peri-wound maceration.

Surgical wound healing process

The wound healing process includes three overlapping phases: the inflammatory phase, the proliferative phase and the remodelling phase which culminates in scar formation. While the inflammatory and proliferative phases are faster than a standard process of wound healing when there is a suture, as in surgical wounds, the remodelling phase takes 1 to 2 years to be completed. In a surgical scar, the maximal tensile strength is only 80% of the original skin and it can be reached after 2 months after the surgical operation.
After the achievement of haemostasis, during the inflammatory phase, the incisional wound bed venules dilate and inflammation cells migrate to promote healing. A moist environment promotes migration and matrix formation, leading to a complete healing 40% faster than a wound exposed to air. A moist wound healing can also reduce tenderness and pain and produce better cosmetic outcomes, so a dressing that offers protection and a balanced moisture environment can be suggested.
When primary closure is not possible or dehiscence occurs, surgical wounds will heal from the bottom up, through a granulation and epithelization process, presenting a significant management challenge (healing by secondary intention). If a dehiscent wound is closed with approximation, suture, grafting or flaps, the healing process is called tertiary intention.

Surgical wounds dressings

At the end of surgical intervention, the incision created with a scalpel is closed by suture, staple or glue and usually protected with a sterile dressing, applied with an aseptic technique. Traditionally the wound is covered with gauze and tape or gauze and a polyurethane transparent film. Wound dressings applied after skin closure should absorb exudate, maintaining the skin dry, provide physical support and protect wounds from external environment contamination.

The dressing should be left in place for at least 48 hours: during this time a natural skin barrier is formed and the protective role of the dressing from the external environment can be considered completed. A Cochrane Review published in 2015, showed no significant differences between dressing removal after 48 hours or more, in clean or clean contaminated surgical wounds, as far as surgical site infection rate, even if the quality of evidence is low. Early dressing removal may result in significantly reduced costs and shorter hospital stays. Dressings should be changed within 48 hours if wet or saturated with blood or serum: it allows the evaluation of the surgical wound, to prevent bacterial contamination from the environment and to avoid the gauze sticking to the suture line. The wound should be evaluated even if the patient shows signs or symptoms of infections, such as unusual pain or fever or if there is evidence of dehiscence, excessive exudate, leakage or peri-wound skin blisters.

A particular care is needed for peri-wound skin: if an excess of exudate occurs, moisture-associated skin damage could happen, when not highly absorbent gauze is applied.

Many different dressing types are available to manage particular situations but it is still not clear whether one type of dressing is better than any other. An ideal dressing for acute and chronic wounds should absorb and contain exudate, provide thermal insulation and impermeability to the external environment (fluids, microorganisms), do not release particulate contaminants, assure comfort and lack of trauma or pain on dressing removal, promote proper healing and aesthetic scarring.

A Cochrane Review published in 2016 examined different RCTs comparing standard dressings (absorbent gauzes) with different interactive dressings (films, hydrocolloids, polyurethane matrix, hydro-active dressings, antimicrobials dressings as silver-containing or dressing with polyhexamethylene biguanide-PHMB). The evidence to support that interactive dressings are more advantageous than standard dressings and that one dressing is better than others in preventing SSIs, is insufficient. The use of any type of advanced dressing on primarily closed surgical wounds, to prevent infection, can't be suggested. However, the low quality of evidence of RCTs made the strength of the recommendation conditional.

National Institute for Health and Care Excellence (NICE) guideline, published in 2019, suggests covering surgical incisions with an appropriate interactive dressing at the end of operations. An interactive dressing promotes the healing process through the creation and maintenance of a moist environment. Some advanced dressings include the term "surgical" in their name: they usually contain long active antimicrobials, provide greater absorption than standard gauze (e.g. hydrofiber, alginate or foam layer) and are designed to stay several days (from 5 to 7 days) on surgical wounds, protecting them from trauma and external contamination (**Figure 1**).

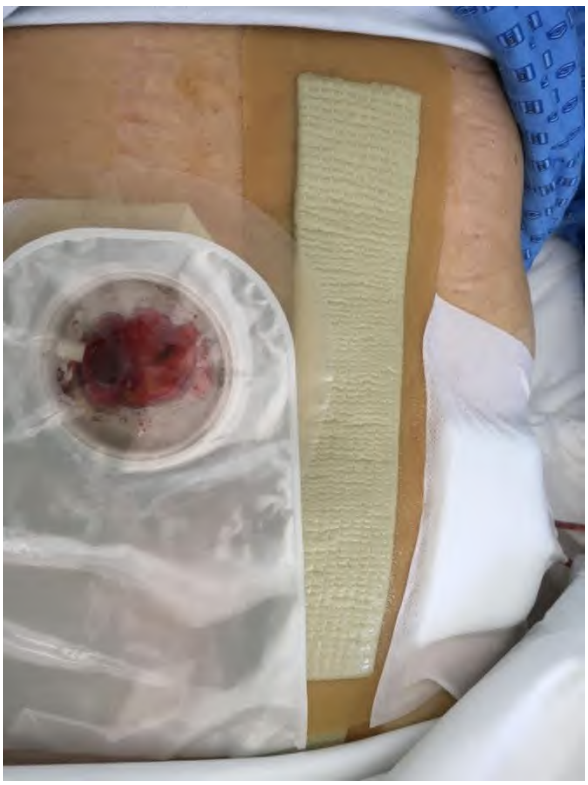

Figure 1. Post-surgical dressing: hydrocolloid protective and waterproof barrier joined with an *hydrofiber* soft absorbent material layer with ionic silver, that transforms into a gel on contact with wound fluid. It can be used with a contemporary ostomy to protect wounds from environmental contamination.

Surgical dressings borders are made of hydrocolloid or silicone, to minimize surrounding skin damage. Some surgical dressings are semi-transparent, to consent surgical wound inspection.
The dressing choice should be considered as well as patient comfort and desire for wound coverage, cosmetic result, reduction of frequency of dressing change and protection from external contamination especially if there is a stoma nearby. Other items to be considered are availability and cost of dressings, ease of application and nursing time consumption.
Patients' experiences and feelings about surgical wounds and dressings begin to be considered by the surgical team too, even if data produced from patients' interviews need to be supplemented and integrated by further randomised controlled trials.

Topical application of antibiotic and antiseptic

NICE 2019 guideline suggests do not use topical antimicrobial agents to reduce the risk of SSIs for surgical wounds that are healing by primary intention. Topical antibiotic use may increase bacterial resistance and cause additional skin injuries related to the potential risk of allergy so they shouldn't be used routinely to prevent SSIs. A Cochrane Review published in 2016 analyzed the role of topical antibiotic application after wound closure, in the form of ointment, cream, gel, foam, paste and powder, with or without a secondary dressing, in clean, clean-contaminated and contaminated surgery. The review concluded that the use of topical antibiotic may reduce the risk of SSIs if compared with no antibiotic and no topical antiseptic (moderate quality of evidence) but the relative effects of different antibiotics are unclear and definitive data about

adverse outcomes, as allergic contact dermatitis or impact on antibiotic resistance development, are still not available. A worldwide rational use of antibiotics is extremely important to reduce the risk of bacterial resistance and the evidence for the use of topical antibiotics on surgical closed wounds is still conflicting. A cost analysis should be conducted in further studies, too.

Incisional-negative pressure wound therapy (i-NPWT)

There is rapidly emerging literature on the effect of incisional-Negative Pressure Wound Therapy (i-NPWT) devices applied on closed surgical wounds for preventing surgical site events such as infection and dehiscence. I-NPWT system is an evolution of the standard device: the pump is smaller, lighter and more portable and the dressing system is easier to apply and remove, allowing greater utilization. The device is composed of a closed sealed system connected to a battery-powered vacuum pump which maintains a level of negative pressure between -75 mmHg and -125 mmHg on the wound surface. In canister-free devices, the exudate is managed predominantly by evaporation (approximately 80%) through a multilayer easy-to-place dressing composed of a perforate flexible silicone wound contact layer, bonded to a lower airlock layer, an upper fluid absorption layer that delivers negative pressure and a highly breathable film layer, that aids evaporation of fluids. Some devices are connected to a multilayer peel-and-place or customizable dressing and equipped with a small canister (from 45 to 150 ml) (**Figure 2**).

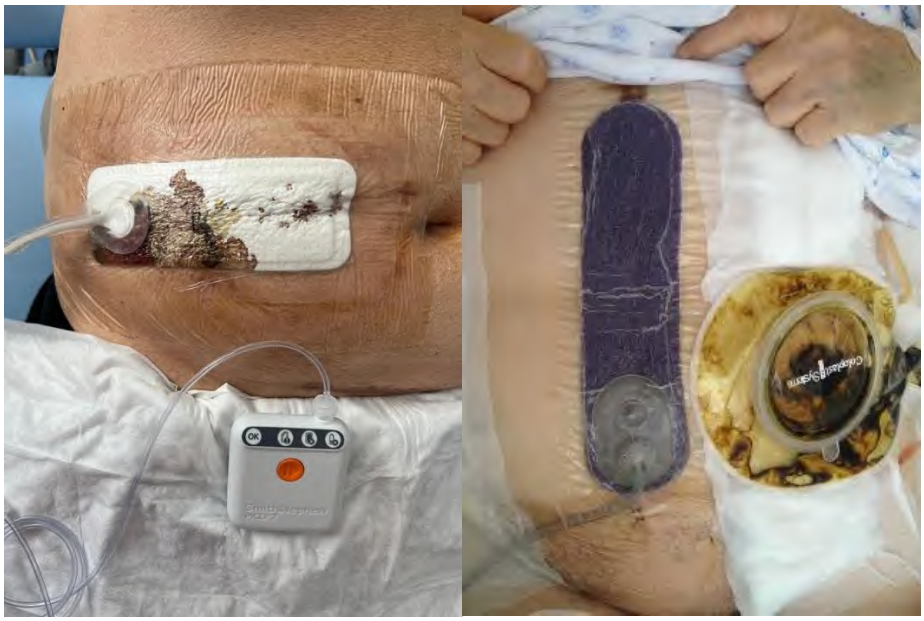

Figure 2 Incisional-NPWT: pre-shaped dressing with canister less single-use device and device with a small canister.

The application time is between 1 and 14 days. I-NPWT devices should possess an imperfect seal or leak detector and a low battery indicator.

Animal studies and clinical experiences reported that i-NPWT can reduce lateral tension on incision lines, increase the breaking strengths of wounds, increase blood flow, decrease oedema (increasing the activity of

lymphatic drainage) and risk of hematoma and seroma formation. Avoiding the collection of blood and serum in sub-incisional tissue, the risk of infection and dehiscence is reduced, and the speed, strength and quality of scarring are improved.

I-NPWT may be considered in high-risk surgical wounds as far as sternotomies in cardiothoracic surgery, vascular surgery, abdominal surgery (as ventral hernia repair, open colorectal surgery, perineal wound in abdominoperineal resection for rectal cancer, reversal of temporary ileostomy or colostomy, pilonidal cyst removal), orthopedic surgery as prosthetic surgery or major limb amputation.

Even if the clear benefits of standard NPWT are described in the literature, the evidence for i-NPWT compared with standard dressing is still low or very low due to studies at high risk of bias. Several recent studies and a 2019 Cochrane Review claim that the role of i-NPWT remains uncertain about the reduction of incidence of seroma or hematoma, wound dehiscence and wound-related readmission to hospital within 30 days, even if there is an association between NPWT and reduction in SSI rates, especially in general and colorectal surgery. World Health Organization (WHO) Global guidelines for the prevention of surgical site infection, published in 2018, suggest the use of prophylactic NPWT on primarily closed surgical incisions only in high-risk wounds, for the purpose of preventing SSI, considering available resources (conditional recommendation, low quality of evidence).

I-NPWT should be considered pre-operatively when patient-related risk factors such as BMI < 18 or > 40 Kg/m^2, uncontrolled insulin-dependent diabetes mellitus, renal dialysis, and smoking are identified, in case of high-risk surgery (e.g. prolonged surgical time, high perioperative blood loss, hypothermia, re-operation, emergency surgery) and/or when a surgical site complication may result in a life-threatening condition. The surgical team can also reconsider i-NPWT application if risk factors arise during surgery.

Surgical risk calculators were developed to identify high-risk patients, based on the results of the pre-operative assessment (ASA score), surgical wound classification (from clean to dirty-infected) and duration of operation. A limitation of the Risk Index score is that it does not consider details of different surgical procedures, as far as the placement of implants. A risk calculator should be developed for every different surgical specialty and used for pre-operative patient education and counselling and to identify the required interventions to reduce SSI risk. Some calculators may be accessed via the internet as www.riskcalc.sts.org by the Society of Thoracic Surgeons (STS), www.brascore.org by Breast Reconstruction Risk Assessment (BRA) Score and www.riskcalculator.facs.org by American College of Surgeons (ACS).

During surgery, there are some tips that must be considered for an effective application of i-NPWT. The placement of the incision, ostomy (colostomy, ileostomy, urostomy) and surgical drains must be considered if a i-NPWT dressing should be placed. The dressing should not be placed over drains or wires. The place of the port and tubing must be evaluated to avoid pressure damage. The patient's skin must be dry and hair-free to achieve good dressing adhesion and sealing. In difficult areas, a double-sided adhesive gel or hydrocolloid strips may be used. The dressing must be applied under aseptic conditions and according to the manufacturer's instructions.

During the post-operative period the dressing, the canister (if present) and the power unit must be inspected regularly. The dressing may be left in place for 5-7 days; if a dressing change is required, an aseptic technique must be used. If the surgical wound is closed and dry when the dressing is removed, there is no need to reapply i-NPWT or any other standard dressing. If the patient is discharged from the hospital with i-NPWT device, written information and contact number of health professionals must be provided. If the application of i-NPWT is defined pre-operatively, the aim and the surveillance of the device should be described to the patient or to his caregiver, after the evaluation of the domestic setting in case of a rapid discharge.

To verify the cost-effectiveness of i-NPWT application in preventing SSIs, the cost analysis can't be carried out just with a comparison between a standard dressing and a device unit cost, but it should be performed

regarding the SSI treating costs that can be avoided (further dressings, laboratory or diagnostic exams, length of hospital stay or readmission rate, antibiotic and analgesic drugs, etc.). The human suffering, the implications for social and working life and the consequences related to delate in adjuvant therapies in oncological patients, unfortunately, cannot be reduced to a numerical calculation. Studies regarding the economic and organizational sustainability of i-NPWT for SSI prevention are in progress.
When the surgical wound is not suitable for the peel-and-place single-use device dressing application, due to length or not linear shape, a standard NPWT device with antibacterial gauze as dressing may be considered (**Figure 3**).

Figure 3. Standard NPWT device: dressing with antibacterial gauze.

Surgical wounds healing by secondary or tertiary intention

When surgical wounds are intentionally left open to heal by secondary intention (e.g. in case of abscess, contaminated-dirty wounds or when dehiscence occurs), proper and gentle dressings are required. Standard gauzes can cause trauma to healthy granulation tissue and pain when removed, can leave remnants in the wound bed and, if the absorption power is not sufficient, peri-wound skin damage may occur. Interactive dressing or NPWT may be chosen, considering the wound bed and the exudate characteristic (quantity and density). A surgical wound that is left open with the intent to be closed by tertiary intention also requires interactive dressing or standard NPWT with foam or gauze filler as a bridge to subsequent closure.

Postoperative care of the surgical wound

During the postoperative period, international guidelines suggest avoiding unnecessary touching of dressing for at least 48 hours after surgery, unless leakage or other complications occur; using the aseptic non-touch technique for removing or changing the dressing and for any wound-related procedures; using sterile saline for wound cleansing up to 48 hours after surgery (tap water can be used after 48 hours). Antiseptic agents are considered unnecessary for general wound cleansing but they can be considered in infected wounds. Patients may shower safely 48 hours after surgery.

As a consequence of the reduction of postoperative hospitalization, the number of post-discharge SSIs diagnosed continues to rise and they are the most common reason for readmission to hospital. The improvement of post-discharge surveillance and the development of a high-quality homecare plan can contribute to achieving an accurate and efficient system to better measure surgical outcomes and to estimate the human, social and financial impact of complications. To improve the quality of education and discharge instructions, a simple leaflet with information for patients regarding the monitoring and symptoms of an infection of the surgical wound may be delivered. Patients with suspected SSI may contact the hospital, allowing a timely diagnosis. Direct patient contact, with a telephone survey or questionnaire at 30 days, can be used to collect data prospectively to calculate rates of surgical wound infection and to improve the standard of care. A specialist wound care service should be useful to guarantee a structured approach to improve the management of surgical wounds.

Conclusion

Surgical wounds are the most common wounds managed in acute care settings and are associated with a variety of complications such as infection and dehiscence. SWCs are also the most preventable hospital-acquired infection. The large number of published clinical practice guidelines (with variable quality and different recommendation ratings), the growing number of wound care products and the absence of strong supporting evidence, cause a high risk of ineffective and often expensive care of surgical wounds. Wound dressings are only one part of post-operative care of surgical wounds because there are many intrinsic and extrinsic factors related to SWCs prevention. There is still limited evidence about the use of interactive wound dressing and a lack of evidence for the use of one dressing over another for the prevention of SSIs, due to a considerable shortage of controlled studies. The body of evidence on i-NPWT is growing. Few formal cost-effectiveness analyses about the role of NPWT compared to standard dressing in surgical wound management have been conducted. However, improving healing and reducing SWCs, NPWT use in high-risk patients and surgery may be considered cost-effective if compared to the cost of managing complications.

As far as future perspectives, the creation of care bundles focused on SSIs prevention may promote positive outcomes; the adherence to evidence-based guidelines is necessary to reduce the SWCs risk; constant communication between healthcare providers and patients can improve the proper management of surgical wounds even after discharge.

Competing interests

The author has no financial and non-financial competing interests to declare.

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Chapter 111

Surgical site infections in oncologic patients

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Introduction

Cancer dramatically impinges on patients' lives and healthcare expenditures. Global occurrence and mortality are rising; only in 2020, nearly 10 million demises were blamed on malignancies, making it the leading global death cause. By 2040, this is forecasted to ascend to 16,400,000. In light of this concerning scenario, around 60% of cancer patients (CPs) undergo surgical treatment annually, either for palliative or curative intents, facing high healthcare-associated infections (HAIs) risk, principally surgical site infections (SSIs).

The WHO states SSIs are the second most frequent HAI globally, affecting roughly one-third of subjects. They are ubiquitous in low—and middle-income countries (LMIC) and second most common in Europe and the US. However, there is marked variability in incidence within countries and regions.

Twain, HAIs and SSIs cause setbacks in patients' rehab and contribute to raised morbidity, mortality, and length of stay (LS), and delayed postoperative recovery (post-R), ushering in increased inpatient expenses and additional therapies needed, especially in CPs who hold a pronounced-probability of experiencing SSIs.

Surgical CPs are especially vulnerable to developing SSIs influenced by inherent cancer characteristics, which serve as SSI-predisposing factors; malnutrition, immunosuppression, chemotherapy and radiotherapy effects, and multiple-antibiotic stewardship further promote the susceptibility odds.

Surgical site infections represent a world health challenge with severe after effects on inpatient facilities; notwithstanding, in LMICs and limited healthcare protocol adherence ambiences, overall HAI prevalence, predominantly SSIs, results in a lofty affected individual amount. The SSI bailiwick has garnered outstanding heedfulness within the medical community, mainly among surgeons, who shoulder forthright commitment; at least, that is how the majority feel, and briefly, we have to face it straight. This upheaved keenness is

adjudicated to the hefty SSIs' impact on post-R, the compromised quality of otherwise successful procedures, and their considerable weight on health metrics.
This chapter traces SSIs in CPs, encompassing epidemiological statistics, risk factors, prevention measures, and treatment. Our SSI-on-cancer patients' appraisal delves into this topic through diverse medical discipline lenses, predominantly drawing from papers in neurosurgery, head and neck, thoracic, breast, oesophagogastric and colorectal surgery.

Incidence

The HAI burden varies meaningfully, highlighting heterogeneity in compiling and diagnosing them. HAIs remain the most expected inimical threat within the hospital environment. Despite underreporting and untrustworthy input making a murky HAI global burden, hundreds of millions of cases are registered annually, affecting all nations. The exact SSI oftenness has lingered doubt as a result of surveillance systems' lack of comprehensiveness within national health frameworks, making it difficult to reckon the overall incidence among CPs. For example, the 2017 NHS Getting It Right First Time Report in General Surgery revealed that only 8.0% of participating centres knew about SSI incidence.
Recent literature has discussed global SSI incidence. While the WHO recognises SSIs as the second most common HAIs, contemporary publications have made clashing claims. Some authors argue that SSIs rank third in frequency, while others contend, they are the most prevalent. High-income countries (HIC) generally report low SSI rates, typically 1.2%–5.6%. Current articles have indicated SSIs are the second-most common HAIs in both the US and Europe. The 2011–2012 Surveillance Report, analysing 31,459 subjects across 947 European centres, conveyed an SSI incidence of 19.6%, making it the second-most common. Additionally, in Europe, 17,399 SSI cases occur daily.
Conversely, LMIC exhibits noticeably loftier SSI occurrence rates, the most common and extensively researched HAI. A comprehensive systematic review and meta-analysis of 43 studies from 30 countries involving 798,712 individuals showed SSI's overall pooled incidence was 2.5%. Surgical site infection measurements differ wildly across regions, with Africa harbouring the highest observed incidence.
The alarming SSI disparity between HICs and LMICs consists of sundry factors, including health infrastructure challenges, limited access to cutting-edge medical technology and resources, and dissimilarities in sanitary benchmarks and practices, such as handwashing frequency or sterile equipment use. Socioeconomic plights, inadequate sanitation, and narrow preventive care further snowball SSI's occurrence in these backdrops.
Research on SSI often takes a global approach, undiscriminating between CPs and the general population or focusing on specific cancers, making it challenging to analyse factual SSI incidence in oncologic subjects and acquire an exhaustive understanding. Accordingly, hereinafter, we will delve into prime SSI-related aspects of each type of cancer to provide a more detailed overview.

Aetiology

In every infectious process context, three determining elements interlope: the pathogenic agent (virus, bacteria, fungi, parasites), the host, and the environment, which interact. Infectious agents alter according to their origin and attributes to produce disease—virulence, toxicity—and antimicrobial resistance capability. Surgical site infection aetiology is multifactorial and typically occurs through direct pathogen exposure during

surgical procedures. The bacterial load threshold required to render infection depends on the organism's virulence, the wound condition and the host's immunocompetence. It should be noted that the primary pathogen frequency traits will vary depending on the region where the surgeries are performed and the hospital environment.

Risk factors

Surgical site infection susceptibility varies among patients and is influenced by well-established risk factor assortment, with distinctions based on the surgery performed. The Asia Pacific Society of Infection Control guidelines for SSI prevention have spotlighted a pre-, intra-, and postoperative SSI-associated risk factor spectrum. Besides, it is critical to underscore that WHO, CDC, and Cochrane guidelines also have outstanding risk factors, broken down into patient-related and surgical-setting-related.

Pivotal patient-related factors such as compromised nutritional status (NS), high ASA-score, advanced age, smoking, alcohol consumption, comorbidities—diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), and anaemia—blood transfusion (BT), hypoalbuminemia, intraoperative blood loss and immunosuppression can contribute to heightened SSI vulnerability.

In CPs, SSI patient-related risk factors do not differ from the overall general population factors reported; nevertheless, these patients exhibit an augmented SSI susceptibility due to the inherent cancer nature. Alongside previously named factors, considerations specific to this patient group, such as advanced TNM stage, tumour location, reconstructive surgeries, and previous chemotherapy and radiotherapy, compound the aforementioned risks.

Surgical-setting-related factors beset surgical unit conditions, asepsis and antisepsis measures, prolonged surgical time (PST), perioperative hypothermia, clean-contaminated surgical procedures, emergency surgery, ICU stay, and invasive device and implant placement. In addition, multidrug-resistant (MDR) organisms and the potential need for reoperation contribute substantially to this population's elevated SSI occurrence.

Head and neck oncological surgery (HNOS)

Annually, 650,000 new HNC cases and 350,000 deaths are reported. This figure is expected to increase 38% by 2030. Surgery is a worthwhile but intricate tool in this context, and it is not exempt from the SSI peril; by the same token, as this region's high functionality, reconstructive techniques, adjuvant radiotherapy, and chemotherapy are often necessary, further increasing the likelihood. The HNC patient's SSI incidence varies widely, with occurrences ranging from 10% to 50%. However, studies suggest that SSI prevalence typically falls between 19% and 29%. Surgical site infection rates in non-received antimicrobial prophylaxis patients with clean HNOS are generally below 1% to 3.8% in HICs. Contrariwise, non-experienced antimicrobial prophylaxis patients with complicated HNOS tend to have higher SSI rates, ranging from 24% to 87%.

Numerous SSI risk factors have been pinpointed in HNC patients. However, there is some disagreement among authors and heterogeneous outputs. Anyhow, there are points of like-mindedness regarding the foremost risk factors. These include those familiar with other oncological surgeries and HNOS-specific SSI factors such as tracheostomy, flap reconstruction, tumour location, and neck lymphatic dissection.

Many authors concur that a weighty correlation exists between SSIs and factors such as advanced ASA score, ICU stay, chemotherapy and radiotherapy, tumour location, BMI, smoking, alcohol consumption, DM, and

preoperative Hb. Nevertheless, Pecorari *et al.* present divergent outlooks, contending that these variables are not strongly linked to SSIs following HNOS. Then again, a meta-analysis considered that these risk factors correlate positively with SSI occurrence. Notwithstanding this discrepancy, the authors recognise that age over 65 years, advanced TNM stage, PST, surgical technique, neck dissection, nasogastric tubes and peripheral/central venous catheter placement, tracheostomy and flap reconstruction are mighty associated with SSIs. Concerning the Hb assessment, it is noteworthy that Pecorari *et al.* found a significant association between postop Hb on the first day and SSIs.

Certain factors have been identified as SSI predictors in HNOS. These include advanced TNM stage, tracheostomy, PTS, and RS. Even DM has been identified as an oral cancer-independent risk factor. Considerable patients undergoing HNOS necessitate tracheostomy, which exacerbates the likelihood of SSI. Tracheostomised patients face a three-fold increased SSI risk, irrespective of whether a tracheostomy is performed before, during, or after surgery.

Other SSI risk factors invoked are cervical lymphatic dissection, DM, and tumour location. Studies indicated that following neck dissection for OrC, bacteria from the oral cavity are likely to migrate to the surgical site through new communication courses. A comprehensive review examining SSI odds ratios in CPs with DM showed the highest rates, at 62.1%, associated with OrC surgeries. Addedly, a case-control study revealed that out of 23 patients in the SSIs cohort, 15 (65.2%) had DM [$\chi^2 = 15.78$; $p<0.01$]. Discussing tumour location, some researchers have observed no big-wheel differences in SSI development across anatomical sites. Based on this factor, a study encompassing seven precisely defined neoplasm locations did not identify an increased SSI likelihood.

The predominant bacteria in the upper respiratory and salivary tract are Gram-negative and facultative anaerobic, albeit Gram-positive bacilli are also present. Wound-infected microbiology cultures often reveal a polymicrobial bacterial burden. In a study of 130 culture-positive pus samples, Rao *et al.* identified *Klebsiella* spp. and *Acinetobacter spp*. as the prevailing Gram-negative pathogens. In contrast, *Staphylococcus aureus* and *Enterococcus* spp. were the predominant Gram-positive bacteria. The researchers also noted a high prevalence of methicillin-resistant *S. aureus* (64.28%) and significant resistance to aminopenicillins, third-generation cephalosporins, co-trimoxazole, and fluoroquinolones among the Gram-negative bacteria. Importantly, *S. aureus* blazoned no resistance to anti-MRSA drugs such as vancomycin, linezolid, and teicoplanin.

Oncological neurosurgery

Neurosurgical approaches may bollix the body's natural defence mechanisms and endogenous bacteria activity, boosting various post-neurosurgical infection risks. These infections can manifest either locally or diffusely. Initially appearing at the incision site, SSIs can spread to deeper structures. Consequently, SSIs may present as sSSI, like cellulitis, affecting the bone flap, causing osteomyelitis or leading to more severe conditions such as meningitis subdural collections, empyema, or brain abscesses.

The neurosurgery SSI incidence ranges from 1% to 41% within the first 30 postop days, running from 2.6% to 6% in craniotomies. Informed rates are 1.4 per 100 patients and 0.8 per craniotomy; however, varying incidences have been registered, ranging from 1% to 8% in cranial procedure-related cases and 0.5% and 18.8% for spinal interventions, as well as mortality rates of roughly 14%. Risk factors for SSIs in neurosurgery are similar to those turned up in other types of surgeries; nevertheless, certain factors have evinced notable correlation with SSI. These factors encompass age over 65, comorbidities, malnutrition, and, more specifically, Glasgow Coma Scale scores lower than ten and cerebrospinal fluid fistula development.

Neurosurgical procedures are typically time-consuming, and SSI risk increases with longer surgical durations. The SSI odds are 12. 6% in surgeries under two hours, rising to 24.3% over three hours. Other critical factors include shaving location—in the theatre or emergency ward—aseptic technique adherence, antiseptic choice, surgical team size, bacterial contamination in large surgical fields, drain use, and incision closure methods. In DM instances, it is essential to stress that the lowest SSI occurrences related to this comorbidity are observed in spinal surgeries.

Causative agents are categorised into superficial, deep, or organ space based on infection type. The most prevalent superficial infections are primarily associated with cutaneous flora, with *Staphylococcus aureus* the predominant bacteria in 50% of cases. Other pathogens comprise *Staphylococcus epidermis*, *Klebsiella*, *Enterococcus*, *Escherichia coli*, *Serratia*, *Aspergillus*, and *Peptostreptococus*.

Thoracic oncological surgery

The thorax is an anatomically and physiologically convoluted region housing vital organs. Present-day surgical techniques have increasingly incorporated avant-garde technology in thoracic surgery, yielding improved postoperative outcomes and lessened complications, mainly surgical wound-related. Despite these postop-R advancements, SSI remains a critical concern.

Lung cancer

Lung cancer is a widely prevalent and aggressive neoplasm with a high fatality rate. It is commonly categorised as non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). The incidence of SSI in patients undergoing thoracic oncologic surgery for lung cancer varies and is influenced by the surgical approaches utilised.

Minimally invasive techniques used have led to a reduced SSI frequency. Many studies comparing open surgery *versus* video-assisted thoracoscopic surgery (VATS) have shown that SSIs are significantly lower with the VATS approach. Different authors have reported incidences of 0.2%, 1.0%, and 2.3%. Notwithstanding, despite these low incidences, a recent study focusing on VATS and robot-assisted thoracic surgery (RATS) observed an overall incidence of 7.0% [VATS 7.1% *vs.* RATS 6.8%; p=0.871]. The authors also noted that though RATS led to a higher rate of surgical time prolongation than VATS, this did not contribute to the increase in SSIs.

Various meta-analyses have revealed distinct VAST-lobectomy advantages regarding SSI development over thoracotomy. One, which comprised 3,457 stage I NSCLC patients undergoing lobectomy, found a significant association between VATS and diminished SSI incidence [OR 1.82; p<0.01]. Consistent with prior research and after a broad patient cohort analysis comprising 30,365, Qiu *et al.* demonstrated that patients undergoing VATS exhibited downsized SSI incidence complications, mainly SSIs [OR 3.00; p<0.00001] and air leaks [OR 1.30; p=0.02].

A comprehensive study scrutinised SSI risk factors on 130 subjects who underwent VATS lung radical resection and uncovered that gender, age, advanced TNM stage and tumour type did not have statistical significance as SSI predictors. Natheless, the authors found that DM, PTS ≥3 hours, C-reactive protein, and procalcitonin were strongly associated with SSIs. Furthermore, antibiotic prophylaxis was identified as a protective factor [β= -1.1889; p=0.013]. Contrarily, Gomez-Hernandez *et al.* did not identify a significant SSI-PST link.

Robotic-assisted surgery has been increasingly employed in thoracic oncologic cancer, but its accessibility is limited due to high costs. Controversy exists regarding whether RATS is more efficacious than VATS in reducing SSI. A recent 1231-underwent lobectomy subjects study showed no statistically significant differences.

Moreover, the researchers found that dSSI occurred more frequently than sSSI. They further identified several risk factors significantly associated with SSI occurrence, including older age, COPD, ASA III-IV, hypoalbuminaemia, hyperthermia, PTS, intraoperative blood loss, heavy smoking, male sex, uncontrolled DM, BMI over 27.9 kg/m^2, and higher NHSN risk index score, being these last seven independent SSI risk factors after minimally invasive lobectomy.

Mediastinal cancer

Mediastinal neoplasms encompass a wide tumour range with diverse epidemiological characteristics. They predominantly afflict reproductive-age adults. Surgical intervention is the treatment's mainstay in the bulk of cases, outtake lymphomas, seminomatous germ cells and certain metastatic tumours, for which chemotherapy and radiotherapy are the preferred course of action.

Our research background involves broadly investigating postop complications in CPs undergoing mediastinal and lung surgeries. A study hailed our centre, which focused on mediastinal tumours, evaluated 37 subjects, 67% of whom had malignancies. The study revealed a 5.4% SSI incidence, girding both two sSSI and an o/sSSI involving pulmonary parenchyma, 5% among overall mortality, and 33.3% among subjects who SSIs. These figures display that SSI mortality may be high in mediastinum conditions when encircling spaces or organs.

Most mediastinum malignancy studies do not painstakingly assess SSI behaviour, making it difficult to weigh up their impact thoroughly. Nonetheless, drawing from our expertise in thoracic surgery, we consider that SSIs are not the most common or concerning complication in these cases, especially in those performed by VATS.

Thoracic cage cancer

Thoracic cage primary tumours are relatively rare, with sarcomas, including soft tissue and osteosarcomas, being the most common. The reported SSI rate for thoracic cage tumour-related varies between 5.3% and 18.6%. A recent Italian multicenter study, which analysed patients who underwent titanium mesh reconstruction, assets an 8% SSI incidence and emphasised the import of titanium—a highly resistant material to bacterial colonisation—and the need to ensure well-vascularised tissue coverage to reduce SSI risk. Additionally, in our literature search, the lowest SSI incidence was associated with reconstructive surgery using rigid and non-rigid methods, with only a tiny percentage requiring prosthesis removal post-surgery.

The preoperative-chemotherapy impact on SSI development has been extensively studied. Due to chemotherapeutic agents and their dosage variability, there is open-ended debate and controversy surrounding their influence on healing. Early studies, such as the one by Shamberger *et al*., accentuated that specific chemotherapy agents induce immunosuppression, thereby increasing SSI risk; these stress tailoring preoperative-CT regimens to individual needs and overall patient health. Sundry studies have taped big-wheel disparities in outcomes related to this issue in the thoracic oncologic surgery framework. Some report a notably low probability of chemotherapy-SSI association, whilst others identified a higher likelihood, suggesting a complex correlation between specific chemotherapeutic regimens and postoperative outcomes.

Oncological breast surgery

Breast cancer

Breast cancer stands as the most prevalent neoplasm globally, with 2,300,000 new cases annually registered. The primary breast cancer treatment remains surgery, particularly radical mastectomy. Regardless, while radical mastectomy offers benefits, its aggressive nature introduces postoperative complications due to vast

tissue and lymph node dissection, which compromises the surgical site's immunity and integrity, rendering it susceptible to microbial colonisation.

Reported SSI rates in the US and Japan are lower at 2.9 to 7.7%, while higher rates have been observed in LMIC. Studies indicate that SSI rates can significantly alter based on the surgical procedure and individual patient-specific traits. For instance, radical mastectomies have been reported to range from 33.3% to 64%, especially among subjects over 60 years and those presenting with ductal invasion. Howbeit, a low SSI incidence of 10.4% has been reported in non-reconstructive breast surgeries. Similarly, a study that examined a patient cohort that underwent quadrantectomy, simple mastectomy, nipple-sparing mastectomy, and skin-sparing mastectomy reported an incidence of 9.1%.

In studies involving mastectomies plus immediate reconstruction, the SSI odds also vary, ranging from 2.9% to 17.8% in non-immediate reconstruction, 1.0% to 19.1% in immediate reconstruction mastectomies using implants, and 0.8% to 12.3% in autologous flap immediate reconstruction, which can stem from various factors beyond the scope of this text.

A risk factor array has been described, showing varied associate grades with SSIs; some authors identified factors such as hospital stay, BMI ≥ 25 kg/m^2, age, and blood loss as not significantly relevant SSI predictors, while conversely, anaemia, PST ≥ 3h, advanced TNM stages, DM, drainage time for over seven days, hypoalbuminemia, WBC < 4x10^9/L and preoperative chemotherapy were identified as critical risk factors being the last six SSI predictors. However, diverged findings have been reported by other scholars who recognised that DM, BMI > 25 kg/m^2, and chemotherapy were not linked to SSI and emphasised the tissue inflammation markers association, such as WBC, neutrophils, neutrophil-to-lymphocyte ratio, D-dimer, and fibrinogen, with SSIs in breast cancer surgery, suggesting their potential for diagnostic utility.

Studies in the SSI context in breast cancer surgery have indicated that *Staphylococcus aureus* is the most frequently isolated pathogen. According to a report on mastectomies, this pathogen accounted for 70.41% of cases, followed by *Staphylococcus epidermidis* at 11.24%. Meanwhile, Gram-negative bacteria were isolated in only 11.24% of the cases, and 2.37% of the patients had polymicrobial infections. Among patients with SSIs caused by *Staphylococcus aureus*, 19.32% were found to have MRSA infections. Viola *et al.* highlighted the MRSA or *Pseudomonas* predominance in early SSIs occurring within 30 days postoperatively.

Reconstructive procedures following mastectomy have exhibited an unusual microbiological pattern, documenting non-tuberculous mycobacteria colonisation. Gram-negative pathogen incidence can also reach as high as 50%, exceeding the expected percentage for this surgical procedure. Dealing with non-tuberculous mycobacteria and antibiotic-resistant Gram-negative bacilli poses a challenge, as standard empirical therapy for breast surgical wounds typically does not cover antibiotics that are effective against these bacteria.

Varying antibiotic resistance rates have been observed among pathogens. *Staphylococcus aureus* shows resistance to oxacillin, ciprofloxacin, and levofloxacin at 19.13%, 11.30%, and 8.7%, respectively. Meanwhile, resistance rates for other Gram-positive bacteria exhibit 23.19% for oxacillin, 15.22% for ciprofloxacin and 13.67% for levofloxacin, respectively. Compared to Gram-positive bacteria, Gram-negatives displayed higher ceftriaxone [0 *vs.* 33.33%], cefoxitin [23.53 *vs.* 55.56%], chloramphenicol [2.97 *vs.* 20%], minocycline [0 *vs*. 9.09%] and tetracycline [6.52 *vs.* 25%] resistance. Gram-negative bacteria showed lower resistance to gentamicin [23.91 *vs.* 8.7%].

Oesophagogastric oncological surgery

Oesophagus cancer

Oesophagus cancer surgery, whether curative or palliative, is increasingly common in various healthcare settings, especially endemic regions. Oesophagectomy has historically been recognised as one of the most complex operations. Documented SSI rates for oesophagogastric surgeries, like other oncological interventions, vary but are generally high, ranging from 25% to 45%. According to Japanese data, they portray 17%, being more prevalent than other gastrointestinal SSIs; those also indicate anastomotic leaks, considered o/sSSIs, depicted 3% to 30% of all SSIs.

A vital paper hails the early 2000s involving 2,704 individuals who underwent oesophagectomy, with 2,585 of them having malignancies; SSI incidence demanding wound opening or antibiotics was only 1.5% as per ECCG Definitions. Howbeit, a closer report's analysis reveals postop-snags such as oesophagoenteric leak, staple line or localised conduit necrosis, conduit necrosis/failure requiring surgery, *Clostridium difficile* infections, and intra-abdominal/intra-thoracic abscess. These complications, which may be categorised as dSSI or o/sSSI, would result in a significantly greater utter SSI incidence.

In our centre, where we conduct numerous oesophagus cancer interventions, sundry studies have been undertaken to assess outcomes. By-our-recent research revealed that overall SSI oftenness was 32.8%—36.2% amid epidermoid carcinoma and 21.9% among adenocarcinoma. Additionally, anastomotic leaks were espied in 20.0% of subjects who underwent curative intent.

Divers SSI risk factors succeeding oesophagus cancer surgery are not dissimilar to those minded in other gastrointestinal surgeries. However, peripheral vascular disease, previous thoracic surgery, preoperative surgical antibiotic prophylaxis failing within 120 prior-incision minutes, hypoalbuminaemia and low pre-albumin on postoperative days zero to three have been pegged as stand-alone SSI contributors. Correspondingly, some authors have demonstrated an independent association between postoperatively Clavien Dindo score over three and SSI with $p<0.001$. Likewise, optimal antibiotic prophylaxis duration can impact SSI development in patients undergoing oesophagectomy via the thoracic approach. A shorter prophylaxis span has been linked with a higher rate of 14.8% compared to 8.5% for a prolonged spell, although this factor was not strongly blended with SSIs.

Good spin-offs have been warned in minimally invasive techniques for oesophageal cancer. A study has shown that minimally invasive oesophagectomy promises to improve patient upshots with poor glycaemic control and suggests that elevated preoperative HbA1c levels considerably raise SSI risk after open oesophagectomy compared to minimally invasive oesophagectomy. Beyond, robotic-assisted oesophagectomy adoption potentially enhances postop-R, whereas its long-term efficacy prevails uncertain. Nevertheless, rates of 5.9% for both SSI and anastomotic leaks have been informed.

A hefty variety of bacteria have been isolated in wound infections following open oesophagectomy, the primary pathogen being methicillin-sensitive *Staphylococcus aureus* (32%), *Candida albicans* (29%), and *Escherichia coli* (14%). In addition, poly-bacterial infections have been identified in 32% of cases.

A latter-day ISDE publication on open oesophagectomies recommends a comprehensive pre-, intra- and postoperative care bundle. Preoperative bounds include morning before-surgical showering, chlorhexidine gluconate drapes, and prophylactic antibiotic prophylaxis stewardship relative to local policies for gastrointestinal procedures employing amoxicillin/clavulanic acid—1.2 g IV; maximum 1.5 g—adjusted on kidney function. Intraoperative measures subsume using ChloraPrep 2% for skin preparation, antibiotic ministration within 60 before-incision minutes, and administering a second dose if surgery lasts longer than four hours or blood loss exceeds 1.5 L. Maintaining normothermia throughout intervention is also essential, as is ensuring

oxygen saturation remains above 95% and blood glucose levels in diabetic patients below 11 mmol/L. Keeping postoperative dressing undisturbed for 48 hours is part of postoperative measures

Gastric cancer

Gastric cancer is a broadly prevalent and fatal disease; in 2020 alone, there were 1,089,000 new cases, and 769,000 reported demises, resulting in a mortality rate of 7.7%. Under this scenario, surgical intervention remains the utmost treatment. However, after oncologic stomach surgery, postoperative drawbacks can be expected, mainly a great deal of SSIs, which are the most common, with incidence rates varying from 3.24% to 18.79%; such variability results from differences in surgical techniques, patient demographics, oncologic factors, and even collecting data methods used by diverse scholars. Further, the ageing population has led to a significant buildup of elderly patients undergoing oncological gastrectomies, who befall complications due to these remarkably complex and aggressive procedures and their advanced age.

On the other hand, an accurate SSI sub-categorising analysis represents a thorny topic in stomachical malignancies because different researchers have employed diverse definitions and do not assort them using homogeneous criteria. Nevertheless, it has been observed that patients who withstood gastrectomy are more likely to build up deep SSI. A 790-gastrectomies study categorised SSI into iSSI and o/sSSI, apprised 5.2% and 8.6%, respectively. Addedly, high o/sSSI incidence was significantly associated with open surgery, concurrent splenectomy, BMI ≥ 20.8 kg/m^2, PST ≥ 220 min, and male sex.

Differing standpoints about SSI risk factors following gastrectomies can be encountered. Sundry articles have conflicting perspectives on gender influence, age, BMI, and TNM stages. It has been suggested that a 1.33-fold increased SSI risk among male patients may be attributed to gender differences in bacterial skin colonisation and sex hormone influence on the immune system. Some research has bound ages over 65 with a higher SSI oftenness, although dissenting studies indicate no such strong association exists. Respecting BMI, a decrease below average values or an increase above 20 kg/m^2 may influence SSI advent. A higher BMI can increase the tissue amount to be operated on and make it more challenging to establish surgical boundaries betwixt the pancreas and lymph nodes in overweight or obese individuals. Other contributors may include oxygen levels in avascular adipose tissue, variability in healing, more extensive surgical wounds, and technical challenges.

Malnutrition is a multifactorial syndrome characterised by skeletal muscle mass loss due to cancer-related metabolic changes, reduced nutrient intake, altered food perception, switches in digestive processes, impaired nutrient absorption, and metabolic distortions related to oncological therapies. The highest malnourishment percentage occurs in oncological patients, roughly 30%–90%, and prevalence among them is gauged at 20%–70%, depending on age, type, and stage of malignancy. Digestive tract tumour patients, mainly gastric, pancreatic, and oesophageal, and the elderly populations flaunt a high malnutrition incidence. In an 800-oncological gastrectomy subject study, 19.0% were diagnosed with malnutrition, and it was spotted that there were remarkably higher SSI odds in malnourished compared to well-nourished patients. Additionally, those who seized adequate energy support (≥ 25 kcal/kg per day) for at least ten days had a weighty squatter SSI rate compared to those who received inadequate or no energy succour.

Evidence regarding comorbidities' impact on SSI occurrence in gastric cancer procedures is also inconclusive. As per a few publications, sicknesses such as DM, asthma, hypertension, and cardiovascular infirmities may not have a sinewy correlation with SSI. Netheless, others have indicated a conspicuously higher SSI risk among hypertensive and diabetic patients and also suggest that cardiovascular, liver, and chronic kidney diseases are not linked to either sSSI or o/sSSI.

Surgical technique and neoplasm characteristics have been found to correlate markedly with SSIs in oncologic gastrectomies. These factors include stage III/IV, total gastrectomy, open surgery, extensive resection,

combined resection, D2 or more lymph node dissection, neoadjuvant chemotherapy, and PST. Amid the elderly, neoadjuvant chemotherapy and operative time of 240 minutes or longer have been identified as independent SSI risk factors. Beyond, minimally invasive surgery has demonstrated advantages in gastric neoplasm management. It has been shown to reduce postoperative complication risk, with studies indicating a lower SSI rate in geriatric patients compared to open gastrectomy. Nonetheless, no big-wheel differences have been noted among laparoscopic and robotic-assisted techniques. Barely a 0.8% difference between both procedures has been registered.

Oncological colorectal surgery

Colorectal cancer (CRC) is highly prevalent and ranks as the second leading neoplastic-related death cause worldwide. Even though notable advancements, SSIs continue to be a common complication following colorectal surgery. Extensive research on SSI's occurrence and its overriding risk factors resulted in a wealth of literature, offering varying incidence rates depending on whether the surgeries are open or minimally invasive, elective or emergency. The incidence is generally estimated to be between 5% and 26%; however, lower rates have been reported. What is certain is that colorectal surgery is linked to high SSI rates due to the bacterial load in organs where surgery is performed.

A 31-studies meta-analysis identified twelve risk factors sturdily associated with SSI development after colorectal interventions. Such factors include male sex, DM, obesity, ASA score III/IV, smoking, wound classification, inflammatory bowel disease, open surgery, stoma performance, emergency surgery, PST ≥ 180 minutes, and preoperative BT. Additionally, obesity and BT were identified as factors strongly bracketed with o/sSSI, while stoma formation was linked to iSSI.

As is well known, emergency surgeries have higher postoperative complication odds, mainly if critical steps are overlooked due to the extreme need for operation. In addition, patients who undergo emergency surgery do not meet ideal conditions to ensure a one hundred per cent lower complication rate. Emergency colorectal surgery reports higher SSI frequency than elective surgeries and has been pinpointed as an SSI-predictive factor. Netheless, a recent Welsh study reported that SSI exhibited a relatively lower rate in emergency surgery (13%) compared to elective (14.3%).

Various authors have emphasised the significance of nourishment status assessment in surgical patients by determining serum albumin levels, an inverse acute phase reactant. Hypoalbuminemia has been identified as a critical SSI potential risk indicator in CRC surgery. Multicentre studies have advertised hypoalbuminemia as an independent SSI development predictor and anastomotic leakage pursuing gastrointestinal interventions. Liao *et al.* analysed 1,206 CRC patients over 75 years who underwent curative surgery and determined that hypoalbuminaemia was an overall survival-independent prognostic factor and was heartily linked with SSIs.

Blood transfusion is a frequent procedure for patients undergoing surgery, particularly for those with cancer. Diverse studies have shed light on the conceivable liaison between blood transfusion and SSI in oncological patients. Shaffer *et al.* report that BT of five or more allogeneic blood units augments SSI likelihood in CRC patients by 3.26-fold, possibly due to BT's immunosuppressive effect. Other studies have provided similar results; one compared autologous and allogeneic BT in CRC patients and found a greater extent of infectious complications in autologous transfusion recipients.

Biological evidence suggests DM can upgrade SSI susceptibility by compromising immune function; this compromise primarily involves decreased leukocyte bactericidal activity, reduced chemotaxis, and diminished neutrophil oxidative killing potential. Likewise, perioperative hyperglycaemia is implicated in SSI upshot, particularly within the first postop day. These conditions are a significant SSI predictor in oncologic surgeries.

Sundry CRC reports have demonstrated a considerable correlation between DM and increased SSIs; for instance, an investigation exploring DM2's influence on stage III rectal adenocarcinoma found that DM2 subjects evince a notable preoperative peril of elevated CEA levels and a higher SSI likelihood than non-DM2. Further, a meta-analysis revealed a remarkably higher SSI rate among CRC patients (OR 1.24; $p<0.001$) compared to non-CRC.

In like manner, PST has been consistently tied to higher postoperative complications risk in oncologic patients. However, the clear-cut mechanisms by which SSI increases due to PST are not thoroughly delineated; it is theorised that PST leads to heightened environmental exposure, thereby elevating bacterial infiltration jeopardy, subjecting the tissue to desiccation, and reducing antibiotic concentrations. As demonstrated by plentiful studies, interventions exceeding 180 minutes are associated with exponential enlargement in SSI risk. Cheng *et al.,* ensuing an 81-studies pooled analysis, observed a well-nigh twofold increase in SSI development likelihood owing to PST, and avowed SSI plausibility escalated by 5% for every 10 minutes of surgery, 13% for every 15 minutes, 17% for every 30 minutes, and 37% for every 60 minutes.

The PH implication in SSI has long been a spotlight for surgeons and anesthesiologists, and awareness of PH has increased. Despite that, currently informed incidence after general anaesthesia is 20%, and it usually affects up to 70% of patients in the perioperative period. Several academic papers address PH's impact on SSI, especially in CRC surgery, and some support positive PH-SSI linkage. Netheless, others differ from this criterion; even another briefed a low SSI oftenness at low temperatures. Although the mechanism by which SSIs occur in hypothermic patients is not entirely clear, two main factors are invoked: impaired immune function due to flawed neutrophil oxidative and macrophage phagocytic function and decreased tissue blood flow with subsequently downsized oxygenation. A relationship has also been formed between hypothermia, altered protein metabolism and pared collagen synthesis, all of which delay healing. It has been notified that each hypothermia outbreak ≤ 35.5°C increase SSI likelihood by 6.2%. A cohort study that evaluated the effects of intraoperative warm and humidified CO_2 insufflation on the PH-SSI association in 173 CRC patients found increased SSI risk in hypothermic subjects. The study also noted that CO_2 conditioning significantly decreased SSI by 66%.

Prevention of surgical site infection in oncological patients

Preventing SSI in cancer patients is crucial to improving surgery outcomes and reducing HAI metrics; in line with this, WHO, CDC, ASPIC, and other organisations have developed guidelines for stemming SSIs. The preventive measures recommended do not differ between general and oncological surgical procedures. Compliance with these measures must be strict and adhere to locally established patterns. Due to the heightened oncologic patient susceptibility to SSIs, effective prevention benchmark implementation must be riveted on stringent preoperative screening for risk factors, such as malnutrition, immunosuppression, and previous chemotherapy or radiotherapy. Du reste, it is essential in this population to look for comorbidities identified as SSI predictors, especially DM, which has been described as intimately related to developing SSI in different neoplasms. Furthermore, optimising perioperative antibiotic prophylaxis, adhering to uptight aseptic techniques during surgery, postoperative wound care and surveillance for early SSI detection are integral to prevention strategies. By emphasising comprehensive infection control practices and tailoring prevention efforts to the specific CP needs, healthcare facilities can work towards minimising the SSI burden in this vulnerable population.

Conclusion

Healthcare-associated infection's global burden, specifically SSI on oncologic patients, is substantial. Surgical site Infection incidence varies significantly between HICs and LMICs, with LMICs experiencing notably higher rates. Factors contributing to this difference embody health infrastructure challenges, limited access to medical technology, and sanitary practice differences. Despite the difficulties in accurately determining SSI incidence, it is evident that SSIs have a significant impact on CPs, leading to increased morbidity, mortality, healthcare expenditures, and prolonged recovery. Addressing SSIs in CPs requires a multidisciplinary approach, focusing on epidemiological surveillance, risk factor identification, prevention strategies, and effective treatment protocols. Research and concerted efforts are also needed to mitigate the SSI's impact and improve healthcare outcomes globally.

Competing Interests

The authors affirm they have no competing financial and non-financial interests to disclose.

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Chapter 112

Clinical and economic burden of surgical site infections

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Introduction

Surgical site infections (SSI) are among the most common healthcare-acquired infections (HAIs), with rates varying by type of surgery. European surveillance data shows that the rate of SSI between 2008 and 2016 could not be reduced in all major surgical subpopulations and, related to the capture of current surveillance data, the actual number of SSIs is likely underestimated. SSIs increase postoperative mortality and morbidity, resulting in increased length of stay (LOS), surgical procedures related to the SSI, and a higher need for postoperative intensive care. Consequently, SSIs increase the financial burden of surgical procedures, leading to a significant impact on national health expenditure.

Definition and risk factors

In the 1970s, the U.S. Centers for Disease Control and Prevention introduced definitions of three classes of SSI that are still in use in nearly all surveillance systems and publications worldwide. These three classes are:

- Superficial SSI (cutis, subcutis; A1)
- Deep SSI (muscle, fascia, A2) and
- Organ-space associated SSI (A3).

The causes of wound infections are multiple and complex, involving both patient-related and pre-, intra- and postoperative factors. SSI prevention is a multidisciplinary task, that extends beyond the operation itself and is certainly not restricted to the administration of antibiotics.

Epidemiology of SSI

The number of surgical procedures undertaken has increased over the last decade, averaging at 15.9 million per year during the 2010–2016 period alone in Germany. According to the latest European Centre for Disease

Prevention and Control (ECDC) point prevalence data, Germany has one of the lowest rates of SSI. The overall prevalence of HAI in Germany in 2016 was reported to be 4.6%, with SSI representing 22.4% of HAI (an overall prevalence of 1.08%) based on data from 64,412 patients in 218 participating hospitals. The individual SSI rates for German hospitals are published on the National Reference Centre System for Surveillance of Nosocomial Infections (Krankenhaus-Infektions-Surveillance-System; KISS) website.

Surveillance of SSI – data collection

Reporting of SSI data in Germany is conducted via the Hospital Infection Surveillance System with a focus on SSI (OP-KISS) at the National Reference Center for Surveillance of Nosocomial Infections (NRZ). This is based on the US surveillance systems of the National Healthcare Safety Network (NHSN) from the Centre for Disease Control and Prevention (CDC). The NRZ provides participating hospitals with their electronic system for documenting data. The hospitals which want to participate in the data collection must first take an introductory course. In this course, the method of surveillance is taught, and the diagnosis of postoperative wound infection (SSI) is additionally explained by using sample illustrative cases of postoperative wound infection regarding the method of surveillance. The comparability of the data across centers is therefore not necessarily guaranteed, and the quality of the data collection is inherently subject to human error or omission. Based on these circumstances, it can be expected that the inpatient SSI may be under-reported in individual hospitals or individual departments of the reporting hospitals. Additionally, actual SSI rates are likely to be higher after discharge due to incomplete or missing SSI documentation.

Real-world data on the economic burden of SSI in Germany – methods

The considerable economic impact of SSI has been established in several European countries and the US, however, no economic analysis has been conducted to establish the direct costs associated with SSI based on standardized real-world data. Therefore, a recently published study was designed to assess the clinical and economic burden of SSI in German hospitals using prospectively collected routine data which was captured as part of the annual German diagnosis-related group (G-DRG) hospital resource use and reimbursement scheme. It was a retrospective, cross-sectional, multicenter database study designed to assess the prevalence of SSI in a representative sample of German hospitals, and to compare LOS as well as costs for patients who experienced an SSI, compared with those who did not, over the period 2010–2016. The study population included the hospital performance data of all patients in a dataset of 79 hospitals which had undergone predefined surgical procedures, as captured by German OPS-301 codes. Surgical procedures of interest broadly covered cardiac, colorectal, gynecological, spinal, thoracic, upper gastrointestinal, orthopedic and trauma specialties; The population was then separated into two groups based on whether they had experienced an SSI during their hospital stay or did not (defined as ‘SSI’ and ‘non-SSI’ groups), mapped to the NRZ classification within the framework of the systemic schemes: A1/A2 (superficial incisional/deep incisional SSI) or A3 (organ and body cavity/ pace SSI). Patient reports were excluded if i) cost or reimbursement data were missing; ii) the patient had more than one surgical procedure causal to the admission diagnosis undertaken during their billed hospital stay; and iii) the patient did not have an ICD-10-GM code for SSI. The primary outcome was the period prevalence of SSI in the overall population. SSI cases were then stratified by procedure type and NRZ classifier. Secondary outcomes were mortality, median overall LOS, median pre-surgical LOS and

median case cost for the SSI and non-SSI groups. For three cost centers, detailed analyses were undertaken: general ward, intensive care unit (ICU) and operating room.
Further outcomes of interest were total ICU stays, median G-DRG reimbursement and median contribution margin (reimbursement per case minus costs per case). Propensity score matching (PSM) was performed on the SSI and non-SSI groups to minimize bias from possible confounding variables.

Real-world data on the economic burden of SSI – biographic data

For the study period 2010-2016, the database included 4,830,083 anonymized hospital cases from 79 German hospitals that are known to DGVS, the owner of the database. After the exclusion of ineligible cases according to the index procedures, 221,113 remained for analysis. An SSI that was determined from the time of admission to discharge of the patient was reported in 4.9% (10,807/221,113) of the unadjusted study population. A significant difference in the SSI rate was reported between open and laparoscopic colorectal and thoracic procedures and between primary and revision orthopedic procedures. Of the 10,807 instances of SSI, 5,997 (55.5%) were classified as an A1/A2 infection and 4,810 (44.5%) as an A3 infection. A1/A2 infections were more prevalent for upper GI, colorectal and heart procedures, whereas A3 was the prevalent SSI for orthopedic revision procedures.

Real-world data on the economic burden of SSI – risk factors

Age, sex, procedure type, immunosuppression, body mass index (BMI) ≥30 kg/m² diabetes mellitus, Charlson comorbidity index (CCI) score (calculated via ICD-10 coding16) and preoperative length of stay were found to be statistically significant confounders for the occurrence of SSI and were adjusted for in the PSM. The prevalence of immunosuppression (3.4% *vs.* 2.7%; $p<0.001$) was significantly higher for patients who had SSI compared with those who did not. Procedure type and primary diagnosis were also significantly different between the groups ($p<0.001$). In terms of hospital stay, patients who developed SSI had statistically significantly longer median overall and pre-surgical LOS than those who did not (median [IQR] overall LOS: 28 days *vs.* 12 days [$p<0.001$]; median [IQR] pre-surgical LOS: 2 days *vs.*1 day [$p<0.001$]). Further, a statistically significantly higher proportion of patients with SSI was admitted to the ICU (55.2% *vs.* 30.9%; $p<0.001$). Mortality was also statistically significantly higher in the SSI group than in the non-SSI group (9.3% *vs.* 4.5%; $p<0.001$). The incidence of peritonitis (11.9% *vs.* 2.8%; $p<0.001$) and sepsis (17.7% *vs.* 3.3%; $p<0.001$) was also significantly higher in the SSI group. Median case costs were statistically significantly higher for patients who had SSI compared with those who had no SSI (Median (IQR): € 19,008 (25,162) vs. €9,040 (7,376); $p<0.001$). Also, the median reimbursement was significantly higher for the SSI group (€15,084 *vs.* €9,689; $p<0.001$); however, there was a negative median contribution margin for SSI cases compared with a positive median contribution margin for non-SSI cases (-€1,534 *vs*. €633; $p<0.001$). From this, it can be seen that SSI cases were underreimbursed compared to non-SSI cases.

Clinical and economic burden of SSI – international data

As one of the most common HAIs worldwide, SSIs require the attention of all disciplines involved in patient care, from healthcare professionals to hospital managers and payers.

The above-mentioned study was the first to analyze risk factors, prevalence, clinical consequences and economic burden of SSI in German hospitals from a single large dataset that is reflective of the actual hospital treatment required for the different types of SSI. Furthermore, the study shows gender-specific results with an increased expression of male SSI cases, as already shown in existing clinical studies.

SSI is a complication of a surgical procedure and is associated with a significant medical, and personal, burden for affected patients. It is associated with a perceived negative view of the quality of surgery performed and potentially the reputation of the surgeons and hospital. Therefore, surveillance based on self-reporting and voluntary participation may be susceptible to under-reporting. By contrast, the capture of data, for reimbursement, is of interest to hospitals to receive remuneration for actual cost. A clinical trial conducted in the Netherlands is an example of this and supported the scientific approach as well as the findings of this study, with an SSI prevalence of 2.2% for patients undergoing spine surgery (2.4% in this study). The total SSI rate of procedures including post-discharge surveillance may have been even higher than the rates mentioned in the international literature

The impact of SSI on mortality has been repeatedly emphasized. The findings of a currently published study support those previously reported. Future studies should focus more on this issue.

The results from our study also show that patients who develop SSI have, with 16 additional days, a significantly longer median LOS and incur much higher case costs for the hospital provider. Accordingly, it is in the clinical, hospital, and social and economic interest to avoid as many SSIs as possible through appropriate infection prevention measures and the use of prophylactic care bundles. International studies on the economic impact of SSI are mostly based on comparatively small or midsize sample sizes. Studies of healthcare-associated infection and costs on large patient populations are published for individual European countries. In a 2013 study, there was an estimated average daily cost of €131 to €189 per day in private hospitals and of €166 to €304 per day in public hospitals for hospital care following a healthcare-associated infection, which was reported from France based on the evaluation of the compulsory hospital patient database PMSI (n=520,715). For the UK a 2005 surveillance study based on the Nosocomial Infection National Surveillance Service (NINSS) for SSI dataset from 140 hospitals, including 67,410 patients, identified an extra LOS due to SSI ranging from 3.3 days for abdominal hysterectomy to 21.0 days after limb amputation with an estimated additional ward cost of £290,60 per bed day due to SSI.

Evidence-based prevention of surgical site infection

To prevent postoperative wound infection, patient management should be protocol-defined, by evidence-based measures and recommendations. The WHO recommendations on the prevention of postoperative wound infection, published in 2016, were intended as a concise summary of a wide range of measures. **Table 1** contains a listing of individual measures for the prevention of SSI that are supported by evidence of the highest level according to a recent review of meta-analyses, systematic reviews and Cochrane reviews that appeared after the WHO recommendations were published in 2016 as well as a further meta-analysis. Moreover, indications and modalities of perioperative antibiotic prophylaxis, which can reduce the SSI rate substantially in selected collectives (for instance colorectal surgery) are discussed in detail elsewhere.

Table 1. Evidence-based measures for prevention of surgical site infections (Adapted from Eckmann C *et al.*, 2024).

Measure (reference)	No. of RCTs	SSI rate without measure (no. of pt.)	SSI rate with measure (no. of pt.)	RR (95% CI)	*p* value	Approximate change of SSI rate
Shaving	n=7	2.1% (19/887)	4.2% (34/819)	1.82 (1.02-3.14)	0.03	+ 80%
Nasal decolonisation and washing with chlorhexidine*	n=5	2% (253/12790)	0.8% (152/19940)	0.41 (0.30-0.50)	<0.001	- 60%
Normothermia	n=3	13% (37/290)	4.7% (14/299)	0.36 (0.20-0.66)	0.008	- 65%
Normoglycemia	n=15	16% (392/2488)	9.4% (231/2464)	0.59 (0.50-0.68)	<0.001	- 40%
Skin desinfection with alcohol and chlorhexidine	n=20	4.8% (725/15263)	2% (425/13743)	0.65 (0.55-0.77)	<0.001	- 35%
Use of negative-pressure systems[#]	n=28	14% (315/2205)	8.8% (194/2193)	0.61 (0.49-0.76)	<0.001	- 40%
Use of triclosan-coated suture material	n=25	9.7% (581/5949)	6.9% (420/6008)	0.73 (0.65-0.82)	0.005	- 30%

* effect statistically significant only for high-risk procedures (cardiac surgery, orthopedic surgery).
[#] effect statistically insignificant for visceral surgical, gynecological and urological procedures.
Abbreviations. CI: confidence interval; pt., patients; RCT: randomized and controlled tiral; RR: risk reduction: SSI, surgical site infection.

Conclusion

Real-world data demonstrate the clinical and economic burden of SSI (**Figure 1**). The prevalence of SSI, the statistically determined mortality and the significant underfunding of SSI cases call for improvements: Pre-, intra- and postoperative efforts should be undertaken in the form of prevention and prophylactic interventions to reduce the impact of this financially burdensome, and potentially fatal, postoperative complication.

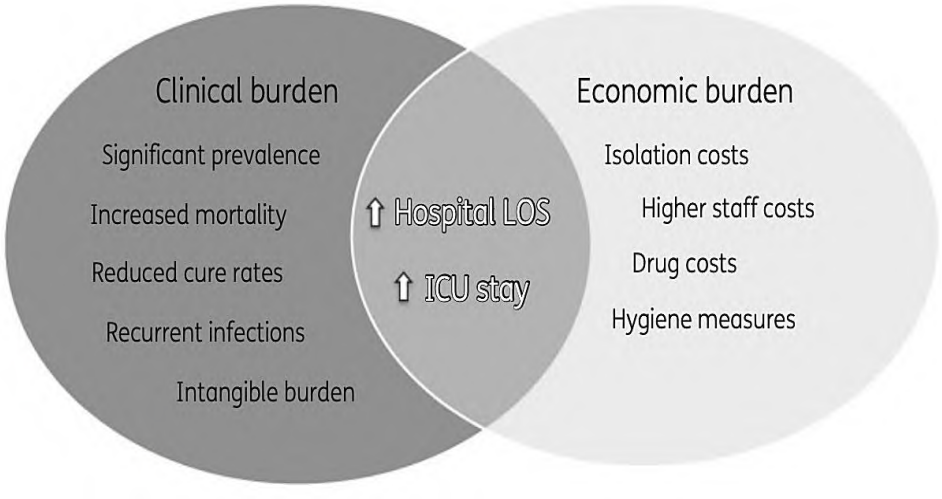

Figure 1. Clinical and economic burden of surgical site infections (Adapted from Eckmann C *et al.*, 2021).

Competing interests

The authors have no financial and non-financial competing interests to declare.

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Chapter 113

Defining and organizational model for the prevention of surgical site infections in low-resource settings

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Introduction

Surgical site infections (SSIs) remain a substantial cause of morbidity, accounting for 25% of hospital-acquired infections (HAIs). SSIs are a major cause of hospital mortality, increasing to a factor 10 the risk of death. SSI is the costliest HAI type and increases hospital length of stay by 9.7. In addition to this, they also have a significant quality of life and economic impact on the population and society. Considering this epidemiology, SSIs may be the « Achille's heel » of surgical practice. However, effective infection prevention and control organization can prevent 50% of these infections. But there is not yet a universal coverage in the prevention of SSIs.

The context of low resources settings

Individuals from different backgrounds, social groups, and countries enjoy different levels of health access and quality. The consequences of the inequities of safe healthcare delivery are that SSIs continue to affect 10% of patients in high-income countries (HICs) and 30% in low- and middle-income countries (LMICs). Inequities also exist in some HICs, so low-resource settings (LRSs) may be better terms to indicate low-resource areas. This concept of LRSs, can be described with nine themes including: financial pressure; suboptimal

healthcare service delivery; underdeveloped infrastructure; paucity of knowledge (lack of education and training); research challenges and considerations; restricted social resources; geographical and environmental factors; human resource limitations; influence of beliefs and practices.
Considering this epidemiology and context, SSIs are the « Achille's heel » of surgical practice in LRSs. Despite the availability of guidelines on SSI prevention, LRSs have not gone as far as to implement such guidelines to satisfactory degrees. Existing SSI prevention guidelines are of high quality, but adapting and implementing them in LRSs has proven difficult for several reasons, including poor healthcare infrastructure, lack of financial and logistical assistance, lack of training and sufficiently qualified healthcare professionals. However, SSIs are an example of HAIs that can be efficiently prevented and avoided by a Multi-modal and Integrated (inclusive) Strategy (MIS). This approach, when taking into account the local context and available resources, is proven to be efficient in LRSs.

The multimodal approach

SSI prevention is complex because the risk of SSI results from multiple factors including: the patient, the pathology, the environment, the practicians, the compliance towards guidelines and the IPC (infection prevention and control) organization. When taking into account all factors, a multi-modal (multifactorial) approach is mandatory to achieve efficient control.
The multi-modal strategy comprises several elements or components implemented to improve an outcome and change behavior. It includes tools, such as bundles and checklists, developed by multidisciplinary teams that take into account local conditions. The most common components for improvement identified by the World Health Organization (WHO), include:

- System adequacy (availability of the appropriate infrastructure and supplies to enable infection prevention and control good practices);
- Education and training of health care workers and key players (managers…);
- Surveillance (monitoring practices, processes, outcomes and providing data feedback;
- Communications (reminders in the workplaces);
- Culture of safety (empowering leadership and accountability in patient safety).

Through this process, preoperative, operative and postoperative measures are identified, tailored and engaged. This multimodal improvement strategy is the most effective way to implement IPC recommendations and improve best practices at both national and facility levels; as it is widely accepted that focusing on only one approach to ensure IPC will not achieve or sustain behavioral changes. The Multi-modal approach shows the way to put in place measures and change practices; to avoid risk factors of SSIs.

The integrated approach

Scientific evidence and global experience show that effective and sustainable impact in improving patient outcomes and healthcare practices is achieved by integrating the implementation of different elements of the WHO multimodal strategy in a complementary and concurrent manner.
Indeed, each element of the multimodal improvement strategy is crucial, no component can be considered optional. The implementation strategy itself is designed to be adaptable without jeopardizing its fidelity and

intended outcome. Therefore, depending on the local situation and available resources, some elements may be given more emphasis than others or may be practically implemented in different ways.
Persons leading SSI prevention activities should be “multimodal thinkers” and should consider the implementation of each SSI intervention (including the potential challenges and opportunities) through a multimodal « integrated » lens.
The integrated strategy is thought and created according to the behavioral, organizational and cultural complexity in health care systems. The aim is to improve the local safety climate and motivate local teams to consistently perform best practices by shaping the attitudes, beliefs and values of clinicians. This could include engaging leadership, improving collaborations and teamwork, and facilitating staff ownership of the intervention. The success in the improvement of clinical practice and outcomes is attributable to the motivation of teams to improve their practices, and the status of local project leaders as influential members of their respective departments. Infection prevention and control best practices are most successfully implemented when embedded within a culture of safety and teamwork that is facilitated by an adaptive approach. Implementing an integrated strategy passes through the empowerment of front-line providers to develop local solutions to address preventable SSIs. This concept is the basis of the Comprehensive Unit-Based Safety Program (CUSP), developed by the Agency for Healthcare Research and Quality (AHRQ); and the WHO Implementation Manual to support the prevention of surgical site infections at the facility level. An interdisciplinary team, including surgery, anesthesia, nursing, hospital epidemiology and infection control leaders, is engaged to support the development of an SSI Prevention Team (SSI-PT). The SSIs-PT approach initiates thinking on the way to translate MIS into concrete measures and routine practice for the prevention of SSIs. In brief, the Comprehensive Unit-based Safety Program is a five-step iterative and dynamic process that includes:

- Education of staff on the science of improving patient safety;
- Identification of defects (anything clinically or operationally that should not recur);
- Engagement of local leadership and Promotion of accountability of front-line staff and senior leaders;
- Identification of how to learn from defects;
- Implementation of tools to help improve teamwork and communication.

The integrated approach shows the way to engage and foster local teams; in order to appropriate themselves the challenges of SSIs in LRSs.

Conclusion

« To err is human », nevertheless SSI is an avoidable risk. An avoidable risk means that it can be avoided, prevented, or minimized at its very low consequences. Surgical care must respect that « Primum non nocere » is the essence of healthcare. Surgery in LRSs is facing more challenges when addressing the burden of SSIs. To address this issue, the organizational model must consider the epidemiology and the local context. Indeed, prevention of SSIs encompasses a Multi-modal and integrated model; « built, taught, executed, checked, sold and lived » by a devoted SSIs-PT.

Competing interests

The authors have no financial and non-financial competing interests to declare.

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Chapter 114

Challenges in surveilling surgical site infections

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Introduction

Healthcare-acquired infections (HAIs) are one the most frequent in-hospital adverse and impacting outcomes in healthcare. Among HAIs, surgical site infections (SSIs) are the most frequent. The proportion of preventable HAIs is estimated to be 35-55% through the implementation of multifaceted infection prevention and control (IPC) interventions. To operate the process of HAI reduction is crucial to set up a program based on 3 mandatory elements: best practices, surveillance and feedback.

Surveillance as a tool for reducing surgical site infections

A comprehensive definition for SSI surveillance is the systematic data collection, analysis and interpretation of infections, surgical procedures and patient characteristics, followed by the dissemination of relevant results to surgeons surgical teams and administrators.
The role of surveillance in a program that aims to reduce SSIs is to measure the magnitude of the problem, identify the risk factors and allow monitoring the effectiveness of IPC measures through time.

Challenges in the surveillance of surgical site infections

There are a number of challenging elements to setting up a system for the surveillance of SSIs; these include: the need for a clear definition of the case and a shared protocol; a good epidemiological framework; and guidance for the implementation and sustainability of the system over time.

Which are the methods for surgical site infection surveillance?

The surveillance of HAIs can be either carried out by passive or active data collection. The major surveillance networks recommend active surveillance based on the systematic collection of data by a designated unbiased surveillance team. This method requires a specific infrastructure but provides accurate information.
Nowadays, longitudinal prospective data collection is the most frequently applied method for SSI surveillance in major networks worldwide. This allows follow-up of the patient after the surgery, particularly in the post-discharge period. Despite this is a resource-consuming approach, it allows the calculation of incidence rates and a wider range of data analysis which can aid the interpretation of the results.
An alternative method is the cross-sectional study. In this model, all the patients are screened for SSIs at the same moment, regardless of the time passed from the surgical procedure. This approach is less demanding in terms of resources and time needed for data collection. However, it exposes to the overestimation of the infection rates. Moreover, it is often based on in-hospital surveillance which is more likely to intercept the most severe infections because they may lead to a prolonged hospital stay or require another hospitalization whilst may underestimate the mild infections, as the superficial, which are often managed in the outpatient setting. Due to this limitation, the use of prevalence data to estimate SSI incidence is recommended only in situations where incidence surveillance of SSIs is not performed, and where sufficiently large samples of PPS data are available.
The most accessible strategy is passive surveillance, which relies on legally regulated reporting systems (e.g. notification system) or pre-existing agreements that are used to obtain the data of interest. Notification systems, disease registries, and hospital records are examples of passive surveillance. Although passive surveillance systems are less time-consuming and less expensive to operate, they have some important limitations such as bias resulting from under-reporting and the lack of a clear denominator.

Which are the crucial elements of a surveillance protocol?

In general, a number of key elements must be taken into account when defining a surveillance protocol. Moreover, it is important to constantly ensure the entire process is sustainable, over time.

Case definitions

Case definitions are one of the most important factors for a reliable protocol. Defining surgical site infections in a valid, strong and meaningful manner to ensure standardisation of results allows valid comparison of SSI rates within the same unit (e.g. at ward or hospital level) or between different institutions (e.g. hospitals participating in worldwide surveillance networks). In general, definitions should be simple to use, accepted by clinicians, applied consistently and remain stable over time. Many authors suggest “there is no single, objective gold standard test for surgical wound infection”. Many definitions of SSIs are available from literature but for the purpose of surveillance, major networks worldwide use the Centers for Disease Control (CDC) which define SSIs in 3 categories:

- Superficial are those involving only the skin and subcutaneous tissue at the incisional level.
- Deep are those involving deep soft tissues (fascia and muscles) under the surgical incision.
- Organ/space are those involving any part of the body deeper than the fascial/muscle layers that is opened or manipulated during the operative procedure.

Definitions may include clinical manifestations (e.g. purulent drainage from the incision, fever), isolation of pathogens from relevant biological specimens, and diagnosis by a competent physician (e.g. surgeon).

Risk stratification

The various categories of surgery entail a different risk of infection, and a comparison between operating units that have completely different activities per surgery category would not be adequate (for example, one cannot compare general surgeries that mainly perform abdominal interventions with general surgeries which perform breast interventions, the former having a significantly higher basic risk than the latter). Furthermore, within each category of surgery, it is important to consider the characteristics of the patient and the basic risk of the individual surgical procedure; operating units that operate on critical patients and perform very complex surgeries have a higher basic risk than operating units that operate on less complex patients. To solve this problem and ensure the correct interpretation of comparisons, risk stratification must be applied. An example is the basic SSI risk index (IRI) used in the US National Healthcare Safety Network (NHSN): It is a composite risk index that captures the joint influence of the three major risk factors present at the time of the operation: operation lasting more than the duration cut point; wound contamination class; the patient ASA classification and can take the following increasing risk values: 0, 1, 2 and 3. For example, a patient with colon surgery and an IRI equal to 3 is at greater risk of having an infection than a patient with the same colon surgery but an IRI equal to 0. In order to fairly compare the incidence of infections in different realities, surveillance results should be stratified for each intervention category for each IRI value.

Sustainability of the surveillance process

It was observed that the longer the surveillance is in place, the better the SSI rates are affected. However, the sustainability of the surveillance process can have an impact on achieving the reduction of the infection. To facilitate this, a surveillance protocol must be essential and collect only the information that is strictly necessary, avoiding duplication or the collection of data that are not useful for the analysis and interpretation of results. In this process, it is important to regularly reassess the reliability and usefulness of the data collected and to update the protocol as necessary. However, it is also important that certain critical elements, as SSI definitions, remain stable as much as possible to ensure comparability of results over time.

Feedback of results

The feedback of results is the last step of the surveillance process. Sharing findings with those who need to know and who can act on these findings can improve patient safety by raising awareness of the personnel about the results of process and outcome monitoring. For this reason, a plan for the distribution of surveillance information should be incorporated into the development of each surveillance component. The return of results should be on a periodic basis (e.g. half-yearly or yearly). However, a more frequent return should be considered in the case of specific situations (e.g. clusters of infections or organisational changes to be monitored). Surveillance reporting should present information in a concise but consistent manner, avoiding redundant or complex descriptions. The use of a report which includes indicators, tables, charts and infographics could be of help. Often, when the surveillance is based on an incidence survey, two metrics are calculated:

SSI ratio (or cumulative incidence) is the proportion of surgical procedures in which an SSI was found and is calculated*:*

$$Percentage\ of\ SSIs = \frac{all\ first\ SSIs * \ in\ that\ category}{all\ operations\ in\ that\ category} \times 100$$

SSI rate (or incidence density) is the number of SSIs occurring over time and depends on the follow-up. The formula is*:*

$$Incidence\ density = \frac{all\ first\ SSIs *\ in\ that\ category}{postoperative\ patient\ days\ with\ known\ date\ end\ follow-up} \times 1000$$

Periodic reporting should be easy to access and based on a format in order to be recognised by the users, and when changes are needed, they should be explained. When relevant, a discussion section should be included to report interpretations of the results or information useful for future uses of the data. A description of the population (characteristics of the patients), risk factors and risk stratification should be included in the surveillance report. The interpretation should be the result of collaboration between those who conduct surveillance and have specific training (e.g. epidemiologists or data scientists) and clinicians. Interpretation should also take into account relevant elements that were not directly detected by surveillance, but which might have influenced the trend of the SSIs (e.g. organisational changes). Caution is recommended when surveillance data are used for inter-facility comparison. Comparisons are valid only when all data contributors have: employed the same level of surveillance intensity, utilized comparable data collection methods, applied consistent surveillance definitions, accounted for variations in population or case mix, and appropriately stratified the data.

How to implement an SSI surveillance?

The US Association for Professionals in Infection Control and Epidemiology (APIC) suggests a minimum set of requirements for the implementation of surveillance of HAIs which is applicable to SSIs.
The surveillance of SSI should be officially acknowledged by the organization and incorporated into the IPC program. A protocol, accessible to all personnel within the organization, should clearly outline the objectives, surveillance components, and resources allocated to sustain the process.
The appropriate number and type of resources should be guaranteed. This includes those with specific training in epidemiology and surveillance; data collection, management and analysis; and computer skills useful for process automation (data collection and report production). In addition, access to continuing education programmes should be ensured for all those engaged in surveillance. Likewise, the use of dedicated tools should be ensured, such as data collection software designed around surveillance data, which facilitates the process of collection, verification and consolidation, and analysis.
Including surveillance of SSIs in the organisation's performance indicators could stimulate active participation and attention to the process, from data collection to feedback on results, and increase the perception of the problem of SSIs and the importance of IPC measures. As an example, the European Centre for Disease Prevention and Control (ECDC) included IPC indicators (perioperative antibiotic prophylaxis, preoperative skin preparation, perioperative normothermia and blood glucose levels) in the 2.2 surveillance protocol allowing the monitoring the application of practices for prevention in parallel with the surveillance of SSIs.
Surgeons and operating staff are the main recipients of surveillance. Involving these actors in the process is important to raise awareness of the usefulness of the tool and to stimulate proactivity in the process of data collection, interpretation of results and subsequent implementation of prevention measures. Appropriate knowledge of how surveillance works (e.g. the protocol and limitations of analyses and results) will ensure that objectives are met; it will encourage active participation and defuse the dangerous stigma of being judged by those conducting surveillance.

Alternative approaches for surveillance of SSIs

Although surveillance of SSIs has been shown to be effective in reducing rates of this type of infection, the implementation of prospective systems is difficult due to the associated costs and required resources. This is due in particular to the long post-discharge follow-up (equal to 30 or 90 days from the date of surgery). Therefore, in many cases, the duration of follow-up may be shorter than optimal, especially for more serious SSIs (e.g. organ space) that have a longer incubation period and often appear after discharge. A systematic review of several primary studies has provided the algorithms used to identify SSIs based on diagnoses and procedures performed during hospitalization, using the hospital discharge database. However, the review has highlighted how these data sources may in many cases have low accuracy in identifying SSIs and indicated how there is a need to work on health databases to make them suitable for automated surveillance (AS). More recently, validation studies have been published that highlight how the use of health databases allowed for automated or semi-automated surveillance with good levels of accuracy. The difficulties and limitations of conventional surveillance have led to the development and use of AS in specific contexts. However, large-scale implementation of AS based on accurate data requires leadership, coordination within and between surveillance networks, and considerable resources. For this reason, a network bringing together experts from several European countries has prepared a roadmap for large-scale implementation of AS.

A recent review analyses innovative techniques for infection control and surveillance in hospitals and long-term care facilities. The introduction of alternative methods utilizing automated detection strategies, powered by artificial intelligence (AI) and machine learning (ML) algorithms, shows promise in addressing the limitation of actual approaches for surveillance of SSIs, reducing the workload and the burden of costs, and is gaining popularity in healthcare. These automated surveillance systems can either assist with (semi-automated) or completely replace (fully automated) manual surveillance processes through the use of AI-driven algorithms. By harnessing AI and ML, these new methods can manage the growing volume of health data generated by automated collection systems, performing analyses that would otherwise demand unsustainable levels of time and human resources. However, integrating these novel technologies into existing healthcare systems necessitates interdisciplinary collaboration and strong leadership, each of which presents its own set of challenges.

Conclusion

To ensure the success of an infection and prevention program is fundamental to implement a consistent, sustainable, strong and reliable surveillance protocol and timely convey the results to surgeons to reinforce the IPC measures and hospital management to ensure the allocation of resources for IPC practices as surveillance.

Competing interests

The authors have no financial and non-financial competing interests to declare.

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Chapter 115

Principles for appropriate surgical antibiotic prophylaxis

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Introduction

Surgical antibiotic prophylaxis has been commonly used since the 1970's, and the details on its efficacy and ideal indications for use have evolved over the years with increasing detail becoming available. The data show that the risk of surgical site infection (SSI) is reduced with prophylaxis for all surgical procedures, but the relative benefit of prophylaxis varies depending on the magnitude of SSI risk and the severity of its consequences. Using an effective drug for cases that benefit, starting before incision, using an adequate dose, and stopping when the incision is closed are supported by the evidence.

Principles for appropriate surgical antibiotic prophylaxis

In examining the principles for appropriate surgical antibiotic prophylaxis, it is helpful to address the following five important questions:

1. Which cases benefit?
2. Which drug should you use?
3. When should you start?
4. How much should you give?
5. How long should antibiotics be continued?

On examination of the literature on prophylaxis covering mixed GI cases, colectomy, vascular, cardiac, craniotomy, spinal operation, joint replacements, breast and hernia operations, and hysterectomy one can find a per cent reduction in SSI rates ranging from 12% to 90% and number needed to treat to prevent one SSI varying from 2 to 100. A review of prophylaxis meta-analyses from 2009 found a consistent relative risk of wound infection of less than one in all cases examined that was independent of the type of operation or the baseline (placebo) rate of infection. We sometimes hear advice that we shouldn't use prophylaxis for inguinal hernia repair or laparoscopic cholecystectomy, but recent meta-analyses show a reduction of inguinal hernia SSIs from 5.3% to 3.1% (p=0.004) and for laparoscopic cholecystectomy from 2.9% to 1.9% (p=0.04). The bottom line is that the relative reduction of SSI with prophylaxis is essentially the same for all procedures in the range of 30-70%, but the absolute reduction is less if the baseline rate is less. The decision on whether or not to use prophylaxis should depend on the cost of prophylaxis ($, side effects, promotion of resistance) and the cost of infection ($, disability).

When deciding which drug to use it helps to consider whether the procedure includes exposure to *Bacteroides* or not. If *Bacteroides* is expected, then cefazolin or another first or second-generation cephalosporin combined with metronidazole is an effective choice. Without *Bacteroides*, the cephalosporin alone is good. For colectomy prophylaxis many surgeons have used cefoxitin, the first cephalosporin with anti-anaerobic activity, for many years. However, cefoxitin has a very short half-life requiring frequent redosing and in recent years has lost much of its activity against anaerobes. A recent study examining over 90,000 colectomies found cefoxitin significantly inferior to cefazolin with metronidazole which can be dispensed in the same IV bag and given efficiently before the incision.

Another consideration for prophylaxis choice occurs in certain settings where targeted prophylaxis may be indicated such as a high rate of colectomy patients having ESBL infections, or a significant number of SSIs in an institution with resistance to standard prophylactic agents. Another setting where special choices can be indicated is for patients with biliary stents scheduled for pancreaticobiliary operations. Preoperative rectal swabs can reveal if the patient is colonized with ESBL organisms which should lead to targeted prophylaxis.

Regarding when to initiate prophylaxis, many studies show the importance of infusion before the incision. One of the earliest of these showed an increasing infection rate as the interval after incision increased. Most guidelines recommend infusion between 120-0 minutes or 60-0 minutes before incision. Many years ago, it was common to have the prophylactic agent injected in the surgical ward when the patient was called to go to the operating room. A study in 1985 compared serum levels of the antibiotics at different intervals during the operation and found higher levels consistently for the antibiotic infused by the anesthesia team at the time of induction compared with intramuscular injection on call. A more recent study performed a logistic regression of the pre-incision time of infusion with infection risk in 4,453 patients and found that the lowest risk occurred at 4 minutes before incision. Multiple studies demonstrate a strong correlation between infection risk and the concentration of the prophylactic agent in serum and tissue throughout the duration of the case. One way to assure adequate levels throughout the case is to standardize giving a repeat dose of prophylaxis within 2 half-lives of the antibiotic calculated from the time of pre-incision infusion rather than the time of incision. Another way to ensure adequate levels of prophylactic agents during the operation is to increase the dose for morbidly obese patients.

Another common issue for antibiotic prophylaxis is the duration of administration. One of the earliest studies of successful antibiotic prophylaxis was published in 1969 at a time when most surgical patients were admitted to the hospital a day before the operation. This study compared a dose of cephaloridine given on call to the operating room. followed by 2 more doses given at 5 and 12 hours after the first dose and this became a common practice in the following years. Over time longer duration of prophylaxis became common, and a subsequent paper in 2005 found that more than half of all Medicare patients received prophylaxis for more than 24 hours and more than a fourth for over 48 hours. Subsequent guidelines recommended stopping prophylaxis within 24 hours. Over time as evidence increased that postoperative administration of prophylaxis did not reduce SSI rates both WHO and CDC published guidelines recommending that no prophylaxis be given after the incision is closed. A very comprehensive meta-analysis showed that if prophylaxis was administered within 60 minutes before incision and repeated if the operation extended more than 2 half-lives beyond the first dose there was no benefit at all to any doses given after incision closure. Subsequent papers demonstrating the same results for a variety of surgical cases have been published. Other papers demonstrate an increase in antibiotic resistance and infections with resistant organisms with prolongation. There is also an increased risk of *Clostridioides difficile* infections in patients when prophylaxis is prolonged.

Another issue that has been controversial for many years is the use of oral antibiotic prophylaxis with or without a mechanical bowel prep (MBP) the day before a colorectal operation. In the 1970's MBP alone before colectomy was common practice but without evidence for its benefit. The first controlled trial of oral

antibiotics comparing neomycin plus tetracycline in 1974 showed an SSI reduction from 43% to 5% (p<0.01). This was followed by a study of neomycin plus erythromycin that showed an SSI reduction from 43% to 9% (p=0.0001) and a study of neomycin plus metronidazole with a reduction from 42% to 18% (p<0.01) and a study of kanamycin plus erythromycin with a reduction from 41% to 8% (p<0.001). Over the next several decades oral prophylaxis became mostly standard in North America but not in Europe. The introduction of ERAS protocols in Europe showed fairly good results with the elimination of MBP in patients not getting oral antibiotics, and as this information circulated in North America, many surgeons stopped doing MBP and also dropped oral antibiotics. An analysis of over 27,000 patients in the NSQIP program showed that 23% received no prep at all while 33% received MBP without oral antibiotics. For the remaining patients, MBP plus oral antibiotics had an odds ratio for SSI of 0.39 (0.33-0.46). A meta-analysis from 2020 covering 55 publications and 12,297 patients concluded that the combination of oral plus IV prophylaxis compared to either IV alone or oral alone had an odds ratio of 0.48 (0.38-0.62). The issue of whether MBP is needed in addition to oral antibiotics for best results continues to be controversial, but recent retrospective reviews show better results with the combination.

Conclusion

In conclusion, when all of the evidence is examined for surgical antibiotic prophylaxis, one finds that risk is reduced for all procedures. The benefit depends on the baseline risk for SSI and the morbidity when it occurs. It is important to choose a drug that is effective against the organisms that commonly are found in SSIs that follow that procedure. If SSIs in the institution where the procedure is being done typically exhibit resistance to commonly used prophylactic agents then consideration should be given to changing the protocols. If a patient is known to be colonized with resistant organisms, then prophylaxis should be altered to account for that. An adequate dose should be given considering the patient's weight. If prophylaxis is given only during the operative case and stopped at incision closure it is advisable to give a larger dose for optimal benefit. The prophylaxis should be given before incision, and giving it fairly close to the incision ensures good antibiotic levels for longer durations of the case. If the operation continues past 2 half-lives after the precision dose, then it should be repeated during the procedure. Stop when the incision is closed. For patients having colo-rectal procedures, current evidence supports the combination of preoperative MBP with oral antibiotics the day before the operation and IV prophylaxis at the time of the procedure.

Competing interests

The author has no financial and non-financial competing interests to declare.

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Chapter 116

The strict synergy between Enhanced Recovery After Surgery programmes and infection prevention and control

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Introduction

Enhanced Recovery After Surgery (ERAS), is a multimodal perioperative care pathway designed to minimize the impact of surgery on patients, facilitating early recovery. Enhanced recovery programs incorporate various interventions aimed at reducing perioperative stress, restoring physiological functions early in the postoperative phase, minimizing biochemical and metabolic alterations caused by surgery, and accelerating discharge times. These protocols are changing the dogmatic approach to perioperative care by introducing and promoting the application of evidence-based medicine.
The key element of the enhanced perioperative care protocols is their multimodal, holistic and interdisciplinary approach, which is patient-centred and focuses on optimizing patients' physical condition before and during surgery. Moreover, these protocols aim to identify, during the intra- and postoperative phases, the main factors that cause stress and are thus responsible for outcomes, with the goal of minimizing their effects.
Surgery leads to several changes in patients, such as neurohormonal alterations. Although these changes represent a cellular defense mechanism triggered by surgical trauma, they appear to be involved in the development of significant postoperative complications in patients who are likely predisposed. All interventions of the perioperative care protocols focus on reducing trauma related to surgery, catabolic stimulation, cytokine release, and postoperative immunosuppression, in order to promote a faster recovery and decrease the risk of complications.
Perioperative care protocols include different interventions, each strictly linked to the others, applied during the preoperative, intraoperative and postoperative periods. Each intervention is interconnected: when used together as a bundle of treatment, they can decrease postoperative stress responses, reducing the duration of postoperative ileus, surgical complications, incisional pain, recovery time, and length of hospital stay. Therefore, it is challenging, or even impossible, to assess the effectiveness of any single measure without considering the collective impact of all interventions, applied together (**Figure 1**).

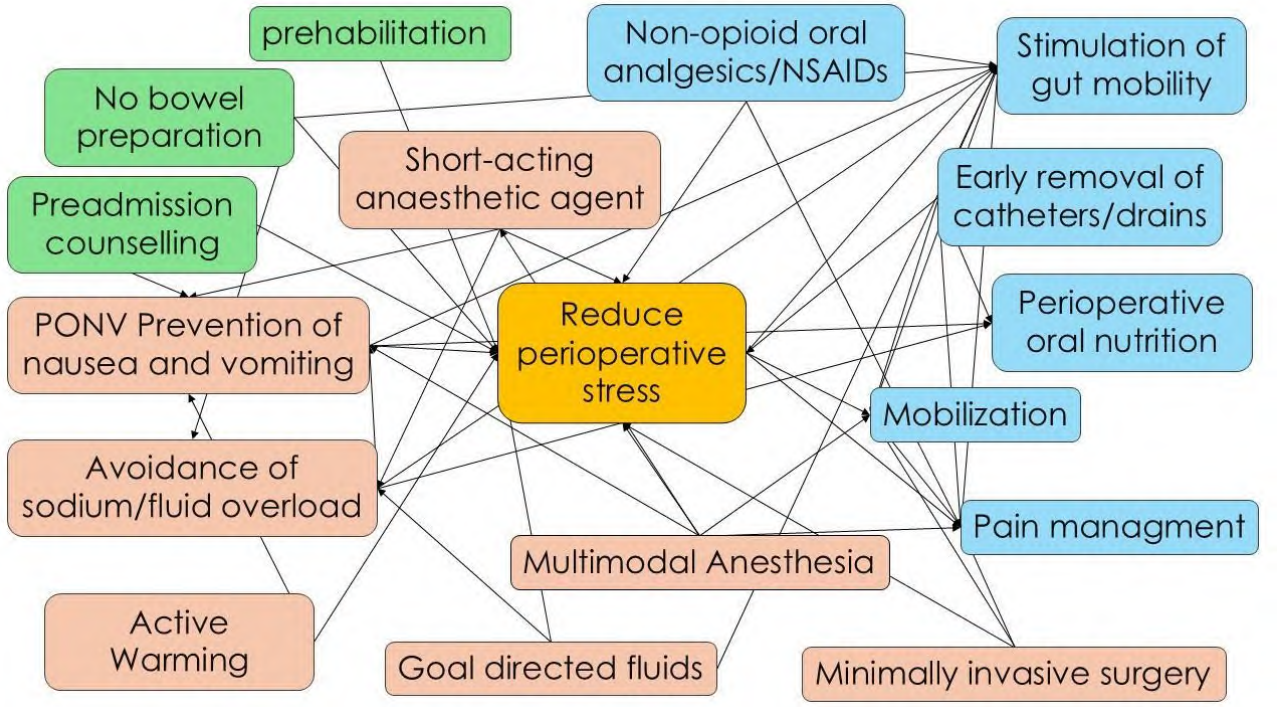

Figure 1. Interconnection among enhanced perioperative care items. Green: preoperative items; orange: intraoperative items; blue: postoperative items (Adapted from Ceresoli M, *et al.* 2023).

Preoperative interventions

Enhanced perioperative care protocols focus on the preoperative phase with the goal of optimally 'preparing' the patient for surgery. These interventions are designed to optimize clinical conditions both in the immediate hours before the surgery and in the days leading up to it. One cornerstone of this approach is patients' counselling and education, with the patient directly involved as the "protagonist and main actor" in the entire perioperative pathway.

Prehabilitation

Prehabilitation is a stage within the continuum of care that takes place from the time of diagnosis until the start of surgery. This process involves physical, nutritional, and psychological evaluations aimed at enhancing physical and mental well-being, thereby reducing the severity of future impairments. Prehabilitation shows promising results in the recovery of functional capacity and it is demonstrated the association between increased preoperative aerobic capacity and a reduction in postoperative complications.

Antimicrobial prophylaxis

Two key components of antimicrobial prophylaxis for preventing surgical site infections (SSI) following gastrointestinal procedures are antibiotic selection and timing of administration, to optimize tissue concentration at the time of surgery. SSIs are common and may account for 16% of all hospital-acquired infections. They are often localized to the incision site but can also extend into deeper adjacent structures.

Antibiotic prophylaxis is strongly recommended, administered as a single dose, intravenously (or orally in patients undergoing mechanical bowel preparation) within 60 minutes before the surgical incision, combined

with skin decontamination using antiseptic solutions, but without the need for trichotomy. This combination of prophylactic measures is associated with a statistically significant reduction in the incidence of wound infections.

Bowel preparation

Traditionally colorectal surgery was preceded by mechanical bowel preparation to reduce the intestinal bacterial flora and minimize the risk of intraoperative contamination. However, mechanical bowel preparation can lead to dehydration and electrolyte imbalances, which are known risk factors for complications, particularly in frail patients. Several studies demonstrated the non-inferiority of avoiding mechanical bowel preparation in SSI rates. Current guidelines do not recommend any type of bowel preparation before surgery, as the risks outweigh the benefits.

Avoid Fasting

ERAS protocols minimize the perioperative fasting period, allowing patients to eat until six hours before surgery and suggesting preoperative oral hydration up until two hours before anaesthesia, including up to 500 mL of clear liquid or an oral carbohydrate drink two to three hours before surgery. This practice has been suggested as a method to shift the patient from a "fasted" to a "fed" state, reducing postoperative insulin resistance and weight loss. Additionally, this approach helps avoid symptoms of dehydration and hypoglycemia, and reduces the incidence of preoperative fluid and electrolyte deficits, thereby decreasing the need of intraoperative fluid.

CHO load e blood glucose control

Preoperative administration of oral carbohydrates (complex CHO-maltodextrin, 12.5%, 285 mOsm/kg, 800 ml in the evening before surgery and 400 ml 2–3 h before induction of anaesthesia) has been shown to attenuate the catabolic response induced by overnight fasting and surgery. Carbohydrate loading improves preoperative well-being, reduces postoperative insulin resistance, decreases protein breakdown and better maintains lean body mass and muscle strength, with additional beneficial cardiac effects. It is also associated with a reduced risk of hyperglycemia.

Perioperative hyperglycemia has been linked to adverse clinical outcomes, including poor wound healing and increased postoperative infection rates. Hyperglycemia increases the risk of postoperative morbidity, mortality, intensive care unit admission and hospital length of stay. So, careful blood glucose control positively impacts the reduction of surgical site infections.

Smoking and alcohol cessation

ERAS guidelines recommend smoking cessation in the preoperative period with 4-8 weeks of abstinence necessary to reduce respiratory and wound-healing complications. Indeed, patients who smoke have an increased risk of intra- and postoperative complications. Alcohol abuse also increases postoperative morbidity, particularly infections, so preoperative abstinence for 4 weeks is recommended.

Intraoperative interventions

Enhanced perioperative care involves several interventions by the surgeon and the anaesthesist, all focused on reducing surgical stress. Intraoperative strategies in ERAS protocols include the selection of anaesthetic agents and techniques, lung-protective ventilation, fluid management, prevention of hypothermia, surgical approach choice and drain placement.

Anaesthetic protocol

The ERAS anaesthetic approach includes using only short-acting anaesthetic agents, at the lowest possible doses, avoiding long-acting opioids and premedication to reduce the risk of dose-dependent postoperative sedation and respiratory depression, in particular, if an opioid is administered. This opioid-sparing approach allows for rapid awakening with minimal residual effects. Multimodal analgesia is the backbone to reduce opioids, in combination with spinal or epidural analgesia or TAP block when indicated. The benefit of using a multimodal approach to pain management is based on the concept that several multiple pain-reducing mechanisms will improve pain control while avoiding the side effects of each drug. Multimodal analgesia is central to this approach, reducing opioid use and side effects like ileus, respiratory depression and postoperative nausea and vomiting (PONV), which are common and can negatively affect postoperative recovery.

In addition, long-acting neuromuscular blocking agents should be avoided. Cumulative dosing of intermediate muscle relaxants increases the risk of postoperative pulmonary complications. So, monitoring of the level and complete reversal of neuromuscular block is recommended.

Goal-directed fluid therapy

Another cornerstone of the ERAS protocols is goal-directed fluid therapy, a patient-specific approach to hydration, based on hemodynamic monitoring to accurately determine fluid requirements, during the preoperative and intraoperative phases. It is crucial to avoid overly restrictive fluid administration, which can lead to hypotension, hypovolemia, impaired peripheral perfusion, and organ dysfunction. Conversely, excessive fluid administration can increase interstitial oedema, compromised wound healing, and cardiopulmonary complications. A reduced fluid load decreases cardiovascular and respiratory complications. Moderate evidence supports the positive role of goal-directed fluid therapy and epidural anaesthesia in preventing postoperative pulmonary complications. Fluid therapy should be guided by hemodynamic invasive monitoring systems.

Prevention of hypothermia

Perioperative hypothermia impairs host defenses against surgical wound contamination, reducing tissue perfusion and scar formation, which are essential for preventing wound dehiscence and recontamination. Other adverse effects of persistent hypothermia include coagulopathy, decreased platelet function, surgical site infection and sepsis. These complications are associated with longer hospital stays and increased mortality. Trials indicate that temperatures below 35.5°C are associated with various complications in surgical patients. Moreover, patients who are kept normothermic during surgery usually remain normothermic postoperatively. Therefore, monitoring body temperature and applying active warming to maintain normothermia are strongly supported by evidence. Forced air warming or underbody warming mattresses should be used to avoid hypothermia. As mentioned earlier, hypothermia can cause alterations in drug metabolism, negatively affect coagulation, and increase the risk of bleeding, wound infections, and cardiovascular complications.

Surgical technique

The advantages of the laparoscopic approach over open surgery in elective settings are well established. Randomized trials comparing laparoscopic and open colorectal surgery within an ERAS protocol have shown that laparoscopic surgery reduces hospital stay length and complication rates. Minimally invasive surgery is associated with reduced blood loss, shorter hospital stays and recovery times, and lower rates of complications related to the surgical wound, such as infections and incisional hernias It is therefore the recommended approach. Even in emergency settings, when deemed appropriate, guidelines support the use of the minimally invasive approach, which is associated with reduced mortality, blood loss, and length of hospital stay.

The American College of Surgeons recommends using a fascial abdominal wound protector and new closure instruments after abdominal irrigation, along with a glove change, as part of the National Surgical Quality

Improvement Program bundle to reduce SSIs. This has been demonstrated to be an effective way of reducing both superficial and deep SSI.

Abdominal drain

Abdominal drains are placed at the end of surgery to prevent or evacuate hematomas or seromas and detect anastomotic leakage early. However, recent evidence does not show a statistically significant difference in outcomes between patients who receive drains and those who do not. Indeed, drains are not associated with reduced rates or earlier detection of collections but are linked to delayed hospital discharge and an increased risk of surgical site infections. Abdominal drains do not reduce the rate of anastomotic leaks, re-operations, wound infections, or mortality. Therefore, ERAS protocols, which aim to minimize invasiveness and restore physiological status quickly, do not recommend the routine use of drains. Additionally, the presence of abdominal drains can hinder patient mobilization, increasing the risk of infectious complications.

Postoperative interventions

The postoperative phase of an enhanced perioperative care protocol is characterized by the rapid recovery of physiological functions. The cornerstones of treatment are early nutrition and mobilization, with the removal of drains and catheters. These interventions are both goals and outcomes of the preoperative and intraoperative phase.

Nasogastric tube

The placement of a nasogastric tube after surgery has the aim of reducing gastric distension and the risk of vomiting. However, all recent data show that the routine use of a nasogastric tube is associated with negative consequences, such as respiratory tract infections and delayed return of intestinal function. As a result, guidelines recommend early removal in the postoperative period or, if there are no contraindications, at the end of surgery.

Pain management and mobilization

Optimal perioperative pain management enhances recovery after surgery by facilitating early mobilization and rehabilitation. Early mobilization is crucial in reducing the risk of postoperative pneumonia and venous thromboembolism. Indeed, it is a fundamental component of ERAS programs.

Prolonged immobilization is associated with an increased risk of pulmonary complications, thromboembolism, insulin resistance, and sarcopenia. Among the factors mentioned, early mobilization is likely the most patient-dependent, influenced by various factors such as inadequate pain control, administration of infusion therapy, persistence of the urinary catheter, patient motivation and pre-existing comorbidities. It is essential for medical and nursing staff to encourage adherence to mobilization, including potential physiotherapy support.

Urinary catheters

To aid with early mobilization, urinary catheters should be removed as soon as possible, a practice that also reduces the incidence of urinary tract infections after surgery. Significant complications of catheter-associated urinary tract infections (UTIs) could include sepsis, bacteremia, and upper urinary tract involvement. It is important to note that approximately 20 percent of healthcare-associated bacteremias originate from the urinary tract, with a mortality of about 10 percent.

Oral feeding

Delaying the resumption of oral feeding after major surgery does not benefit the recovery phase; instead, it increases the risk of infectious complications and prolongs the length of hospital stay. In contrast, early refeeding reduces the risk of postoperative nausea and vomiting, accelerates the return to normal gastrointestinal function, and facilitates rapid discharge without increasing readmission rates. Guidelines recommend that, for most patients, oral feeding should be resumed on the day of surgery or as soon as possible.

Postoperative fluids

Postoperative intravenous fluids should be limited and maintained only until patients can adequately consume fluids orally. Fluid therapy should ensure sufficient hydration and tissue perfusion until oral intake is resumed. This approach allows fluids to be taken physiologically, reducing the presence of venous catheters, and consequently lowering the risk of associated infections.

Evidence supporting ERAS positive impact on infections

Numerous meta-analyses comparing standard care with the enhanced perioperative care approach demonstrate that the application of ERAS protocols reduces the length of hospital stay and the rate of postoperative complications, particularly non-surgical complications. This is a significant finding, as reducing the length of hospital stay is inevitably associated with a lower risk of hospital-acquired infections. Additionally, no statistically significant difference has been observed in the rate of readmissions within 30 days of surgery or in the average 30-day mortality rate.

The correlation between adherence to ERAS protocols and the reduction in complication rates, particularly infectious complications, is causal. Data from an important meta-analysis, which includes 16 RCTs, confirm that the ERAS pathway significantly shortens the length of stay, while readmission rates remain similar to those of the control group.

Early removal of the nasogastric tube at the end of surgery, along with early mobilization, reduces the incidence of respiratory complications. Similarly, a reduced fluid load decreases both cardiovascular and respiratory complications, and early removal of the urinary catheter lowers the incidence of urinary tract infections. The ERAS pathway significantly reduces overall postoperative morbidity, particularly non-surgical complications.

In addition, the application of ERAS protocols results in a reduction in respiratory complications and urinary tract infection rates. Actually, respiratory and cardiovascular complication rates were very low in the ERAS group. This is likely due to the beneficial effects of perioperative fluid restriction, the absence of a postoperative nasogastric tube, epidural analgesia, avoidance of long-acting opioids, and earlier mobilization. The restriction of intra- and postoperative intravenous fluids improves both lung and cardiac function, and early bladder catheter removal reduces urinary tract infections. Evidence of the significant reduction in non-surgical complications is consistent with the beneficial effects of the ERAS pathway, even in elderly patients and those with severe comorbidities.

Conclusion

In conclusion, the evidence demonstrates that the application of ERAS protocols significantly improves surgical outcomes, leading to a notable reduction in postoperative complications, particularly SSIs, pulmonary complications and urinary tract infections. The strict synergy between enhanced recovery after surgery

programmes and infection prevention and control is a reality. The broader the application of ERAS pathways, the greater the positive impact, making a meaningful difference in the global alliance against infections.

Competing interests

The authors have no financial and non-financial competing interests to declare.

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Chapter 117

Deciding on the extent of source control in patients with surgical infections

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Introduction

We must make challenging decisions regarding the extent, type and timing of source control required in the treatment of patients with surgical infections. This decision is made based, in part, on patient-related (comorbidities and physiologic condition) and infection-related (type and severity of infection) factors. In patients with necrotizing soft tissue infection, immediate aggressive surgical debridement is required to reduce mortality. But in other surgical infections (necrotizing infected pancreatitis, intra-abdominal abscess) a percutaneous and minimally invasive approach is associated with better outcomes. Even in patients with acute cholecystitis or acute appendicitis, optimal source control ranges from a surgical approach (cholecystectomy, appendectomy) to percutaneous cholecystostomy or percutaneous appendiceal abscess drainage. It is important to understand our knowledge to date regarding the extent and adequacy of source control procedures in different types of surgical infections.

Source control

Source control in surgical infections

Source control is defined as all measured undertaken to eliminate a source of infection and control ongoing contamination. This may require abscess drainage (percutaneous or open), infected or necrotic tissue debridement, resection of a diseased or infected organ (appendix, gallbladder), suture or resection of perforated bowel, ongoing microbial contamination control, or infected device removal (**Figure 1**). Failure to obtain adequate source control is a significant risk factor associated with increased adverse outcomes and mortality. However, we do not yet have a universally accepted definition of the “adequacy” of source control in all different types of surgical infections, particularly related to the extent, type and timing of source control.

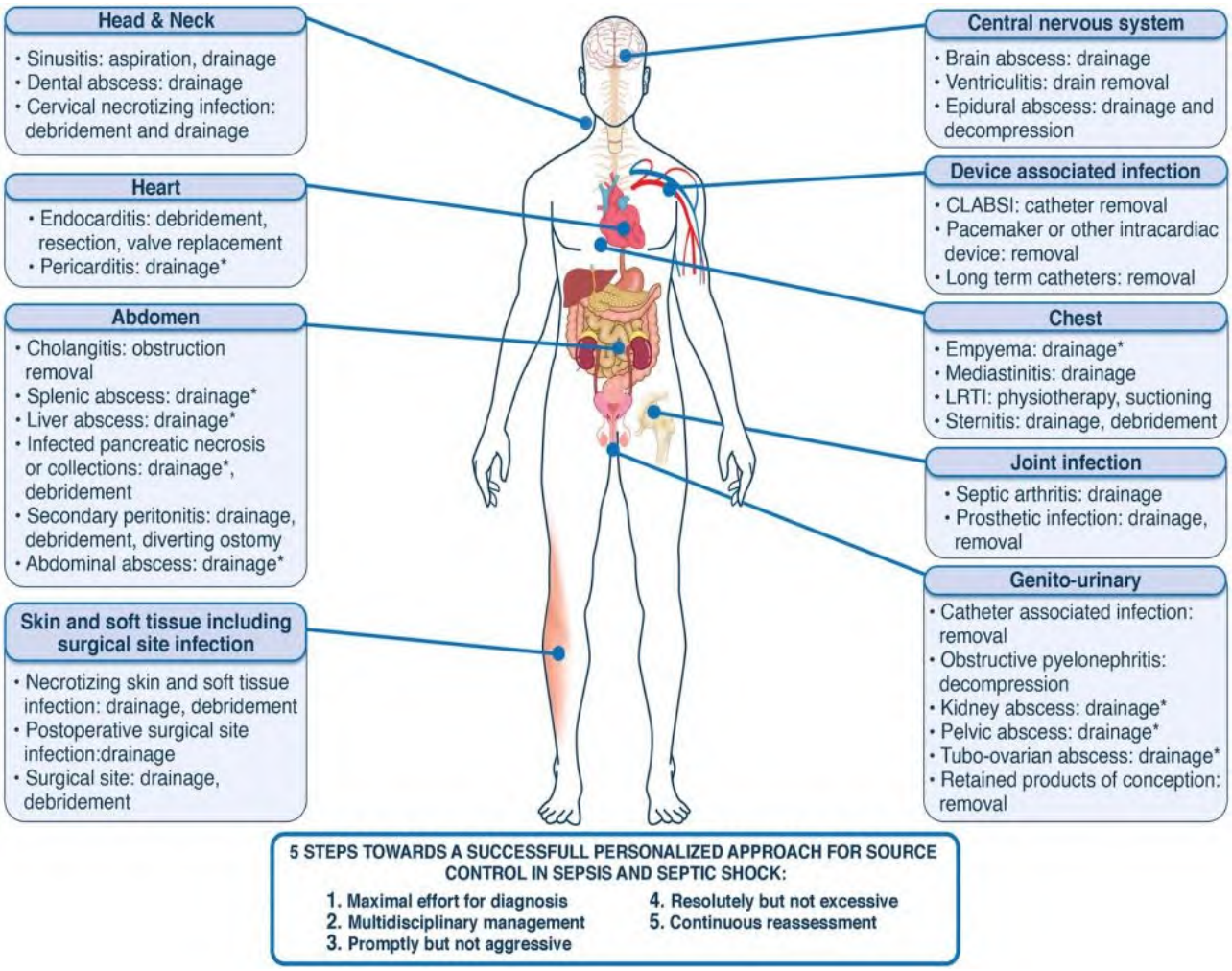

Figure 1. Overview of the different types of infections where source control should be considered, including possible approaches to achieve source control. *Minimally invasive approach preferred (Adapted from DeWaele JJ, *et al.* 2022).

Source control in Intra-abdominal Infection (IAI)

The 2023 multi-society Guidelines for Source Control in Emergency General Surgery proposed a detailed working definition of comprehensive source control in IAI. This includes the removal of all macroscopic gross intra-abdominal contamination to ensure the cessation of any further contamination, and "all physiological/pharmacological/interventive measures used to control a focus of infection, to modify factors in the infectious milieu promoting microbial growth or impair host antimicrobial defenses, and to allow recovery to homeostasis or "physiological equilibrium".

Patient stratification includes:

- Class A: Healthy patients with no or well-controlled comorbidities and no immunocompromise, where the infection is the main problem.
- Class B: Patients with major comorbidities and/or moderate immunocompromise but currently clinically stable, in whom the infection can rapidly worsen the prognosis.
- Class C: Patients with important comorbidities in advanced stages and/or severe immunocompromise, in which the infection worsens an already severe clinical condition.

They also provided recommendations regarding the appropriate timing of source control that includes both the patient's clinical condition, the type and severity of the infection and the potential evolution of the infection and disease (**Figure 2**).

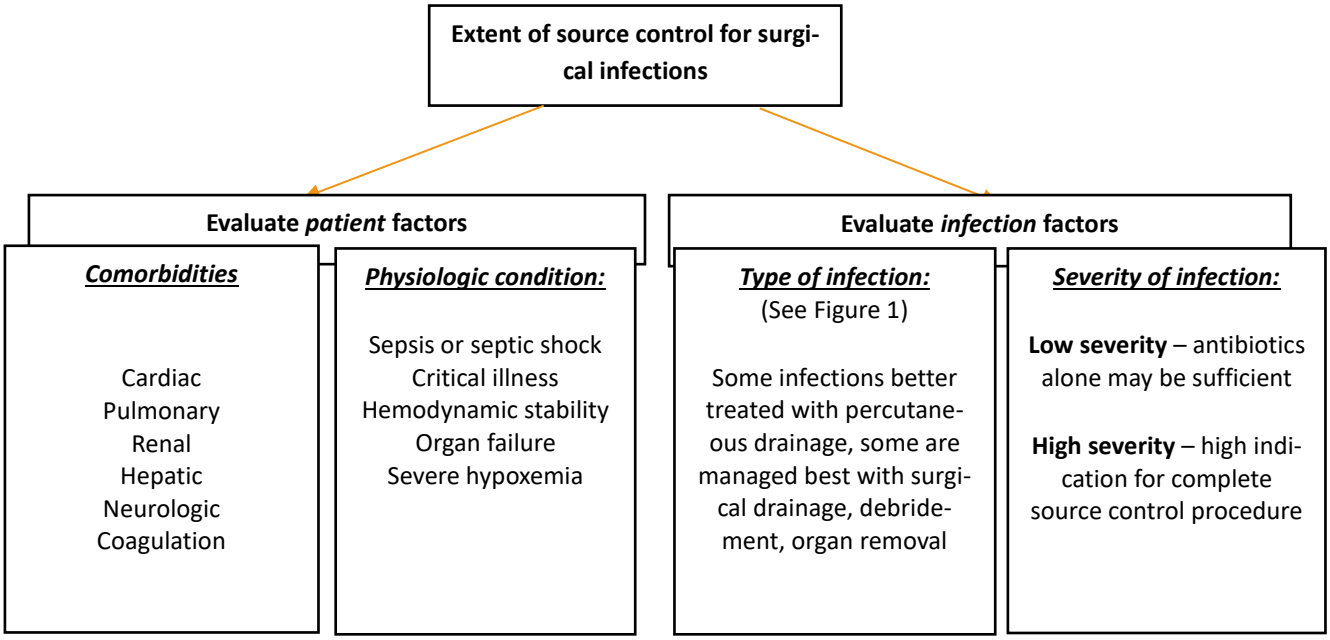

Figure 2. Factors to consider when determining optimal source control for surgical infections for an individual patient. The least invasive procedure that provides maximal source control is optimal.

Time to source control

A shorter time to source control is associated with reduced mortality, particularly in patients with complicated IAIs, cholangitis and necrotizing soft tissue infections. The Surgical Infections Society Guidelines on the Management Intra-abdominal Infection (IAI) 2024 recommends undertaking source control within 6 hours in high-risk patients with associated septic shock (Grade 1-B) and within 12 hours in lower-risk patients (Grade 1-B).

A systematic review and meta-analysis (9 studies, n=3,373) of patients with IAI (acute diverticulitis, gastrointestinal perforation, complicated appendicitis, or peritonitis) requiring surgical intervention reported that early surgical source control (before 12 hours) was associated with significantly lower mortality, procedure-related complications and hospital length of stay. Surgical source control within 6 hours on subgroup analysis had significantly higher survival. Specifically in the subgroup analysis of patients with septic shock due to gastrointestinal perforation, mortality significantly increased with delay in source control and was 100% with delays greater than six hours.

A planned secondary analysis of a cluster-randomized, multi-center trial of 4,792 adult ICU patients with sepsis with at least one new organ dysfunction and 1595 patients undergoing surgical source control reported that delay in surgical source control significantly increased the risk of death in patients with septic shock (adjusted OR = 1.013 [1.001, 1.026], p=0.04).

A recent cohort study of community-acquired sepsis patients (n=4962) undergoing source control interventions across a 14-hospital integrated healthcare system (community and academic hospitals) reported that source control within 6 hours was associated with a 29% reduction in the risk-adjusted odds of 90-day mortality compared with delayed source control. In multivariable models, early source control was associated

with decreased risk-adjusted odds of 90-day mortality (aOR, 0.71; 95% CI, 0.63-0.80). This association was greater among gastrointestinal and abdominal (aOR, 0.56; 95% CI, 0.43-0.80) and soft tissue interventions (aOR, 0.72; 95% CI, 0.55-0.95) compared with orthopedic and cranial interventions (aOR, 1.33; 95% CI, 0.96-1.83; p<0.001 for interaction). These data support prioritizing rapid identification of septic foci and initiation of source control interventions within 6 hours of sepsis onset.

The optimal time to source control in specific surgical infections has not yet been delineated in different types of surgical infections. There is an urgent need to define the critical time period for establishing source control for different infections, and when to consider a staged approach.

Source control in sepsis/septic shock and bacteremia

Adequate and early source control is particularly important in patients with sepsis and septic shock, as delay in adequate source control is associated with adverse outcomes including death. The 2021 Surviving Sepsis Campaign guidelines recommend rapid identification of septic foci with prompt source control (within 12 hours after diagnosis) as logistically feasible.

The European Society of Intensive Care Medicine-endorsed Abdominal Sepsis Study (AbSeS, n=2621) found that patients who did not achieve source control had a significantly increased risk of death (1.9-fold higher). Achievement of adequate source control at day 7 was associated with significantly lower mortality (17.2% *vs.* 51.8% for persistent inflammation and 28.3% for those requiring surgical revision, p<0.001). In a post-hoc analysis of the AbSeS study of 1077 cases of secondary peritonitis, the highest mortality risk was associated with septic shock (OR 3.08), late-onset hospital-acquired peritonitis (OR 1.71) and failed source control (OR 5.71).

The EUROBACT multicenter cohort study (n=1156) reported that uncontrolled infection source was an independent risk factor for 28-day all-cause mortality (OR, 5.86; 95% CI, 2.5–13.9) in hospital-acquired bloodstream infection patients. Septic shock was present in 45.8% of patients, with multi-drug-resistant (MDR) pathogens identified in 50.7% of patients and the overall 28-day all-cause fatality rate was high (36%) in these patients. These data confirm that adequacy of source control and appropriate antibiotic therapy are needed to optimize ICU patient outcomes.

Types of source control

Source control can be achieved by both surgical and non-surgical (percutaneous drainage) methods. Source control in patients with surgical infections should be achieved in the least invasive method as long as the adequacy of source control is not compromised. Adequacy of source control is much more important than the particular method used to achieve source control.

A personalized approach to source control is recommended, and a number of factors should be considered when determining the optimal method of source control. Specific patient characteristics (coagulopathy, bleeding risk, hostile abdomen, stability of ICU patient, need to perform procedures bedside, etc.), infection characteristics (abscess size and location, localized or diffuse infection, intestinal perforation, device-related infection, etc) and institutional resources will all influence this important decision-making of best approach for source control.

When percutaneous drainage approaches are chosen for source control, these are best performed with image guidance, including ultrasound- or computed tomography (CT)-guided percutaneous drainage, to minimize the risk for procedure-associated complications. In some cases, an abscess may be too small for image-guided percutaneous drainage, and aspiration of the abscess is recommended if feasible to determine the pathogenic bacteria and antimicrobial susceptibilities to ensure appropriate antimicrobial therapy.

Extent of source control

We all agree that we should use the least invasive procedure that provides maximal source control in the treatment of surgical infections.

Percutaneous drainage and minimally invasive surgical procedures (laparoscopic or robotic) are preferred if feasible, as long as infection source control can be achieved with these methods.

An area of significant controversy is how to determine the optimal extent of source control in surgical infections, and when to consider a potential staged approach. For instance, it is clear that immediate source control with surgical debridement is required for necrotizing soft tissue infection – decreased time to adequate surgical debridement is associated with significantly reduced mortality. But for select patients with localized infection and no evidence of sepsis or septic shock (such as acute diverticulitis with pericolic abscess, no peritonitis), percutaneous infection drainage with appropriate antibiotics is the recommended approach, with consideration for potential surgical intervention for colectomy at a later date dependent on the patient's response.

Stable patients can be considered for a personalized approach to source control of infection, including the patient in the decision-making process. For instance, stable patients with infected abdominal wall mesh and an abscess might choose a staged approach. This could include initial percutaneous drainage of associated abscess and culture-directed antimicrobial therapy to determine if this is adequate treatment, with consideration of surgical removal of infected mesh if the patient did not respond to the initial non-surgical treatment strategy.

The initial recommended source control for complicated appendicitis patients with abscess and phlegmon is percutaneous drainage and antibiotics since early definitive surgical intervention might warrant a more extensive operative procedure (ileo-cecectomy *vs.* appendectomy). Most patients fully resolve this IAI with this approach and then undergo interval appendectomy at a later time point related to the potential risk of recurrent appendicitis and possible underlying cancer.

The recommended optimal treatment strategy for source control in patients with necrotizing infected pancreatitis is non-surgical, with a "step-up" approach. Percutaneous and endoscopic drainage are recommended for walled-off infected necrosis, with transition to video-assisted retroperitoneal debridement (VARD) if percutaneous drainage or endoscopic drainage alone is not successful. Multiple randomized trials have definitively confirmed that this approach significantly reduces mortality. This is an excellent example of modification of the extent of source control of necrotizing infected pancreatitis over time, dependent on the patient's response to the initial percutaneous and endoscopic non-surgical therapies. In these challenging cases, it is advantageous to follow evidence-based algorithms with careful and frequent assessment of the individual patient's response to treatment. In some cases, the patient will not respond to this non-surgical approach, or associated complications (such as colon perforation) may occur which will warrant maximal surgical treatment with laparotomy.

In patients with complicated IAI and sepsis/septic shock, which is associated with very high mortality rates, it is unknown whether a staged approach with initial surgical source control followed by an open abdomen approach with negative pressure peritoneal therapy to remove inflammatory ascites and allow a second-look laparotomy to achieve adequate source control may improve patient outcomes. This potential therapeutic paradigm is the rationale being assessed in the COOL trial (Closed Or Open after Laparotomy) (https://clinicaltrials.gov, NCT03163095, https://coolstudy.ca/), the largest prospective randomized trial with a primary outcome measure of 90-day mortality.

It is uncertain whether a precision medicine approach would be best in the treatment of surgical infections, including the determination of the extent of the optimal source control procedure. Precision medicine relies on the identification of individual patient characteristics, including genetic profile, to determine optimal

therapies and treatments. This approach is now standard in cancer and cardiovascular therapies, and is emerging in the treatment of sepsis and septic shock, but is not yet standard in the treatment of surgical infections. In order to move successfully toward this personalized approach, future studies are clearly warranted.

Adequacy of source control in surgical infections

We all agree that adequate source control is of crucial importance in the treatment of surgical infections, and incomplete source control has adverse effects on patient outcomes, especially in critically ill patients with sepsis and septic shock. Many studies have confirmed that both inadequate source control and administration of inappropriate empiric antibiotics (did not cover causative pathogens) are independent predictors of increased mortality and adverse outcomes in patients with surgical infections.

However, determination of the adequacy of source control in surgical infections is very challenging. It is very clear that we need an accurate universal definition of adequate source control to be able to determine if the extent of source control that we choose for any individual patient is appropriate and optimal.

Previous definitions of 'adequate source control' have focused on the degree of technical success, i.e. the procedure was performed successfully without complication. However technical success is not always consistent with the resolution of infection by the source control procedure. For instance, if a percutaneous drain was placed in a diverticular abscess successfully by Interventional Radiology, but the abscess did not completely resolve, that may be considered a failed source control procedure. But if the patient improved clinically with that drain and antibiotics, it may be considered a partial success, to bridge to a second percutaneous drain or surgical source control.

In clinical trials of new antimicrobial therapy for complicated IAI, the adequacy of surgical source control has usually been assessed independently and determined by a separate attending surgeon panel review of the source control procedure.

In a classic single-center study of critically ill patients with bacteremia and severe sepsis due to an IAI source (n=108), failure to achieve adequate source control AOR 7.46, p=0.002) and administration of inappropriate antibiotics (AOR 3.86, p=0.16) were independent predictors of mortality (overall mortality 28%). The adequacy of source control was assessed independently by two board-certified surgeons. Inadequate source control required concurrence from both surgeons; if different opinions, the determination was adequate source control. Adequate source control was defined as having a timely percutaneous, endoscopic, laparoscopic, or open abdominal procedure to drain infected fluid collections, debride infected tissues, and control ongoing enteric or other drainage producing peritonitis and performed within 24 hours. When temporizing procedures were performed (damage control laparotomy or temporary abdominal drainage) adequate source control was determined if widespread enteric leakage was addressed, and a plan was established for a more definitive procedure within the next 24–72 hours. In patients with infected pancreatic necrosis, temporizing measures were considered adequate source control as long as further procedures were to be undertaken. Subsequent recurrence or worsening of intra-abdominal infection was not utilized in this study as a criterion for judging the adequacy of the index source control procedure. Using these definitions in this study, 83 of 108 (77%) patients were determined to have adequate source control. This likely reflects an overestimate of adequate source control based on the definitions used in this study.

Future research in source control

So how should we define the adequacy of source control of surgical infections in the future, especially if we are modifying the extent of source control based on patient-related and infection-related factors? Should we consider the inclusion of biomarkers, inflammatory markers, resolution or worsening of sepsis and septic

shock, resolution or worsening of organ dysfunction and failure related to the surgical infection by use of SOFA or multiple organ failure scores from baseline to following source control procedures?
It is critical to ensure that timely adequate source control and initiation of appropriate empiric antibiotics are provided to all patients as foundational treatment of surgical infections in all future clinical trials, particularly in the treatment of complicated IAIs. The PEPPER (Prospective, Randomized Trial of Personalized Medicine with Pentaglobin® After Surgical Infectious Source Control in Patients with Peritonitis) multicenter clinical trial, currently recruiting patients in Germany/Austria, has attempted to ensure this by detailed Inclusion Criteria for the PEPPER clinical trial listed below.
Inclusion criteria:

1. The patient is diagnosed with secondary or quaternary peritonitis
2. The time of the surgical infectious source control is within 6 hours of indication (defined as date and time of registration for surgical or minimal invasive procedure).
3. Sepsis and/or septic shock (according to the current sepsis guideline of the German Sepsis Society).
4. SOFA Score ≥ 8.
5. The concentration of IL-6 is ≥ 1000 pg /ml.
6. Treatment with antibiotics is started within 12 hours of admission to the Intensive Care Unit.

We also need to continue our ongoing global discussions about the adequacy, extent, type and timing of source control in surgical infections. The STOP study [Source Control in the management of abdominal sepsis (STOP)] was conceived and designed as a survey by the World Surgical Infection Society (WSIS) and the World Society of Emergency Surgery (WSES) to assess the practice of emergency and acute care surgeons in performing source control for IAI management. The goal is to assess the standard of surgical practice in source control from a global perspective.
Finally, how much of the patient's clinical improvement is related to the adequacy of source control *vs.* their genetic and immune pre-determined immune and inflammatory response to the surgical infection? An individual's innate immune response to surgical infection is widely variable, with some patients manifesting hyper-inflammation and others immune paralysis. Current research efforts in sepsis have transitioned to providing a "personalized immunotherapy" approach, defined as the classification of patients into distinct subgroups or subphenotypes, in which a patient's immune profile is used to guide personalized sepsis treatment. The ImmunoSep (Personalized Immunotherapy in Sepsis) randomized clinical trial (NCT04990232) is a first-in-class paradigm of precision medicine for sepsis.

Conclusion

The extent of source control of surgical infections requires very careful decision making to achieve optimal patient outcomes. It must include the personalized assessment of patient factors (comorbidities and physiological status) and infection factors (type and severity of infection) to determine the optimal extent, method and timing of source control for any individual patient. It is clear that different surgical infections warrant different source control procedures for optimal patient outcomes. In all future clinical trials to assess the efficacy of antimicrobials or new novel therapies in surgical infections, we must ensure the foundation of adequate and timely source control and appropriate empiric antibiotic therapy. Future studies are warranted to determine a universal definition for adequate source control, particularly if source control procedures are staged, with percutaneous and minimally invasive procedures used first, with subsequent assessment of patient response to determine if additional procedures are required for complete source control. Additional

studies should examine the efficacy of personalized extent of source control based on both patient- and infection-related factors.

Competing interests

The authors have no financial and non-financial competing interests to declare.

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Chapter 118

Non-necrotizing skin and soft tissue infections. Principles of treatment

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Introduction

Skin and soft tissue infections (SSTIs) are widespread conditions that vary in severity, ranging from mild to severe, potentially life-threatening conditions. They occur due to the invasion of the skin and its underlying structures by microorganisms. The incidence of SSTIs has risen in recent years, largely due to an ageing population, an increasing number of critically ill and immunocompromised individuals, and the emergence of multi-drug-resistant pathogens. These infections are associated with high rates of treatment failure, relapses, and significant healthcare costs.

Various classification systems have been used to describe SSTIs, including variables such as anatomic location, causative pathogen(s), rate of progression, depth of infection, and severity of clinical presentation. They are summarised in **Table 1**.

Non-necrotizing skin and soft tissue infections (NNSSTIs) encompass a variety of infections affecting the skin, subcutaneous tissue, and deeper layers, without the extensive tissue destruction seen in necrotizing infections. Conditions within this category—such as cellulitis, erysipelas, impetigo, folliculitis, and abscesses—are common across all demographics but are particularly prevalent in immunocompromised patients and those with chronic conditions. Although NNSTIs are generally less severe than necrotizing infections, they can still cause significant morbidity if not treated properly. Additionally, underlying conditions such as diabetes mellitus, obesity, and immunosuppressive states can predispose individuals to NNSSTIs, complicating their management.

Recognizing the early signs and symptoms and prompt treatment of NNSSTI, including antibiotics and, when required, drainage of abscesses plays a vital role in halting the progression of the infection and reducing the risk of further complications.

Table 1. Skin and soft tissues classification (Modified from: Eron LJ, *et al*. 2003; May AK, *et al.* 2009; Stevens DL, *et al.* 2014; Sartelli M, *et al.* 2014; Sartelli M, *et al.* 2022).

Classification system	Year	Category	Description
FDA classification	1998	Uncomplicated SSTIs	Includes superficial infections such as cellulitis, simple abscesses, impetigo, and furuncles, requiring antibiotics or minor surgical incision and drainage.
		Complicated SSTIs	Involves deep soft-tissue infections, infected ulcers, infected burns, and major abscesses requiring significant surgical intervention (e.g., debridement).
Eron classification	2003	Class 1	Patients with no signs of systemic toxicity or comorbidities.
		Class 2	Patients are systemically unwell with stable comorbidities or have comorbidities (e.g., diabetes, obesity) that may delay resolution.
		Class 3	Patients are toxic and unwell with systemic symptoms such as fever, tachycardia, tachypnea, or hypotension.
		Class 4	Patients with life-threatening infections (e.g., sepsis or necrotizing fasciitis).
Anatomical tissue layers	N/A	Superficial infections	Infections limited to the epidermis and dermis (e.g., erysipelas, impetigo, folliculitis, furuncles, and carbuncles).
		Deeper infections	Infections involving the dermis, subcutaneous tissues, fascia, or muscle compartments (e.g., cellulitis, necrotizing fasciitis, myonecrosis).
IDSA guidelines	2014	Purulent *vs.* non-purulent	Divides infections into purulent (e.g., abscesses) and non-purulent (e.g., cellulitis).
		Severity levels	Mild, moderate, and severe infections based on the clinical presentation and need for intervention.
FDA ABSSSI definition	2018	ABSSSI	Includes cellulitis/erysipelas, wound infections, and major cutaneous abscesses, with a lesion size area ≥ 75 cm^2.
WSES guidelines	2015	Surgical site infections (SSIs)	Divided into two subgroups: (a) incisional (superficial and deep) and (b) organ/space infections. SSIs are postoperative infections and considered a separate category.
		Non-necrotizing SSTIs	Includes erysipelas, impetigo, folliculitis, and simple or complex abscesses. These infections may be managed with antibiotics or drainage alone.
		Necrotizing SSTIs	Require surgical intervention, including drainage and debridement, in addition to antibiotics.
WSES/SIS-E expert panel	2018	Based on infection character	Recommends assessing the necrotizing or non-necrotizing nature, anatomical extension, purulence, and clinical condition of the patient for classification.

Abbreviations. FDA: Food and Drugs Administration; IDSA: Infectious Diseases Society of America; ABSSSI: acute bacterial skin and skin structure infections WSES: World Society of Emergency Surgery; SIS-E: Surgical Infection Society of Europe.

Aetiology and pathophysiology

Non-necrotizing SSTIs are typically caused by bacterial pathogens, though fungal and viral agents can also be involved. Aerobic Gram-positive cocci—specifically *Staphylococcus aureus* and streptococcal species—are the most likely cause of SSTIs involving healthy skin.

Streptococcus pyogenes (Group A *Streptococcus*) is one of the most frequent causes of non-purulent SSTIs, especially cellulitis and erysipelas. These bacteria often colonize the skin and enter through breaks in the skin barrier, such as small cuts, ulcers, or abrasions.

Staphylococcus aureus is commonly responsible for purulent infections, such as abscesses, furuncles, and carbuncles. Methicillin-sensitive *Staphylococcus aureus* (MSSA) is the more frequent cause, but in some settings, methicillin-resistant *Staphylococcus aureus* (MRSA) is an important cause, particularly in healthcare-associated or community-acquired SSTIs.

Beyond Group A *Streptococcus*, other streptococcal species (e.g., Group B, C, G *Streptococcus*) may also cause cellulitis, particularly in elderly or immunocompromised patients.

While less common, Gram-negative organisms such as *Pseudomonas aeruginosa*, *E. coli*, and *Klebsiella* species can cause SSTIs in certain populations, particularly in immunocompromised individuals or those with healthcare-associated infections.

Beta-hemolytic streptococci are responsible for nearly 75% of cellulitis cases, while *S. aureus* is more commonly associated with purulent infections like abscesses.

Though simple infections are usually monomicrobial, complicated infections can be either monomicrobial or polymicrobial.

Methicillin-resistant *S. aureus* (MRSA) is a serious global health concern and it is a common pathogen of SSTIs both in community and health-care settings. There are regional variations in MRSA prevalence, with 36% of *S. aureus* strains in North America being resistant, compared to 29.4% in Latin America and 22.8% in Europe. Increases in MRSA SSTIs have been attributed primarily to the rapid emergence of community-acquired MRSA (CA-MRSA) strains since the late 1990s, particularly in the United States. These involve previously healthy individuals without either direct or indirect association with healthcare facilities and have emerged as an important public health problem. Differing from healthcare-associated MRSA (HA-MRSA), which normally contains the type I, II, or III staphylococcal cassette chromosome mec (SCCmec), CA-MRSA isolates contain type IV SCCmec. Some CA-MRSA isolates produce a toxin, Panton-Valentine leukocidin, which may in part be responsible for their increased virulence. Risk factors for presenting SSTIs are summarised in **Table 2**.

Pathogens typically enter through skin disruptions, such as minor cuts, surgical wounds, or preexisting skin conditions. Once the skin barrier is compromised, bacteria invade, leading to infection. The immune system responds by sending white blood cells to the area, resulting in inflammation, which presents as redness, swelling, warmth, and pain. Although NNSTIs do not cause the extensive tissue necrosis seen in necrotizing infections, they still require prompt medical intervention to prevent progression.

Table 2. Risk factors for skin and soft tissue infections.

Risk factor	Description	Impact on infection risk
Host factors		
Diabetes mellitus	Poor glucose control impairs immune response and delays wound healing.	Increases susceptibility to infections such as cellulitis and abscesses.
Obesity	Excess body weight leads to increased sweating, skin breakdown, and poor circulation.	Creates a favorable environment for bacterial growth, raising infection risk.
Chronic skin conditions	Conditions like eczema, psoriasis, and chronic ulcers provide entry points for bacterial pathogens.	Enhances the likelihood of bacterial invasion through compromised skin barriers.
Immunosuppression	Includes those on corticosteroids, chemotherapy, or with HIV or organ transplants.	Compromised immune systems heighten vulnerability to infections.
Elderly patients	Aging leads to decreased immune function and skin integrity.	Older individuals are more prone to infections due to reduced skin elasticity and immune defenses.
Lymphedema/Venous insufficiency	Impaired lymphatic drainage and poor circulation lead to swelling.	Stagnation of fluids in tissues creates a breeding ground for bacteria.
Smoking	Smoking impairs immune response and disrupts tissue oxygenation and healing processes.	Smoking-related reduction in blood flow and immune system function increases the risk of skin infections and delays healing.
Environmental factors		
Injury or trauma	Breaks in the skin, such as cuts, abrasions, burns, or punctures, provide entry points for bacteria.	Increases the likelihood of bacterial invasion.
Surgical procedures	Surgical wounds, particularly contaminated ones, are prone to infection.	Postoperative infections may occur due to exposure to bacteria during or after surgery.
Poor wound care or hygiene	Lack of proper wound care or hygiene, or use of contaminated dressings/equipment.	Increases risk of infection due to improper cleaning and care.
Contaminated water exposure	Contact with contaminated water, especially with open wounds, introduces pathogens such as *Vibrio* species.	Raises the risk of infection, particularly in individuals with compromised immune systems.
Microbial factors		
Colonization with resistant organisms	Carriage of methicillin-resistant *Staphylococcus aureus* (MRSA) or multi-drug-resistant organisms.	Leads to infections that are more difficult to treat due to antibiotic resistance.
Frequent healthcare exposure	Regular hospitalizations or residence in long-term care facilities increases exposure to resistant organisms.	Increased likelihood of colonization with resistant bacteria, leading to more challenging infections.

(cont.)

Table 2. Risk factors for skin and soft tissue infections *(cont.)*

Risk factor	Description	Impact on infection risk
Lifestyle factors		
Intravenous drug use	Direct introduction of bacteria into the bloodstream or tissue.	Elevates the risk of both localized infections and systemic sepsis.
Alcoholism	Associated with poor nutritional status and impaired immune response.	Leads to heightened susceptibility to infections and slower recovery.
Smoking	Reduces tissue oxygenation, impairs immune response, and decreases wound healing capacity.	Increases the risk of delayed healing and susceptibility to infections such as cellulitis and abscesses.

Diagnosis

Accurate diagnosis is essential for guiding the treatment of SSTIs. Differential diagnosis should consider other causes of soft tissue inflammation, such as autoimmune diseases, insect bites, or neoplasms. NNSSTIs are often marked by signs of an inflammatory response, including erythema, warmth, pain, swelling, "fluor" or secretion, *functio laesa* (loss of function) which typically results from pain and swelling, and alongside other localized and systemic manifestations. A thorough clinical examination is the first step in diagnosis, focusing on the characteristics of the skin lesion and any systemic symptoms. Systemic symptoms such as fever, hypotension, and tachycardia can indicate a more serious infection, possibly affecting deeper tissues. Physical findings like fluctuance, bullae, crepitus, purpura, or necrosis suggest a more severe infection, potentially requiring urgent surgical intervention. Rapid symptom progression, lymphangitic spread, and pain disproportionate to physical findings may signal tissue ischemia or necrotizing infections.

Laboratory tests, such as complete blood counts (CBC), inflammatory markers (CRP, ESR), and blood cultures, are useful for assessing infection severity and identifying pathogens. Simple, localized SSTIs may not require laboratory testing, but CBC, metabolic profiles, and C-reactive protein levels are appropriate if the patient may need higher-level care. Wound cultures can have a low diagnostic yield, especially when differentiating between pathogens and normal skin flora, but may be helpful in hospitalized or febrile patients, or those with underlying diseases. Blood cultures are generally of low yield unless risk factors for bacteremia are present.

Imaging studies, including ultrasound (US) and Magnetic Resonance Imaging (MRI), play a crucial role in evaluating the extent of SSTIs, especially when clinical assessment alone is insufficient. The role of the different imaging techniques is summarised in **Table 3**. US is the first-line imaging modality due to its accessibility and lack of radiation. It is particularly useful for identifying fluid collections, such as abscesses requiring drainage, and for distinguishing cellulitis from abscesses or necrotizing infections. Doppler ultrasound can assess blood flow, helping to detect necrotizing infections by identifying reduced vascularity. Computed tomography (CT) scans are highly sensitive for evaluating deeper tissue involvement, especially for suspected necrotizing fasciitis. CT can identify gas within tissues, a hallmark of necrotizing infections, and is also helpful in detecting abscesses and deep-seated infections. Contrast-enhanced CT provides information on tissue perfusion and can identify infections that are more extensive than they appear clinically. MRI is the gold standard for assessing complex SSTIs involving deeper structures such as muscles, fascia, or bones. It is particularly useful

for differentiating between cellulitis, abscesses, and necrotizing infections, and for detecting infection spread along fascial planes, which is vital for managing necrotizing infections.
Prompt imaging, when indicated, helps to differentiate between superficial and deep infections, identify abscesses, and assess the extent of tissue involvement.

Table 3. Imaging techniques in diagnosis of skin and soft tissue infections.

Imaging	Utility	Advantages	Limitations
US	Diagnosis of abscesses, superficial infections; guide for drainage procedures.	Real-time, no radiation, widely available.	Limited depth penetration; operator dependent.
CT	Deep tissue infections, necrotizing infections, gas in tissues, abscesses, and fascial plane assessment.	High sensitivity, detailed anatomical views.	Radiation exposure, less effective for superficial infections.
MRI	Differentiation of soft tissue, deep infections (myositis, fasciitis), bone involvement.	High sensitivity and soft tissue resolution, especially for deeper infections.	Expensive, longer scan times, less accessible, contraindications in some patients (e.g., pacemakers).
X-ray	Detecting gas in tissues (necrotizing infections), quick evaluation for bone involvement (osteomyelitis).	Quick, widely available.	Poor sensitivity for soft tissue infections.

Abbreviations. US: Ultrasound; CT: Computed Tomography; MRI: Magnetic Resonance Imaging.

Principles of treatment

The treatment of non-necrotizing skin and soft tissue infections is built upon three core principles: source control, appropriate antimicrobial therapy, and supportive care.

Source control

Incision and drainage (I&D). In cases of purulent infections, such as abscesses, effective source control begins with drainage of the infected fluid collection. I&D are the definitive treatments for abscesses and, in many cases, may be sufficient without antibiotics. Timely drainage prevents further tissue damage and reduces systemic spread of infection. Evidence supports I&D as the primary intervention, with antibiotics reserved for patients with severe or systemic symptoms or risk factors like immunosuppression. In some NNSTIs, particularly when there is extensive involvement of deeper tissues or in cases unresponsive to medical therapy, surgical intervention may be required. Such interventions can significantly enhance healing outcomes and reduce the risk of complications.

Debridement. Surgical debridement involves the removal of necrotic or infected tissue to promote healing and prevent the spread of infection. Although more commonly associated with necrotizing infections, limited debridement may be necessary in severe NNSTIs where abscesses have caused significant tissue damage. This procedure is crucial in eliminating sources of ongoing infection, allowing healthy tissue to regenerate

and reducing the overall burden of the infectious process. The decision to perform debridement should be guided by clinical judgment and the extent of tissue involvement

Incisional therapy. For larger, complicated abscesses, or where multiple abscesses are present, a more extensive incision may be necessary to ensure complete drainage. This is often combined with debridement of any surrounding necrotic tissue. Incisional therapy not only aids in drainage but also helps in the thorough assessment of the affected area, allowing for the identification of any additional pockets of infection that may need addressing. Such thorough surgical intervention is essential for preventing recurrence and promoting a favourable healing environment.

Post-operative wound care is crucial for preventing secondary infections. This includes regular wound inspection, cleaning, and dressing changes. In some cases, negative pressure wound therapy (NPWT) may be used to promote healing in large or complex wounds. Effective postoperative management strategies are integral to improving patient outcomes and minimizing complications following surgical intervention.

Antibiotic therapy

The cornerstone of NNSSTIs treatment is antibiotic therapy. The choice of antibiotics should be guided by the likely pathogens, local resistance patterns, and patient factors such as allergies and renal function. Empiric therapy often includes beta-lactams or cephalosporins for *Streptococcus* species and MRSA coverage with drugs like vancomycin or linezolid in cases where *Staphylococcus aureus* is suspected. CA-MRSA risk factors include immunocompromised status, personal or household contact with MRSA in the past 12 months, prior antibiotic use within the last 90 days, and failure to respond to first-line therapy. The duration of therapy typically ranges from 5 to 14 days, depending on the severity of the infection and the patient's response. Empirical treatment is often initiated while awaiting culture results, with adjustments made as necessary to ensure effective coverage.

Empirical antibiotic treatment

For non-purulent infections like cellulitis or erysipelas, early empiric antibiotic therapy is essential to target the most common pathogens, such as *Streptococcus pyogenes* and *Staphylococcus aureus*. First-line therapies typically include beta-lactam antibiotics, such as cephalexin or amoxicillin, which cover methicillin-sensitive *S. aureus* (MSSA) and streptococci (**Table 4**).

In areas with a high prevalence of MRSA or in patients at risk, empiric coverage with agents like trimethoprim-sulfamethoxazole, clindamycin, or doxycycline may be indicated. Antibiotics should be tailored based on culture results, local resistance patterns, and patient-specific factors.

Once culture results are available or if the infection is mild and resolving, narrowing the antibiotic spectrum or discontinuing antibiotics can help minimize adverse effects and prevent antibiotic resistance. For example, mild cellulitis without systemic symptoms can often be managed without antibiotics.

Table 4. Empiric antibiotic therapy for the management of the main common non-necrotising skin and soft tissue infections in the emergency setting.

Infection type	Empiric antibiotics	Dose	Duration
Simple abscess	Amoxicillin-clavulanate	1g every 8 hours	5-7 days
	Cephalexin	500 mg every 6 hours	5-7 days
	Minocycline (if MRSA risk)	100 mg every 12 hours	5-7 days
	Trimethoprim-Sulfamethoxazole (if MRSA risk)	160/800 mg every 12 hours	5-7 days
	Clindamycin (for beta-lactam allergy)	300 mg every 8 hours	5-7 days
Erysipelas	Amoxicillin-clavulanate	1g every 8 hours	7-10 days
	Cephalexin	500 mg every 6 hours	7-10 days
	Trimethoprim-Sulfamethoxazole (if MRSA risk)	160/800-320/1600 mg every 12 hours	7-10 days
	Clindamycin (for beta-lactam allergy)	300 mg every 8 hours	7-10 days
	Cefazolin (Inpatient therapy)	2g every 8 hours	7-10 days
Erysipelas (severe)	Vancomycin	25-30 mg/kg loading dose, then 15-20 mg/kg every 12 hours	7-10 days
Perianal/Rectal abscess	Amoxicillin-clavulanate	1g every 8 hours	5-10 days
	Ciprofloxacin + Metronidazole (for beta-lactam allergy)	500 mg every 8 hours + 500 mg every 8 hours	5-10 days
	Ceftriaxone + Metronidazole (Inpatient therapy)	2g every 24 hours + 500 mg every 8 hours	5-10 days
	Vancomycin (if MRSA risk)	25-30 mg/kg loading dose, then 15-20 mg/kg every 12 hours	5-10 days
Typical cellulitis	Amoxicillin-clavulanate	1g every 8 hours	7-10 days
	Cephalexin	500 mg every 6 hours	7-10 days
	Trimethoprim-Sulfamethoxazole (if MRSA risk)	160/800-320/1600 mg every 12 hours	7-10 days
	Clindamycin (for beta-lactam allergy)	300 mg every 8 hours	7-10 days
	Vancomycin (Inpatient therapy)	25-30 mg/kg loading dose, then 15-20 mg/kg every 12 hours	7-10 days

(cont.)

Table 4. Empiric antibiotic therapy for the management of the main common non-necrotising skin and soft tissue infections in the emergency setting *(cont.)*

Infection type	Empiric antibiotics	Dose	Duration
Purulent cellulitis	Amoxicillin-clavulanate	1g every 8 hours	7-10 days
	Trimethoprim-Sulfamethoxazole (for CA-MRSA)	160/800-320/1600 mg every 12 hours	7-10 days
Burn wounds	Amoxicillin-clavulanate	1g every 8 hours	7-14 days
	Ciprofloxacin + Metronidazole (for beta-lactam allergy)	500 mg every 12 hours + 500 mg every 8 hours	7-14 days
	Ceftriaxone + Metronidazole (Inpatient therapy)	2g every 24 hours + 500 mg every 8 hours	7-14 days
Human/Animal bites	Amoxicillin-clavulanate	1g every 8 hours	7-10 days
	Ciprofloxacin + Metronidazole (for beta-lactam allergy)	500 mg every 12 hours + 500 mg every 8 hours	7-10 days

Antibiotics recommended for MRSA infections are:

Oral options:

Minocycline 100 mg every 12 hours;
Trimethoprim and sulfamethoxazole 160/800 or 320/1600 every 12 hours;
Doxycycline 100 mg every 12 hours;
Clindamycin 300–450 mg every 8 hours (high resistance rate);
Linezolid 600 mg every 12 hours;
Tedizolid 200 mg every 24 hours.

Intravenous options:

Clindamycin 600–900 mg every 8 hours;
Trimethoprim and sulfamethoxazole 320/1600 every 12 hours;
Vancomycin 25–30 mg/kg loading dose then 15–20 mg/kg/dose every 12 hours;
Tigecycline 100 mg IV as a single dose, then 50 mg IV every 12 hours;
Linezolid 600 mg every 12 hours;
Daptomycin 6 mg/kg every 24 hours;
Ceftaroline 600 mg every 12 hours;
Dalbavancin 1000 mg once followed by 500 mg after 1 week or 1500 mg one dose;
Tedizolid 200 mg every 24 hours;
Telavancin 10 mg/kg every 24 hours.

Highlights

- Empiric therapy should always consider patients' comorbidities, clinical features, severity of the disease, and settings, and it should be adjusted based on culture results and sensitivity testing
- In MRSA-endemic areas, coverage for MRSA should be considered in SSTI management.
- CA-MRSA risk factors include immunocompromised status, personal or household contact with MRSA in the past 12 months, prior antibiotic use within the last 90 days, and failure to respond to first-line therapy.
- For bite wounds, amoxicillin-clavulanate is recommended to cover both aerobic and anaerobic organisms.
- For severe infections, intravenous therapy may be necessary initially, with a switch to oral therapy based on clinical improvement.
- Therapy duration should be guided by clinical response and specific patient factors (e.g., comorbidities, site of infection, pathogen resistance). Consider short-course therapy for uncomplicated infections.
- Dosing may need to be adjusted in patients with renal or hepatic impairment.
- Therapy duration is typically extended for severe cases, immunocompromised patients, or if the infection involves deeper tissues.

Supportive care

Supportive care plays a significant role in patient recovery and includes pain management, hydration, and wound care, which can improve patient comfort and promote healing. Additionally, in certain cases, adjunctive therapies such as hyperbaric oxygen therapy or the use of topical agents may be considered to augment the healing process, particularly in patients with risk factors that may complicate recovery. Together, these components work synergistically to ensure comprehensive treatment of NNSSTIs, thereby reducing the risk of complications, such as systemic infection or the development of chronic wounds. Prompt recognition and intervention are crucial for optimal outcomes. The principles of supportive care are:

- *Pain management and symptom relief.* Adequate analgesia is important for patient comfort, particularly in cases of painful cellulitis or large abscesses. Nonsteroidal anti-inflammatory drugs (NSAIDs) or acetaminophen are commonly used to control pain and inflammation.
- *Elevation and immobilization.* Elevation of the affected limb reduces oedema and improves lymphatic drainage, which can help control infection and reduce pain. In cellulitis, immobilizing the area may reduce movement-related discomfort and aid in healing.
- *Hydration and rest.* Encouraging adequate hydration and rest supports the body's immune response to infection. For severe infections, hospitalization may be necessary to provide intravenous fluids and close monitoring.
- *Education and prevention.* Patients should be educated on wound care, hygiene, and measures to prevent recurrence. This includes proper wound cleaning, avoiding trauma to previously affected areas, and monitoring for early signs of infection.

Adjunctive therapies

Adjunctive therapies play a supportive role in the management of non-necrotizing SSTIs alongside the core principles of source control, antibiotic therapy, and supportive care. While these therapies are not first-line treatments, they can enhance outcomes, particularly in complicated or recurrent infections. The main adjunctive options include:

1. *Anti-inflammatory agents*
    - Nonsteroidal anti-inflammatory drugs (NSAIDs). While primarily used for pain control, NSAIDs may also reduce inflammation associated with cellulitis and other SSTIs. However, some studies have raised

concerns that NSAIDs might mask early signs of worsening infection, so their use should be cautious, especially in severe cases.

- Corticosteroids. In selected cases, short courses of corticosteroids may be used as adjunctive therapy for patients with significant inflammation, such as severe erysipelas or cellulitis. Corticosteroids can reduce the inflammatory response and shorten the duration of symptoms. However, their use must be carefully weighed against the potential for immune suppression, especially in diabetic or immunocompromised patients.

2. *Compression therapy*
   - Compression bandaging. In cases of lower limb cellulitis, particularly in patients with chronic venous insufficiency or lymphedema, adjunctive compression therapy may help reduce swelling and improve circulation. Studies have suggested that compression can decrease the likelihood of recurrence in patients with pre-existing venous disease.

3. *Topical therapies*
   - Antimicrobial dressings. While systemic antibiotics are the primary mode of treatment, topical antimicrobial dressings containing silver or iodine may be used as adjunctive therapy for superficial infections or chronic wounds associated with non-necrotizing SSTIs. These dressings can help reduce the local bacterial load and promote wound healing.
4. *Photodynamic therapy*
   - Photodynamic therapy (PDT). PDT, which involves the use of light-activated antimicrobial agents, has shown some promise as an adjunctive treatment for chronic or recurrent SSTIs, particularly in antibiotic-resistant infections. It works by generating reactive oxygen species that kill bacteria. Although not widely adopted, PDT has potential as a non-invasive treatment option.
5. *Probiotics*
   - Probiotic therapy. Though evidence is still emerging, the use of probiotics has been suggested as an adjunctive measure to restore healthy skin flora and prevent recurrent SSTIs, particularly in individuals prone to recurrent infections. Probiotics may modulate immune responses and inhibit the growth of pathogenic bacteria like *Staphylococcus aureus*.
6. *Vaccination (for recurrent SSTIs)*
   - Staphylococcal vaccines. While not yet routine in clinical practice, research into vaccines targeting *Staphylococcus aureus*—particularly MRSA—has been ongoing. In patients with recurrent SSTIs, vaccination might one day serve as an adjunctive strategy to prevent future infections, although the clinical efficacy of these vaccines is still under investigation.
7. *Hygiene measures and decolonization*
   - MRSA decolonization protocols: In patients with recurrent infections due to MRSA, adjunctive therapies such as nasal decolonization with mupirocin and antiseptic body washes (e.g., chlorhexidine) can help reduce the bacterial burden on the skin and mucous membranes. These interventions are often part of broader infection control strategies in healthcare settings or for individuals at high risk.

Most common NNSTIs and management

Simple abscess

Abscesses are localized collections of pus within the soft tissues, often resulting from bacterial infections such as those caused by *Staphylococcus aureus*. The gold standard for abscess treatment is incision and drainage, where the abscess is surgically opened, and the pus is drained. This procedure not only reduces the bacterial load but also alleviates pressure, relieving pain and preventing the spread of the infection. Local anaesthesia is typically sufficient, and the procedure is often performed in an outpatient setting. In cases where abscesses are extensive or complicated by underlying conditions, surgical intervention may be required.

After drainage, the abscess cavity may be packed with gauze to keep it open and allow continuous drainage. This helps prevent premature closure of the wound, which could lead to recurrence. The wound should be regularly monitored, and dressings should be changed to ensure proper healing. The packing material helps maintain an open channel for continued drainage, promoting effective healing. Regular monitoring of the wound is essential to assess for signs of infection and to ensure that healing is progressing appropriately. Dressings should be changed as needed, typically every 1 to 3 days, or more frequently if there is significant drainage or soiling. This proactive approach helps prevent complications such as wound infection and facilitates optimal recovery. While incision and drainage are usually sufficient for uncomplicated abscesses, antibiotics may be prescribed in cases with surrounding cellulitis, systemic symptoms (e.g., fever), or in immunocompromised patients. The choice of antibiotics should cover MRSA when *Staphylococcus aureus* is suspected. Empirical therapy may include options such as clindamycin or trimethoprim-sulfamethoxazole, which provide coverage for MRSA while also considering the local resistance patterns and patient-specific factors.

Perianal and rectal abscesses

Perianal and rectal abscesses (PRAs) are collections of pus that form in the tissues surrounding the anus and rectum. These abscesses can be painful and are often associated with an underlying anal fistula.

Principles of management for perianal and rectal abscesses:

1. *Clinical assessment*
    - Symptoms. Perianal abscess typically presents with severe, constant anal pain, swelling, redness, and sometimes fever. Rectal abscesses might cause deeper pelvic pain or discomfort.
    - Examination. Physical examination includes digital rectal examination and inspection of the perianal area. Palpation may reveal fluctuance, tenderness, and induration.
    - Imaging. If the diagnosis is unclear or the abscess is deep, imaging (e.g., ultrasound, CT scan, or MRI) can help delineate the extent and exact location.
2. *Drainage of the abscess*
    - Incision and drainage. The mainstay of treatment for perianal abscesses. Adequate drainage is achieved through a small incision over the most fluctuant part of the abscess.
    - Anaesthesia. Local anaesthesia is usually sufficient for perianal abscesses; however, deep rectal abscesses may require sedation or general anaesthesia.
    - Microbiological cultures. While not always necessary, cultures of the drained pus can guide antibiotic therapy, especially in immunocompromised patients or those with recurrent infections.
3. *Antibiotic therapy*
    - Antibiotics are not routinely required. They are generally not needed for healthy individuals if adequate drainage is achieved.

- Antibiotics are Indicated for patients with significant cellulitis, systemic infection signs (e.g., fever, elevated white blood cell count), immunocompromised states, diabetes, or those with valvular heart disease.
- Empiric coverage includes agents against skin flora (e.g., *Staphylococcus aureus, Streptococcus* species) and anaerobes. A combination of a penicillinase-resistant penicillin (or clindamycin) and metronidazole is a common regimen.

Pilonidal disease

Pilonidal disease (PD) is an infection of the skin and subcutaneous tissue at or near the upper part of the natal cleft of the buttocks, thought to arise from hair and debris trapped in the natal cleft, leading to infection.

PD clinical features are pain, redness, swelling, and purulent discharge in the sacrococcygeal region. Diagnosis is based on clinical examination; imaging can support decision-making if an abscess is suspected.

Treatment can be divided into two broad categories - nonoperative *vs.* operative- and often there is a combination of the two. Conservative nonoperative management strategies, including persistent improved hygiene, depilation, and lifestyle modification, focus on disease prevention and minimization of disease activity. Epilation techniques using both laser and intense pulse light therapy are also used as primary and adjunct treatment modalities. PD is largely considered a surgical disease, especially in acute instances with secondary infection and abscess. Infection or abscess requires incision and drainage. Definitive treatment is delayed the majority of the time if there is an acute infection or abscess until after the infection has been addressed. Antibiotics can be prescribed if cellulitis is present. Surgical excision is indicated in recurrent cases.

Cellulitis

Cellulitis is a common bacterial skin infection that appears as a swollen, red area that feels hot and tender. The affected skin may also appear shiny and taut, and the infection can spread rapidly if not treated promptly. It most frequently occurs on the lower legs but can develop on any part of the body, including the face and arms.

It is commonly caused by *Streptococcus pyogenes* and *Staphylococcus aureus* (including MRSA). Other less common pathogens involved are *Haemophilus influenzae*, especially in cases involving children. Factors that increase the risk of developing cellulitis include breaks in the skin, such as cuts, insect bites, or surgical wounds, as well as underlying conditions like diabetes, obesity, and immunosuppression.

Cellulitis clinical findings are redness, warmth, swelling, and pain of the affected area. There might also be fever, chills, and lymphadenopathy. In severe cases, patients might exhibit signs of sepsis, including tachycardia, hypotension, and altered mental status. Chronic conditions that impair circulation or immune function can exacerbate the severity of symptoms. Diagnosis is mainly clinical, supported by ultrasound or MRI in complicated cases.

The antibiotic treatment for cellulitis depends on the severity of the infection, the likely causative organisms, the patient's clinical status, and any relevant comorbidities. Most cases of cellulitis are caused by *Streptococcus pyogenes* (Group A *Streptococcus*) or *Staphylococcus aureus* (including MRSA in some settings), and antibiotic therapy should be tailored to these pathogens.

Empiric antibiotic treatment for cellulitis

Empiric therapy should be initiated promptly, especially in cases of moderate to severe infection. The choice of antibiotic depends on whether the cellulitis is purulent (likely caused by *S. aureus*) or non-purulent (likely caused by *Streptococcus* species).

Non-purulent cellulitis (Streptococcal species likely)

For uncomplicated, non-purulent cellulitis (i.e., without abscess or pus), *Streptococcus pyogenes* is the most common cause, and beta-lactam antibiotics are generally effective.

- First-line agents
  - Cephalexin (500 mg orally four times daily for 5–7 days) or
  - Amoxicillin (500 mg orally three times daily for 5–7 days) or
  - Penicillin VK (500 mg orally four times daily for 5–7 days).
- For patients allergic to penicillin
  - Clindamycin (300–450 mg orally three times daily) or
  - Azithromycin (500 mg on day 1, then 250 mg once daily for 4 more days).

Purulent cellulitis (MRSA or MSSA suspected)

For cellulitis with abscesses, purulent drainage, or in patients at risk for MRSA, empiric therapy should cover both streptococci and MRSA.

- First-line agents for MRSA coverage
  - Trimethoprim-Sulfamethoxazole (TMP-SMX) (1-2 double-strength tablets orally twice daily) or
  - Doxycycline (100 mg orally twice daily).
- Alternative agents
  - Clindamycin (300–450 mg orally three times daily) can cover both streptococci and MRSA, but resistance to clindamycin in some areas may limit its use.
- For severe or systemic infections (IV antibiotics)
  - Vancomycin (15–20 mg/kg IV every 8–12 hours) is typically used as the first-line IV therapy for severe MRSA cellulitis.
  - Other IV options include linezolid, daptomycin, or ceftaroline.

Severe or complicated cellulitis

For patients with more severe cellulitis, systemic symptoms such as fever and hypotension, or those with significant comorbidities, hospitalization and intravenous (IV) antibiotics are required. In these cases, empiric therapy should cover both streptococci and MRSA until cultures and sensitivities are available.

- Recommended IV antibiotics for severe cellulitis
  - Cefazolin (1–2 g IV every 8 hours) for streptococcal infections or MSSA
  - Vancomycin or daptomycin for suspected or confirmed MRSA
  - Piperacillin-tazobactam or meropenem may be needed if Gram-negative or anaerobic coverage is required (e.g., in diabetic or immunocompromised patients).

Duration of therapy for cellulitis

The typical duration of antibiotic therapy for uncomplicated cellulitis is 5–7 days, but it may be extended in patients with severe infection, slow clinical response, or underlying immunosuppression.

Shorter courses (5 days) are as effective as longer courses in uncomplicated cases, provided there is a rapid clinical response.

Considerations for special populations

In immunocompromised patients, cellulitis may be caused by a broader range of pathogens, including Gram-negative organisms and fungi. Empiric therapy in these patients should be broader and may include antibiotics like piperacillin-tazobactam or cefepime.

Diabetic patients with cellulitis, especially those with diabetic foot infections, may require broader coverage, including anaerobes and Gram-negative organisms, necessitating agents such as piperacillin-tazobactam or meropenem.

Erysipelas

Erysipelas is a superficial form of cellulitis that affects the upper dermis and lymphatics, typically with sharply demarcated edges. Usually, it is caused by *Streptococcus pyogenes*. Erysipelas lesions are raised, well-defined, bright red areas on the skin, often with systemic symptoms such as fever and chills. Commonly occurs on the face and legs. Diagnosis is based on clinical appearance and history; blood cultures are required if systemic symptoms are present. Given that *Streptococcus pyogenes* is the predominant pathogen, the antibiotic treatment of erysipelas primarily targets streptococcal species. The role of *S. aureus*, and specifically MRSA, remains controversial. The choice of antibiotics depends on the severity of the infection and the route of administration (oral for mild/moderate cases and intravenous for more severe cases).

Antibiotic treatment

Intravenous antibiotics are recommended if signs of systemic inflammation are present.

Oral antibiotics for mild to moderate erysipelas

Penicillin VK (500 mg orally every 6 hours) is the first-line treatment, as *S. pyogenes* remains highly sensitive to penicillin or Amoxicillin+Clav. (1g orally three times daily) or Cephalexin (500 mg orally four times daily) in patients with mild penicillin allergies (not IgE-mediated reactions) or Clindamycin (300–450 mg orally three times daily) is used for patients with severe penicillin allergies or suspected beta-lactam intolerance.

Azithromycin or clarithromycin may be used in patients with penicillin allergies, though resistance rates for streptococcal infections may vary in some areas, making these less preferred unless sensitivities are known.

Intravenous antibiotics for severe erysipelas

Penicillin G (1-2 million units IV every 4–6 hours) is the preferred treatment for hospitalized patients or Cefazolin (1-2 g IV every 8 hours) is an alternative for penicillin-sensitive patients or for broader coverage in patients at risk for *Staphylococcus aureus* co-infection.

Clindamycin (600–900 mg IV every 8 hours) is recommended for patients with penicillin allergies or those who require broader coverage.

Vancomycin (15-20 mg/kg IV every 8–12 hours) should be considered in cases of suspected MRSA or severe allergies to beta-lactam antibiotics.

In patients at risk for CA-MRSA including critically ill and immunocompromised status, personal or household contact with MRSA infection or colonization in the past 12 months, with prior antibiotic use for 5 days during the last 90 days or who do not respond to first-line therapy add one of following intravenous antibiotics:

Vancomycin 25–30 mg/kg loading dose then 15–20 mg/kg/dose every 12 hours or Linezolid 600 mg every 12 hours.

Duration of therapy

The typical duration of antibiotic therapy for erysipelas is 5–10 days, depending on the clinical response. Shorter courses (5 days) may be sufficient for mild cases that respond quickly, while longer courses (7–10 days) may be necessary for more severe or slow-resolving infections.

Treatment for recurrent erysipelas

Recurrent erysipelas is often associated with underlying conditions such as chronic lymphedema, venous insufficiency, or obesity. In cases of frequent recurrences, prophylactic antibiotics such as penicillin V (250 mg orally twice daily) or erythromycin (250 mg orally twice daily) may be considered to prevent future episodes.

Impetigo

Impetigo is a highly contagious superficial skin infection, caused by *Staphylococcus aureus* or *Streptococcus pyogenes* and often seen in children. It is characterized by honey-colored crusted lesions, usually around the nose and mouth; in bullous and non-bullous forms. The infection is classified into two main types: non-bullous (more common) and bullous impetigo. Treatment depends on the extent and severity of the infection, and it typically involves both topical and systemic therapies. Hospitalization is rarely required for impetigo. However, it may be considered for immunocompromised patients, infants, or individuals with extensive involvement, systemic symptoms, or secondary complications (such as cellulitis, sepsis, or post-streptococcal glomerulonephritis).

Topical antibiotic treatment for impetigo

Topical antibiotics are the treatment of choice for mild cases of impetigo, particularly when the infection is localized to a small area. These agents target the causative organisms and help clear the infection. Mupirocin is highly effective against both *Streptococcus pyogenes* and *Staphylococcus aureus*, including MRSA. Retapamulin is effective against streptococcal and staphylococcal infections, though it is not effective for MRSA. Topical therapy is often sufficient for limited, uncomplicated cases of impetigo. These agents help reduce bacterial load and speed healing, with minimal risk of systemic side effects.

Oral antibiotic treatment for severe impetigo

Oral antibiotics are indicated for more extensive cases, for individuals who have multiple lesions, or for patients with systemic symptoms such as fever. They are also used when topical therapy has failed or when there is concern for deeper or more widespread infection.

Cephalexin (500 mg orally twice daily for adults, 25-50 mg/kg/day divided into two to four doses for children) for 7 days. Cephalexin covers *S. pyogenes* and methicillin-sensitive *Staphylococcus aureus* (MSSA). Dicloxacillin (250–500 mg orally four times daily for adults, 25-50 mg/kg/day divided into four doses for children) for 7 days. Dicloxacillin is effective against MSSA and *Streptococcus pyogenes*.

Antibiotics for suspected or confirmed MRSA infections

If MRSA is a concern, especially in cases of community-acquired infections, the following oral antibiotics may be appropriate:

- Trimethoprim-sulfamethoxazole (TMP-SMX) (1–2 double-strength tablets twice daily for adults, 8–12 mg/kg/day of trimethoprim component in divided doses for children) for 7 days. This is effective against MRSA but does not cover *S. pyogenes*, so it should be combined with beta-lactam if streptococcal coverage is needed.
- Clindamycin (300 mg orally three times daily for adults, 20–40 mg/kg/day in divided doses for children) for 7 days. Clindamycin covers both MRSA and *S. pyogenes* and can be used when both organisms are suspected.
- Doxycycline (100 mg orally twice daily for adults) for 7 days. Doxycycline is an option for older children (age >8 years) and adults for MRSA coverage, though it does not reliably cover *S. pyogenes* and may require combination therapy for complete coverage.

Duration of therapy

The typical duration of treatment for impetigo, whether topical or oral antibiotics, is 5–7 days. If lesions are slow to heal or the infection is more severe, therapy may be extended as necessary. Most patients begin to show improvement within 48 hours of starting treatment.

Folliculitis

Folliculitis is a common skin condition characterized by inflammation or infection of the hair follicles. It can be caused by bacteria, commonly *Staphylococcus aureus,* or *Pseudomonas* in hot tub folliculitis, fungal, or viral agents, as well as mechanical irritation (e.g., from shaving or friction). The treatment of folliculitis depends on the underlying cause, severity, and extent of the infection.

Bacterial folliculitis treatment

The most common form of folliculitis is bacterial, usually caused by *Staphylococcus aureus*. Mild cases often resolve on their own, but more persistent or widespread infections may require treatment.

Mild bacterial folliculitis

First-line treatment for localized, mild bacterial folliculitis includes topical antibiotics to reduce bacterial load. The following topical antibiotics may be appropriate: Mupirocin 2% ointment or Clindamycin 1% gel or lotion or Erythromycin 2% gel, for patients who cannot tolerate other topical antibiotics.

Moderate to severe bacterial folliculitis

For more widespread or persistent bacterial folliculitis, or if topical treatments fail, oral antibiotics may be necessary, particularly if *Staphylococcus aureus* (including MRSA) is suspected.

The following oral antibiotics may be appropriate: Cephalexin (500 mg orally four times daily for 7–10 days) is often used for MSSA infections. Dicloxacillin (500 mg orally four times daily for 7–10 days) is another effective option.

For suspected or confirmed MRSA: Trimethoprim-sulfamethoxazole (TMP-SMX) (1–2 double-strength tablets twice daily for 7–10 days) or Clindamycin (300–450 mg orally three times daily for 7–10 days) or Doxycycline (100 mg orally twice daily for 7–10 days).

Fungal folliculitis (*Pityrosporum* folliculitis)

Fungal folliculitis, often caused by *Malassezia* species, commonly affects the back, chest, and upper arms and is characterized by itchy, acne-like pustules. This condition is more common in people with oily skin and is often misdiagnosed as acne. Topical antifungals are:

- Ketoconazole 2% cream;
- Ciclopirox 1% cream.

Oral antifungals (for widespread or resistant cases) are:

- Itraconazole (100–200 mg orally once daily for 7–14 days);
- Fluconazole (150 mg orally once weekly for 2–4 weeks).

***Pseudomonas* folliculitis (hot tub folliculitis)**

This type of folliculitis is caused by *Pseudomonas aeruginosa*, typically contracted from exposure to contaminated water, such as in hot tubs or swimming pools. Most cases are self-limiting and resolve without treatment within 7–10 days. Symptomatic relief can be provided with topical treatments. For severe or persistent cases, ciprofloxacin (500 mg orally twice daily for 7–10 days) may be prescribed for patients with more severe or extensive cases.

Viral folliculitis (herpetic folliculitis)

Folliculitis can also be caused by herpes simplex virus (HSV), presenting as grouped vesicles on an erythematous base, often involving the face or genital area.

Antiviral treatment includes Acyclovir (400 mg orally three times daily for 7–10 days) or Valacyclovir (500 mg orally twice daily for 7–10 days).

Furuncles (boils) and carbuncles

Furuncles are deeper infections of hair follicles that form tender nodules with a central necrotic plug. Carbuncles are larger, deeper, interconnected collections of furuncles. They are primarily caused by *Staphylococcus aureus* and are characterised by painful, swollen areas on the skin, often with pus or drainage. Carbuncles may be accompanied by systemic symptoms like fever. Diagnosis is based on clinical evaluation and bacterial culture from drainage in case of abscesses. Treatment can be divided into three main components: local care, antibiotic therapy, and supportive measures.

Local care and incision & drainage

For small furuncles, applying warm compresses (for 10–15 minutes, three to four times daily) can help bring the infection to a head, promoting spontaneous drainage. This may be sufficient for small boils that are not severely painful or deep. For larger furuncles and all carbuncles, incision and drainage are the primary treatments. This procedure allows for the removal of pus and necrotic material, alleviating pain and reducing the bacterial load. Once adequately drained, many furuncles do not require antibiotics unless there are risk factors or signs of systemic infection. In cases where incision and drainage are performed, the wound should be cleaned regularly, and dressings should be changed to prevent reinfection. Follow-up is often needed to ensure complete healing.

Antibiotic Therapy

Antibiotics are not always required for uncomplicated furuncles, but they are necessary in certain situations, such as when the infection is large, recurrent, involving surrounding cellulitis, or if there are systemic symptoms (e.g., fever). For smaller furuncles, particularly after drainage, topical antibiotics such as Mupirocin 2% ointment can be applied to the affected area two to three times daily for 5–7 days to reduce bacterial colonization and prevent spread. Systemic antibiotics are recommended in the following cases:

- Multiple lesions or large carbuncles.
- Systemic symptoms such as fever, chills, or malaise.
- Recurrent boils or patients with underlying conditions like diabetes or immunosuppression.
- Surrounding cellulitis or abscess formation.

First-line antibiotics targeting *Staphylococcus aureus* (including MRSA in some cases) include: Dicloxacillin (500 mg orally four times daily for 7–10 days) or Cephalexin (500 mg orally four times daily for 7–10 days) for methicillin-sensitive *S. aureus* (MSSA).

For suspected or confirmed MRSA infections: Trimethoprim-sulfamethoxazole (TMP-SMX) (1-2 double-strength tablets twice daily for 7–10 days) or Doxycycline (100 mg orally twice daily for 7–10 days). Clindamycin (300–450 mg orally three times daily for 7–10 days). IV antibiotics (e.g., vancomycin, linezolid) are reserved for severe cases, particularly those with systemic involvement, sepsis, or failure to respond to oral antibiotics.

Hidradenitis suppurativa

Hidradenitis suppurativa (HS), also known as acne inversa, is a chronic inflammatory skin condition that affects the hair follicles and is characterized by recurrent, painful, deep-seated nodules, abscesses, and sinus tracts with subsequent scarring. Smoking is a known risk factor for HS, and quitting smoking can improve outcomes and reduce disease activity. It primarily occurs in areas where skin rubs together, such as the armpits, groin, buttocks, and under the breasts. HS is thought to result from follicular occlusion, inflammation, and subsequent infection of the apocrine sweat glands Common symptoms and signs of HS are:

- *Painful nodules*. The hallmark symptom of HS is the appearance of painful, inflamed nodules or lumps under the skin. These are often tender and may increase in size over time.
- *Abscess*. nodules can evolve into abscesses, which are collections of pus that may eventually drain spontaneously.
- *Sinus tracts and tunneling*. chronic and untreated HS can lead to the development of interconnected sinus tracts (tunnels) under the skin. These tracts can persist for years and cause recurrent drainage.
- *Scarring*. with repeated episodes of inflammation and abscess formation, HS can result in significant scarring. The scars may be thick, and fibrotic, and lead to disfigurement.
- *Recurrent inflammation*. HS is characterized by its chronic, relapsing nature. Flare-ups can occur frequently and may worsen over time without proper management.
- *Systemic symptoms*. In more severe cases, patients may experience systemic symptoms such as fever, malaise, and generalized fatigue due to ongoing inflammation and infection.

A diagnosis of HS is immediate in patients who demonstrate the patient history and recognition of characteristic clinical manifestations:

- Typical lesions (multiple inflamed nodules, tombstone comedones, sinus tracts, abscesses and/or fibrotic scars). A full skin examination should be performed in patients with suspected HS.
- Typical locations (in particular, axillae, groin, inframammary areas; often bilateral distribution).
- The patient history is a valuable tool in the diagnosis of HS (onset in adolescence or young adulthood, a history of recurrent or persistent disease, or a family history).

The Hurley clinical staging system is used to classify patients with HS into three disease severity groups.
- Stage I – abscess formation (single or multiple), no sinus tracts or cicatrization/scarring.
- Stage II – recurrent abscesses with sinus tracts and scarring, single or multiple separated lesions.
- Stage III – diffuse or almost diffuse involvement, or multiple interconnected sinus tracts and abscesses across the entire area

Treatment for HS is aimed at reducing symptoms, preventing complications, and slowing disease progression. The approach depends on the severity of the disease according to the Hurley stage, and a combination of lifestyle changes, medications, and surgical interventions may be needed.
Laser hair removal with intense pulsed light or carbon dioxide lasers can reduce hair follicle involvement and help control symptoms.

Medical treatments
Medical management typically involves a combination of topical, systemic, and biologic therapies depending on the severity of the disease.

Topical therapies (for mild cases)
Topical clindamycin 1% solution or gel, applied twice daily to affected areas, clindamycin is the first-line treatment for mild HS. It helps reduce bacterial colonization and inflammation. Resorcinol 15% cream, a keratolytic agent, helps reduce the formation of new lesions by promoting skin cell turnover.

Systemic antibiotics (for moderate to severe cases)
Systemic antibiotics are commonly used in patients with more extensive disease or when topical treatments are ineffective. Tetracyclines (e.g., doxycycline, minocycline) are often used for their anti-inflammatory effects, and they may be prescribed for prolonged courses. The combination of clindamycin and rifampin is effective in reducing inflammation and lesions in moderate to severe HS. In female patients, especially those with flare-ups related to the menstrual cycle, hormonal therapy, including oral contraceptives and spironolactone may help reduce inflammation and lesion formation.

Biologic therapies (for severe and refractory cases)
Biologic agents targeting TNF-alpha (tumour necrosis factor) have shown significant efficacy in severe HS and are considered a mainstay for patients who do not respond to conventional therapies. Adalimumab (Humira) is the only FDA-approved biologic for HS. It helps reduce inflammation and can significantly improve symptoms in patients with moderate to severe HS. Infliximab (Remicade) is another TNF-alpha inhibitor, used off-label for severe HS with similar effects to adalimumab.

Surgical treatment
Surgery may be necessary for patients with chronic or recurrent HS, especially in advanced cases where medical treatment alone is insufficient. Incision and drainage are used to relieve acute pain by draining abscesses,

but it is not curative and is typically reserved for short-term relief. Excision of affected areas is indicated in more severe cases (Hurley Stage II or III), wide surgical excision of the affected tissue, including sinus tracts, may be necessary. This procedure can be curative but is often accompanied by significant scarring.

Bite wounds

Bite wounds are a common cause of injury and can result from animal bites (e.g., dogs, cats, or rodents) or human bites. These injuries are concerning due to the high risk of infection, tissue damage, and complications. Human bite microbiology generally includes *Streptococcus* spp., *S. aureus*, *Peptostreptococcus* spp., *Fusobacterium* spp. and *Eikinella* spp. Dog bite microbiology generally includes *Pasteurella canis*, *Pasteurella multocida*, *Bacteroides* spp., *Fusobacterium* spp., *Capnocytophaga* canimorsus and *S. aureus*. Cat bite microbiology generally includes *Pasteurella* spp., *Capnocytophaga* spp, *Bartonella henselae* (Cat-scratch diseases should be treated with azithromycin 500 mg day 1, 250 mg/day for the next 4 days), *S. aureus*, *Bacteroides* spp. and *Fusobacterium* spp. The management of bite wounds involves wound care, infection prevention, and, in some cases, surgical and prophylactic measures. The approach varies based on the type of bite, location, and patient factors (e.g., comorbidities).

Initial evaluation

The first step in bite wound management is a thorough clinical evaluation, including:

- *History*. Document the type of animal involved, circumstances of the bite, timing, and any underlying medical conditions (e.g., diabetes, immunosuppression).
- *Wound examination*. Assess for signs of infection (e.g., erythema, warmth, swelling, pus), depth of the wound, presence of foreign material, damage to underlying structures (e.g., tendons, nerves, vessels), and risk of complications.
- *Infection risk*. Consider factors that increase infection risk, such as location (hands, face), patient's health status, and time since the bite.

Wound cleaning and debridement

Proper cleaning and debridement of the wound are essential to reduce the risk of infection, removing bacteria, debris, and contaminants. High-pressure irrigation is recommended for deeper wounds. Debridement removes any devitalized tissue or foreign material to reduce bacterial load and facilitate healing.

Wound management

Primary closure (suturing the wound) is typically avoided in bite wounds due to the high risk of infection, especially in puncture wounds, crush injuries, or bites on the hands and feet. Delayed primary closure (after 3-5 days) or secondary intention healing is often preferred for high-risk wounds to allow time for infection signs to develop and for adequate drainage. However, bite wounds on the face may be closed primarily due to the lower infection risk and the importance of cosmetic outcomes.

Antibiotic prophylaxis

Antibiotic prophylaxis is recommended for certain bite wounds, particularly those with a high risk of infection. The type of antibiotic chosen should cover common pathogens associated with bite wounds, including both aerobic and anaerobic organisms. For animal bites, common pathogens include *Pasteurella multocida*,

Staphylococcus aureus, and *Streptococcus* species. For human bites, *Eikenella corrodens*, *Streptococcus*, and *Staphylococcus* are common.
First-line prophylaxis (for both animal and human bites):

- Amoxicillin-clavulanate (875 mg orally twice daily for 5–7 days) provides coverage against both Gram-positive, Gram-negative, and anaerobic bacteria typically found in bite wounds.

Alternative antibiotics for penicillin-allergic patients:

- Doxycycline (100 mg orally twice daily) + Metronidazole (500 mg orally three times daily) or Clindamycin (300 mg orally three times daily) provides adequate coverage for most organisms, though doxycycline may not cover certain strains of *Streptococcus*.
- Moxifloxacin (400 mg orally once daily) can be used as monotherapy, as it provides broad-spectrum coverage.

Indications for antibiotic prophylaxis are:

- Bites on the hands, feet, or face.
- Deep puncture wounds or crush injuries.
- Wounds near joints or tendons.
- Immunocompromised patients or those with underlying health conditions (e.g., diabetes, liver disease, asplenia).
- Human bites (particularly clenched fist injuries or bites near joints).
- Delayed presentation (>8 hours after the injury).

Tetanus prophylaxis

Tetanus prophylaxis should be considered in all bite wounds, depending on the patient's immunization status and the nature of the wound.
If the patient has not been vaccinated within the last 10 years, a tetanus booster should be administered.
If the wound is high risk (e.g., dirty, contaminated, or deep puncture wound), and the patient has not been vaccinated in the past 5 years, a booster should be provided.
Tetanus immune globulin (TIG) may be needed for individuals with incomplete or unknown tetanus vaccination history.

Rabies prophylaxis

Rabies prophylaxis should be considered for animal bites, especially from wild animals (e.g., bats, raccoons, foxes, skunks) or unvaccinated domestic animals. The risk of rabies transmission varies geographically, and local public health guidelines should be followed. Rabies post-exposure prophylaxis (PEP) consists of:

- *Rabies vaccine*. Given as a series of four doses on days 0, 3, 7, and 14;
- *Rabies immune globulin (RIG).* Administered around the wound site and intramuscularly (on day 0) for previously unvaccinated individuals.

Human bite wound considerations

Human bite wounds, particularly on the hands or from fist injuries, carry a high risk of infection due to the high bacterial load of the oral cavity, including organisms like *Eikenella corrodens*. Human bites may lead to serious infections like septic arthritis or osteomyelitis if not properly managed. Early and aggressive irrigation, debridement, and antibiotics are critical in human bite wounds. Patients with bite wounds should be followed

closely for signs of infection (increased redness, swelling, pain, fever) or other complications. Re-evaluation within 24-48 hours is recommended for high-risk wounds or those at increased risk of infection.

Pressure ulcers

Pressure ulcers, also known as bedsores or decubitus ulcers, are injuries to the skin and underlying tissue resulting from prolonged pressure on the skin. These ulcers are present 70% of the time at the sacrum, ischial tuberosity, and greater trochanter, particularly in individuals with limited mobility. However, they can also occur in the occiput, scapula, elbow, heel, lateral malleolus, shoulder, and ear. Pressure ulcers are classified into stages I-IV, based on the depth of tissue damage as proposed by the National Pressure Injury Advisory Panel (NPIAP) guidelines:

- *Stage 1.* The skin is intact with non-blanchable erythema.
- *Stage 2*. There is partial-thickness skin loss involving the epidermis and dermis.
- *Stage 3*. A full-thickness loss of skin extends to the subcutaneous tissue but does not cross the fascia beneath it. Slough or eschar may be visible, and the lesion may be foul-smelling.
- *Stage 4.* Full-thickness skin loss extends through the fascia with considerable tissue loss. There may be muscle, bone, tendon, or joint involvement.
- *Unstageable*. The depth is unknown because slough or eschar obscures the extent of tissue damage.

Deep Tissue Injury (DTI) is another category mentioned in the NPIAP guidelines. This injury occurs with prolonged pressure and shear forces at the bone-muscle interface. The result is intact or non-intact skin with persistent, non-blanched, deep red, maroon, or purple discolouration. DTI cannot be used to describe vascular, traumatic, neuropathic, or dermatologic injuries.

Pressure ulcers can offer an ideal environment for microbial colonization. This is especially true for those pressure ulcers that may be particularly exposed to Gram-negative and Gram-positive bacterial contamination from faecal material. Infections can range from superficial skin infections to more serious complications such as cellulitis, osteomyelitis, or sepsis. Early intervention with debridement and antibiotics is critical to preventing progression.

Managing pressure ulcers involves a combination of preventive measures, wound care, infection control, and interventions to promote healing. The management of pressure ulcers aims to:

- Prevent ulcer progression.
- Promote wound healing.
- Control infection.
- Manage pain and improve patient comfort.
- Address underlying risk factors.

Prevention is key to managing pressure ulcers, particularly in at-risk populations such as the elderly, bedridden, or immobile patients. The principles of prevention are:

- *Pressure redistribution*. It includes using pressure-relieving devices such as foam mattresses, air mattresses, or specialized cushions to reduce prolonged pressure on bony prominences; repositioning patients at least every 2 hours to relieve pressure, and using pillows or wedges to keep pressure off high-risk areas like the heels and sacrum.
- *Skin care and moisture control.* To keep the skin clean and dry to prevent maceration. Moisture barriers (e.g., zinc oxide, dimethicone) are applied to protect the skin from incontinence-related moisture.

- *Nutrition:* proper nutrition is crucial in both the prevention and management of pressure ulcers, encouraging a diet high in protein, vitamins (especially vitamins C and A), and minerals such as zinc to promote tissue repair and immune function.
- *Patient education and mobility.* Promoting mobility and teaching patients and caregivers to reposition regularly, perform pressure relief techniques, and recognize early signs of pressure injury.

Wound care

The approach to wound care depends on the stage and condition of the ulcer. Basic principles include debridement, infection control, and moisture balance. Removal of necrotic or nonviable tissue is necessary for healing; it can be performed by:

- *Autolytic debridement.* This process uses the body's own enzymes to break down dead tissue. It is supported by moisture-retentive dressings like hydrogels or hydrocolloids.
- *Sharp/surgical debridement.* This is the fastest method and is typically used for large, necrotic wounds. It is performed by a healthcare professional using a scalpel or scissors.
- *Enzymatic debridement.* This involves applying topical enzymes (e.g., collagenase) to break down dead tissue in the wound bed.
- *Mechanical debridement.* This involves the physical removal of necrotic tissue, such as through wet-to-dry dressings or irrigation. However, it can also damage healthy tissue and is not recommended for all cases.

Surgical intervention may be necessary for deep ulcers (stage 3 or 4) that fail to heal with conservative treatment. This may include: Surgical treatment options include the following:

- Excision of necrotic tissues.
- Skin graft: high failure rates in later stages due to low long-term durability.
- Pedicle muscle, myocutaneous, fasciocutaneous flaps, or free flaps: flap choice depends on the anatomical location, the need for ambulation, and comorbidities.

Advanced therapies

For chronic or non-healing pressure ulcers, advanced therapies may be considered:

- *Negative pressure wound therapy (NPWT).* This is a vacuum dressing to promote healing by reducing edema, removing exudate, and increasing blood flow to the wound. It is particularly useful for large or deep ulcers.
- *Biological dressings.* Growth factors, stem cells, and bioengineered skin substitutes may be used to promote tissue regeneration in non-healing ulcers.
- *Hyperbaric oxygen therapy.* Hyperbaric oxygen can be used in certain refractory cases to improve oxygenation to the tissue and promote healing.

Burn wounds

Burn wounds result from thermal, chemical, electrical, or radiation injury to the skin and underlying tissues. The depth and severity of the burn dictate the management approach. The management of burn wounds is based on the severity and depth of the burn, with the primary goals being to prevent infection, promote healing, minimize pain, and restore function. The principles of burn wound management include initial assessment, fluid resuscitation, infection control, and appropriate wound care.

Initial assessment

The initial evaluation of burn wounds is critical in determining the appropriate course of treatment. This process involves assessing both the extent and the depth of the injury, as well as identifying any complications that may affect treatment outcomes. The total body surface area (TBSA) affected is a key determinant in guiding resuscitation and overall management. The Rule of Nines and Lund-Browder chart are commonly used tools for estimating the TBSA affected by burns. Burns are classified into three degrees based on their depth:

- *First-degree (superficial).* Involves only the epidermis and presents as red, painful skin, similar to a sunburn.
- *Second-degree (partial-thickness).* Involves both the epidermis and part of the dermis, characterized by blistering, pain, and possible moisture.
- *Third-degree (full-thickness).* Extends through all skin layers and may involve subcutaneous tissue. The affected area is typically painless due to nerve destruction and appears white or charred.

For burns involving inhalation injury or significant trauma, ensuring airway and circulatory stability is of utmost importance, as respiratory compromise and hypovolemia can be life-threatening.

Fluid resuscitation

In burns that involve more than 20% TBSA, fluid resuscitation is essential to prevent hypovolemic shock and ensure adequate tissue perfusion.

The Parkland Formula [Fluid required in 24 hours=4×TBSA(%)×body weight (kg)] is commonly used to guide fluid administration during the first 24 hours post-injury. It recommends administration of crystalloid at a rate of 4 mL/kg percent of total body surface area (TBSA) burned with half of the total fluid volume administered during the first 8 hours from the time of injury. This formula initially addressed the serious issue of inadequate resuscitation. Half of the total volume is administered in the first 8 hours, and the remaining half over the next 16 hours. Lactated Ringer's solution is the fluid of choice.

Monitoring urine output (target of 0.5–1 mL/kg/hour in adults) and vital signs helps assess the adequacy of fluid resuscitation and avoid complications such as overhydration or under-resuscitation.

Wound care

Proper wound care is critical to preventing infection and promoting healing. The choice of wound management depends on the depth of the burn and its location.

- *Cleansing and debridement.* Initial cleansing with sterile saline or mild antiseptic solutions is necessary to remove debris, bacteria, and nonviable tissue. For deeper burns, debridement of necrotic tissue is essential to prevent infection and encourage granulation tissue formation.
- *Dressings.* Superficial burns typically do not require dressings. The use of moisturizing agents such as aloe vera or over-the-counter burn creams may provide symptomatic relief. Partial-thickness burns require a moist wound environment to facilitate healing. Silver sulfadiazine cream, hydrocolloid dressings, or non-adherent foam dressings can be used to cover the wound and prevent infection. Full-thickness burns often require more advanced interventions such as surgical debridement or skin grafting. Until definitive surgery, antimicrobial dressings or biological skin substitutes may be used.

Infection control

Burn wounds are highly susceptible to Gram-positive and Gram-negative infections due to the loss of the skin's protective barrier. Infection control measures are a cornerstone of burn wound management.

- *Topical antimicrobials*. Common agents include silver sulfadiazine, mafenide acetate, and bacitracin, which help prevent microbial colonization in the wound.
- *Systemic antibiotics*. Prophylactic systemic antibiotics are generally not recommended unless there is clinical evidence of infection (e.g., cellulitis, sepsis). Cultures and sensitivity testing should guide the selection of antibiotics in cases of confirmed infection.

Empiric antibiotic regimens. Normal renal function.
Target Pathogen: Gram-positive and Gram-negative
Outpatient therapy

Amoxicillin/clavulanate 1 g every 8 hours or
In patients with beta-lactam allergy:
Ciprofloxacin 500 mg every 12 hours + Metronidazole 500 mg every 8 hours

In patients at risk for CA-MRSA or who do not respond to first-line therapy add one of the following oral antibiotics:
Minocycline 100 mg every 12 hours
Trimethoprim and sulfamethoxazole 160/800–320/1600 mg every 12 hours
Doxycycline 100 mg every 12 hours
or
Inpatient therapy
One of the following intravenous antibiotics:
Ceftriaxone 2 g every 24 hours + Metronidazole 500 mg every 8 hours
Cefotaxime 2 g every 8 hours + Metronidazole 500 mg every 8 hours
Piperacillin/tazobactam 4,5 g every 6 hours
or
In patients with beta-lactam allergy:
Ciprofloxacin 200 mg every 8 hours + Metronidazole 500 mg every 8 hours
In patients at risk for CA-MRSA or who do not respond to first-line therapy add:
Vancomycin 25–30 mg/kg loading dose then 15–20 mg/kg/dose every 12 hours
Linezolid 600 mg every 12 hours.

Pain management
Effective pain control is a crucial aspect of burn management, as burns can cause significant and prolonged discomfort. Opioids such as morphine are often required for managing severe burn pain, while NSAIDs like ibuprofen or acetaminophen may be used for milder burns. For painful procedures such as dressing changes or debridement, additional pain relief or sedation may be necessary.

Nutritional support
The hypermetabolic response following a significant burn increases the patient's caloric and protein requirements. Burn patients often require nutritional supplementation to meet increased energy demands. Enteral feeding should be initiated early, especially in patients with extensive burns.
Surgical intervention
For deep or extensive burns, surgical intervention is necessary to remove necrotic tissue and promote wound closure.

- *Escharotomy.* For circumferential burns, particularly around the chest or limbs, escharotomy (a surgical incision through the eschar) may be required to relieve pressure and prevent ischemia or respiratory compromise.
- *Skin grafting.* For full-thickness burns, early excision of necrotic tissue followed by skin grafting is essential to prevent infection and promote healing.

Rehabilitation and long-term care

Rehabilitation begins early in burn care to prevent contractures, improve function, and address psychosocial concerns. Early mobilization, stretching, and splinting are necessary to maintain the range of motion and prevent joint contractures. Compression garments and silicone sheets may help reduce the development of hypertrophic scars, which can cause functional limitations and aesthetic concerns.

Conclusion

Non-necrotizing skin and soft tissue infections pose a significant clinical challenge due to their frequency and potential for serious complications. Successful management relies on early detection, accurate diagnosis, appropriate antimicrobial therapy, and supportive care. Preventive strategies also play a critical role. Continued research and clinical vigilance are crucial to improving treatment, especially with the rise of antibiotic resistance. Effective management focuses on timely source control, precise antimicrobial selection, and measures that promote patient recovery. Achieving a balance between early intervention and responsible antibiotic use is key to improving outcomes while minimizing resistance. A multidisciplinary team is essential for optimal care.

Competing interests

The author has no financial and non-financial competing interests to declare.

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Chapter 119

Infection in burns

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Introduction

The cause of death from a burn injury has profoundly changed over the last decades, from anoxic brain injury and inadequate resuscitation resulting in organ dysfunction, to infection, and sepsis-driven complications. The reason for this change in mortality is due to improved acute critical burn care. However, initial survival leads to challenges in the subsequent hospital course. Hyperinflammatory and hyper-stress responses lead to hypometabolism, catabolism, organ dysfunction and immune dysfunction. All of which, in combination with a disruptive skin barrier lead ultimately to a substantially increased risk and incidence of infections and sepsis.

Infection is a major cause of morbidity and is the leading cause of mortality in burns accounting for >50% of in-patient deaths. Risk factors that should not be ignored are medical devices such as urinary catheters, endotracheal intubation, arterial and central venous cannulation, and feeding tubes.

Given that infections are a leading cause of morbidity and mortality in burns, their prompt recognition and treatment can greatly impact burn management.

Primary sites of infection in burn patients are typically the wounds, lungs, bloodstream, and urinary tract. Infections in burns follow a relatively predictable timeline. Early in the course of hospitalization, skin and soft tissue infections occur while urinary tract, pneumonia and bloodstream infections occur later.

In general, treating infections has increased in complexity due to multi-resistant organisms, fungi, yeast, etc. and therefore understanding and treatment of infections in burn patients is paramount.

Burn wound infection

Burn wounds are initially “sterile”. However, due to the decreased blood flow and a nutrient-rich environment, burn wounds become an ideal environment for bacterial growth leading to rapid colonization and

subsequently can progress to infection and sepsis. Colonization is defined as the concentration of less than 10^5 bacteria per gram of tissue with the absence of invasive infection.

Diagnosis

Diagnosing burn wound infection can pose a challenge as the usual clinical presentations associated with local or systemic infection can also be present secondary to burn pathophysiology. For example, erythema around the burn wound typically attributed to peri-wound cellulitis can also be secondary to the inflammatory mediators from tissues surrounding the burn. In addition, systemic signs such as elevated core temperature, tachycardia, tachypnea and decreased systemic vascular resistance seen in systemic infection and sepsis can also be due to burn-induced inflammation or hypermetabolism and not necessarily associated with the presence of infections.

On *examination*, burn wound infection can be identified based on a change in gross appearance with violaceous, dark brown or black patchy discoloration of the wound, sub-eschar hemorrhage, early separation of the eschar and odor changes. Another sign would be the conversion of the burn wound from partial thickness to full-thickness necrosis.

Quantitative wound swabs can be useful; however, their utility remains controversial. Quantitative cultures cannot distinguish infection *vs.* colonization and only represent the area that is tested. Nevertheless, it can be argued that a negative quantitative culture (bacterial density $<10^5$ CFU) is clinically significant as it correlates well (96.1% negative predictive power) with the absence of invasive infection on histopathologic tissue evaluation.

Histologic evaluation is the most reliable method of confirming a diagnosis of burn wound infection. It can determine the depth and the extent of the infection. Burn wound infections are classified based on histology as: Stage I – Colonization of nonviable tissue; IA Superficial colonization: microorganisms present on burn wound surface; 1B Microbial penetration: microorganisms present in variable thickness of eschar; IC Sub-eschar proliferation: multiplication of microorganisms in the sub-eschar space. Stage II Invasion of viable tissue; IIA Microinvasion: microscopic foci of microorganisms in unburned viable tissue immediately beneath burn wound; IIB Generalized invasion: multifocal or diffuse penetration of microorganisms into viable subcutaneous tissue; IIC Microvascular invasion: microorganisms present in unburned small blood vessels and lymphatics.

Biomarkers, discussed in more detail under the section sepsis, are not standard of care nor is there strong evidence of their usage in burn wound infections.

Pathobiology

Organisms leading to burn wound infection typically have a chronological order of appearance. Burn wounds become colonized with the patient's own gram (+ve) flora within 5 days, however, gram (-ve) flora become the prominent organisms beyond the early phase (>5days). Fungal and yeast infection is typically seen in patients whose LOS exceeds 14 days (typically 14-28 days), older patients, and those with large TBSA burns. Risk factors for fungal infection are large TBSA involvement, immunodeficiency, GI complications, renal dysfunction, inhalational injury, multiple surgical interventions and prolonged use of broad-spectrum antibiotics. Lastly, prolonged hospital stays can lead to multi-drug resistant (MDR) organisms such as MRSA, ESBL, and MDR *Pseudomonas* and *Acinetobacter* species.

A variety of bacterial, viral, fungal and yeast pathogens can lead to burn wound infections and a summary of the microorganisms can be found in **Table 1**.

Table 1. Common pathogens of burn wound infection.

Group	Common species
Gram-positive bacteria	*Staphylococcus* and *Streptococcus* species
Gram-negative bacteria	*Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *E. coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Serratia marcescens*
Yeast	*Candida* sp.
Fungi	*Aspergillus*, *Penicillium*, *Rhizopus*, *Mucor*, *Rhizomucor*, *Fusarium*, and *Curvularia* —have greater invasive potential
Multidrug resistant organisms	Methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci, multi-drug resistant *Pseudomonas* and *Acinetobacter* species
Virus	Herpes Simplex Virus, Cytomegalovirus, Varicella Zoster Virus

Clinical management

Treatment of burn wound infection is multilayered and is quite complex.

Early excision and wound closure have been the mainstay of burn care, restoring the skin barrier function, minimizing wound infection and shortening hospital LOS.

Topical antimicrobial dressings have helped reduce the overall wound microbial bioburden. Antimicrobial dressing choice should be based on suspected organisms in the wound, wound bed characteristics, patient factors and wound healing trajectory. See **Table 2** for the commonly used dressings.

The increasing prevalence of *multi-drug-resistant organisms* has become a leading concern in the care of burn patients.

The use of *systemic antibiotics, antivirals and antifungals* should be reserved for patients with cellulitis, invasive infection, or signs of sepsis. The initial antibiotic management should be based on the antibiogram of the burn center (as susceptibilities may differ from other units within the institution), and the patient's length of stay. The antimicrobial coverage should be narrowed as early as possible based on cultures and sensitivity. The involvement of an antimicrobial stewardship team has been demonstrated to be helpful in the prevention of institutional resistance patterns. A clinical pharmacologist is recommended for frequent dose evaluation as drug absorption and elimination is greatly altered with larger %TBSA burns.

As mentioned, Gam (+ve) organisms are the first to colonize the burn wounds. Patients with invasive wound infection or those believed to be septic in the early phase of admission should be started on appropriate antibiotics with Gram (+ve) coverage such as penicillins, cephalosporins, or vancomycin (depending on the prevalence of MRSA). Gram (-ve) infections which occur later are managed with carbapenems, extended-spectrum penicillins, or ß-lactamase inhibitors.

Management of fungal infections can be challenging due to the limited number of antifungals and their inherent toxicities. Antifungals are grouped into azoles, polyenes and echinocandin. Fluconazole is the most commonly used agent in the azole group with excellent coverage against the yeast *Candida albicans* and molds. Itraconazole and Voriconazole are primarily used for aspergillosis and invasive mold infections. The polyene amphotericin B which is highly toxic is the standard of choice for invasive fungal infections. Caspofungin which is in the echinocandin group is used for combination treatment of *Aspergillus* and *Fusarium*.

Commonly seen viral infections are HSV, VZV and CMV, which stem from reactivation of latent infection due to the immunocompromised state of the burn patient. Treatment is commonly started with acyclovir.

Table 2. Commonly used dressings.

Commonly used dressings	Characteristics
Sodium hypochlorite and hypochlorous acid	Effective in breaking down biofilms and has broad spectrum coverage; Gram (+), gram (-), yeast, fungi
Povidone-iodine	Broad spectrum coverage, does not disrupt biofilm
0.5%-5% acetic acid	Broad spectrum antimicrobial activity and works against *Pseudomonas*; inhibits biofilm formation and bacterial growth
Antibiotics *Common drawback of topical antibiotics is the increased risk of fungal colonization with prolonged use	● *Bacitracin/polymyxin* ointments prevents bacterial growth and maintains a moist environment for epithelialization. ● *Mupirocin* ointment inhibits bacterial protein synthesis and is the topical agent of choice for MRSA infections. ● *Mafenide acetate* can penetrate biofilms and inhibits bacterial growth. Inhibits carbonic anhydrase causing pain and metabolic acidosis.
Heavy metals *Bind to bacteria DNA, proteins, and enzymes and cause destruction via an oxidative pathway	● *0.5% silver nitrate* broad spectrum coverage; gram (+), gram (-), yeast, fungi. ● *Silver sulfadiazine* combination of silver ions (+) antibiotic sulfadiazine; Gram (+), Gram (-), yeast; forms a pseudo-eschar on the wound bed, limiting its utility by hindering assessments of wound depths. ● *Nanocrystalline silver* dressings provide a sustained silver release lasting for a few days; requires less frequent changes; gram (+), gram (-), yeast, fungi, MRSA, VRE.

Abbreviations. MRSA: methicillin-resistant *Staphylococcus aureus*, VRE: vancomycin-resistant enterococci.

Conclusion

Early identification and management of a burn wound infection is essential. Early excision and wound closure are the gold standard to reduce the risk of developing burn wound infections. Antimicrobial dressings should be based on the wound characteristics and organisms. Antibiotic management should be guided by the hospital's burn center antibiogram as drug susceptibilities differ based on the patient population of each unit within the institution.

Burn sepsis

Burn sepsis is the major contributor to adverse outcomes including mortality, but paradoxically burn sepsis is very challenging to define and identify given the underlying hyperinflammatory and hypermetabolic response post-burn, which almost completely invalidates the traditional definition of sepsis.

Diagnosis

Numerous definitions for sepsis have been created for burn patients. However, none has been ideal, and at this time SEPSIS-3 criteria appear to be most sensitive in the detection of sepsis in burns in comparison to the ABA criteria or that developed by Mann-Salinas. SEPSIS-3 defines sepsis as a life-threatening organ dysfunction caused by a dysregulated host response to infection.

In SEPSIS-3, sepsis is considered if there is an acute increase of >/= 2 in the SOFA score (Sequential Organ Failure Assessment Score) in the presence of a suspected or documented infection.
Given the difficulty of diagnosis of infection and sepsis in burns, investigators have sought to determine if serum biomarkers could be of value. Commonly studied biomarkers are procalcitonin (PCT), C reactive protein (CRP), interleukin (IL) 6, 8 and 10 and tumor necrosis factor-alpha (TNF〈). Procalcitonin which has undetectable serum concentration in normal conditions correlates consistently in burns with the course of bacterial infection and is an excellent predictor of infection. CRP concentration strongly correlates with burn size. A study by Tan *et al.* noted that CRP has a specificity of 0.61 and a sensitivity of 0.8. However, PCT has a higher diagnostic specificity and sensitivity at 0.8 and 0.77 respectively when detecting between SIRS and sepsis but is not a widely used biomarker. A study by Jeschke showed that CRP cannot predict sepsis, while PCT can increase with infections, but it can also increase with burn injury alone. Burn size and surgery can influence PCT levels. Cytokines are strongly associated with mortality. Interleukins 6, 8 and 10 were noted to be significantly higher in burn non-survivors than in survivors. However, levels can be influenced by organ function, genetics and type of wound dressing. Hence, no specific biomarker is the gold standard in the detection of burn infections.
A novel predictor of burn sepsis onset is the Septic Predictor Index which is a quotient of the site of injury white adipose tissue macrophage proportion and the interleukin 1® production.

Clinical management
Restoring end-organ perfusion is the initial priority in managing burn patients with sepsis. This is followed by antimicrobial management and source control. Resuscitation involves crystalloids as there is no benefit in using albumin in burns. Antimicrobial choice, as with infection should be based on hospital and burn unit-specific antibiograms and specific cultures. Source control and investigations require an individualized approach based on clinical suspicion of infection source (i.e. chest x-ray, computed tomography of the abdomen, urinalysis, wound/tissue/blood/sputum cultures) and executed in a timely manner.

Pneumonia

Pneumonia significantly increases LOS, and morbidity mortality in burns. This is commonly seen in patients with inhalation injuries and mechanically ventilated patients. Organisms can enter the lung through direct contamination or hematogenous spread.
Chest x-ray findings can show lobar consolidation. However, burn patients may have nonspecific radiographic findings secondary to changes in pulmonary vascular permeability and changes secondary to inhalation injury and the presence of ARDS which can confound the interpretation of radiographic findings, and therefore bronchial cultures can aid in the diagnosis.
Nosocomial pneumonias are commonly gram (-ve). Empiric broad-spectrum antibiotic is initially started based on the burn unit's susceptibility pattern which is narrowed appropriately after identification of the specific pathogen. Furthermore, ventilator-associated pneumonia (VAP) bundles which include 3 to 5 independent and evidence-based strategies, and interventions are utilized in the ICU leading to a decrease in the incidence of VAP.

Central line-associated bloodstream infection (CLABSI)

The incidence of CLABSI is significantly high in the burn population. This is secondary to the prolonged need for central venous access, immunosuppression, and breakdown of the protective skin barrier.
CLABSI is diagnosed when there is a positive blood culture in a patient with an indwelling central line, or within 48 hours after removal.
Historically, burn centers change central lines at scheduled intervals; however, there's no consensus on its utility in improving the risk of CLABSI.
Minimizing rates of CLABSI is achieved through proper sterile technique on insertion, avoiding femoral sites when possible using 2% chlorhexidine solution prior to insertion and immediate removal of the central line when not indicated. Antimicrobial-impregnated lines and dressings have shown reductions in microbial colonization; however, a recent meta-analysis noted a nonsignificant association with lower CLABSI risk compared to non-antibiotic-impregnated lines.

Clostridioides difficile infection (*C. difficile*)

The incidence of *Clostridioides difficile* infections is also significantly higher in the burn ICU. *C. difficile* infections are typically seen as a secondary complication due to antibiotic use. Burn patients are at risk for *C. difficile* infection due to burn severity, immunosuppression, use of proton pump inhibitors, enteral feeding with NG tube, prolonged and broad-spectrum antibiotic use and increased hospital LOS.
Diagnosis is based on clinical findings and confirmed by the presence of the toxin in the stool. Typically, hospitalized patients present with persistent diarrhea for 48 hours or longer in duration. *C. difficile-associated* diarrhea (CDAD) can progress to colitis and even pan-colitis which can have devastating and dire consequences for the patients.
Treatment includes discontinuing the causative antibiotics, implementing infection control measures, and administering appropriate antibiotics based on evidence-based guidelines. Metronidazole and oral vancomycin are the most frequently used antimicrobials. Response to treatment is demonstrated by the resolution of diarrhea or the presence of formed stool.

Catheter-associated urinary tract infection (CAUTI)

Urinary tract infection can complicate burn admissions who need monitoring for fluid resuscitation. Risk factors are prolonged catheterization, female gender, age, diabetes, bacterial colonization and improper care on insertion. Implementation of CAUTI bundles has significantly decreased the incidence of CAUTI in hospitals. Adherence to the 4-5 elements of the CAUTI bundle influences the rate of infection and average catheter days per patient.

Prevention strategies to minimize contamination following burn injury

Prevention strategies to prevent infection and sepsis in burns start from the onset of injury and should be considered by treating centers. Burn units must consider endogenous and exogenous sources of infection.

Endogenous sources are found on the patient's skin flora, burns, and respiratory secretions. These remain the primary source of infectious outbreaks in the burn unit. Exogenous factors arise from myriads of factors including healthcare providers' lack of adherence to IP&C protocols, improper cleaning of medical equipment, ventilation equipment, and visitors. The burn unit must have its own dedicated facilities and PPE use must be strictly adhered to during patient care. Furthermore, hospitals must implement VAP, CAUTI, and CLABSI bundles (evidence-based practices) to decrease the risk of infections.

Conclusion

Patients with burn injuries are at a high risk of wound, lung, and catheter-related infections. In order to improve patient outcomes, prevention strategies remain among the important aspects of infection management. The chronological appearance of organisms leading to burn wound infection, lung and catheter-related infection can assist in the choice of empiric antimicrobial management which is also guided by each burn unit's antibiogram and can be subsequently tapered to culture-directed antimicrobials.

Competing interests

The authors have no financial and non-financial competing interests to declare.

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Chapter 120

Anorectal abscesses

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Introduction

Perianal abscess is one of the most common acute proctological pathologies and can be particularly distressing due to its association with severe pain and social embarrassment. The annual incidence of perianal abscess in the UK is estimated between 14,000 and 20,000 cases. A Swedish cohort study estimated the incidence at 16.1 per 100,000 individuals. However, the actual incidence might be higher, as many patients receive antibiotic treatment in the community, and some abscesses spontaneously resolve or discharge. The male-to-female ratio ranges from 2:1 to 5:1 across different cohorts, with peak incidence occurring in the third decade, although it can occur at any age. Due to its prevalence and the potential risk of life-threatening complications, such as sepsis and necrotizing fasciitis, and progression to perianal fistula, accurate diagnosis and treatment can significantly impact associated healthcare costs and antibiotic use.

Anatomy, pathophysiology and classification

Accurate knowledge of the anatomy of the anal canal and adjacent structures is essential for understanding the pathogenesis, staging the disease and planning the best surgical strategy.
During embryological development, the anus is formed at week 8 by perforation of the cloacal membrane. In adults, this membrane corresponds to the dentate line (the boundary between the anal epithelium and the rectal mucosa), at which level the crypts of Morgagni are located (their number varies from 6 to 14) and at the bottom of which is located the ostium of the anal glands. These are mucous secretion glands and they are located in the submucosa, although some have extensions into the intersphincteric space. According to

the cryptoglandular theory, first proposed by Parks in 1961, 90% of anal abscesses are caused by obstruction of the duct of one of these glands, followed by dilatation and bacterial proliferation with subsequent pus formation. Although this is still the most widely accepted theory, it does not explain how all types of perianal abscesses occur.
In 10% of cases, a perianal abscess may develop as a consequence of Crohn's disease, trauma (including ingestion or trans-anal introduction of foreign bodies), anal fissure, anal and rectal cancer, pelvic infections (including tuberculosis and actinomycosis) and hidradenitis suppurativa.
Risk factors include male sex, smoking, chronic inflammatory bowel disease, diabetes and immunodeficiency (especially HIV). It has been hypothesized that the higher incidence of the disease in men may be related to hormonal factors.
Regardless of the underlying cause of abscess formation, pus tends to spread along the path of least resistance, occupying different anatomical spaces depending on the site of origin and individual anatomy. This phenomenon enables the classification of abscesses based on their location. Anorectal abscesses are therefore classified into the following types:

Simple abscesses:
- **subcutaneous** or **superficial** (without involvement of the sphincters);
- **intersphincteric** (located in the plane between the internal and external sphincters);
- **ischiorectal** (when it is outside the external sphincter, but below the levator ani plane).

Complex abscesses:
- **supralevator** (located above the levator ani muscle);
- **deep postanal space abscess** (located posteriorly below the levator ani plane and above the anococcygeal ligament);
- **horseshoe-shaped** (when an ischiorectal abscess extends contralaterally, forming a semicircle).

The natural history of perianal abscesses shows that spontaneous drainage and perianal fistula formation may occur over time.
According to some authors, the perianal fistula represents the chronic form of the same pathological entity, which can be broadly defined as perianal sepsis. In more severe cases (multiple or very large abscesses, immunocompromised patients, Crohn's disease and diabetes, anterior abscess due to the proximity with anterior urogenital triangle) the infection, due to the synergic action of polymicrobial aerobic and anaerobic bacteria, can spread to the surrounding soft tissues (perineum, rectum and external genitalia) leading to pelvic sepsis and Fournier's gangrene. These cases are associated with systemic sepsis that represents a life-threatening condition with a mortality ranging from 20 to 40%.

Presentation

In most cases, a perianal abscess develops over the course of a few hours or days without an identifiable triggering cause. The initial symptom is pain, which can be extremely intense and continuous, often exacerbated by pressure on the affected area. Swelling follows, presenting with a firm, elastic consistency. In the case of larger abscesses, it may also be associated with a fluctuant sensation. The skin over the swollen area appears hyperemic and edematous. In cases of deep collections, such as supralevator or deep post-anal space abscesses, swelling may not be apparent, and the pain may be poorly localized.

Fever is common and, in severe cases, signs of systemic sepsis may develop. In immunocompromised patients, severe forms can occur even in the absence of fever.
If spontaneous drainage has already occurred by the time of the first visit, pus discharge may be evident both from the perianal skin and/or through the anus with the resolution or improvement of the preceding symptoms. In cases of anaerobic bacterial infections, secretions may exhibit a foul odor.

Diagnosis

In most cases, the medical history and clinical examination conducted are sufficient to make the diagnosis. Blood tests are not pathognomonic and usually show increased inflammatory markers (leukocytosis, neutrophilia, elevated levels of C-reactive protein [CRP] and procalcitonin [PCT]). Particularly elevated levels of CRP and PCT may indicate the presence of systemic sepsis.
In case of the suspicion of deep abscesses, recurrent abscesses and the associated presence of fistulae, as well as complex disease, a definitive diagnosis requires imaging techniques and/or exploration under anesthesia (EUA). The most accurate imaging techniques include endoanal ultrasound (EU) and Pelvic magnetic resonance imaging (MRI), used alone or in combination. The advantage of the former is that it is cheaper, can be performed intraoperatively and, in the presence of associated fistulous disease, can be implemented by infiltrating hydrogen peroxide into the fistula, which acts as a contrast agent. Magnetic resonance imaging has the advantage of not requiring an endoanal probe and is less operator-dependent, it also allows the assessment of distant anatomical structures. However, MRI is often not accessible in acute settings and endoanal ultrasound may be not available locally or not feasible due to patient pain.
Although small abscesses, especially in the intersphincteric plan, may not be identified, abdominal contrast-enhanced CT scan is easily available, even in rural settings, and can detect deep abscesses as oval-shaped fluid/air collection or incipient signs of necrotizing fasciitis.
X-ray fistulography and transperineal ultrasound can provide useful information in selected cases, but have lower sensitivity and specificity than EUS and MRI, are not available everywhere, and therefore rarely used.

Therapy

According to multiple guidelines, cases of uncomplicated perianal abscess in patients without significant comorbidities should be managed within 24 hours of diagnosis. In case of complicated disease and/or high-risk patients (immunocompromised, diabetic, Crohn's disease, etc.), treatment should begin as soon as possible (**Figure 1** and **Figure 2**).