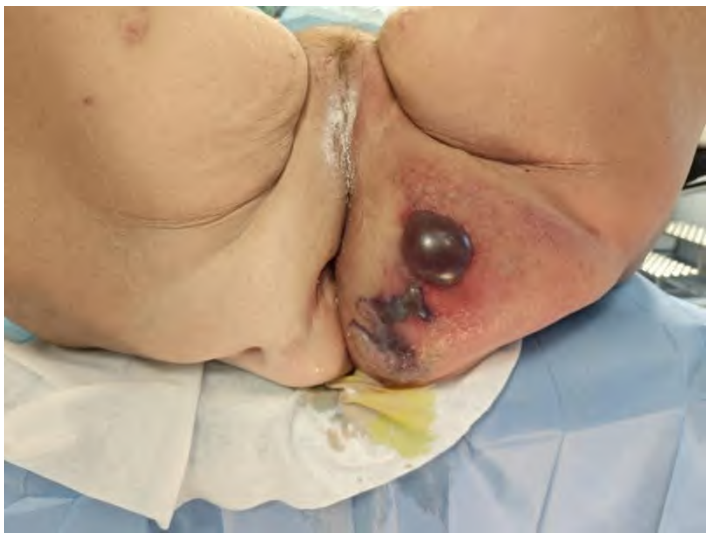

Figure 1. Perianal abscess with features of skin necrosis, requiring prompt surgical drainage due to the high risk of progression to Fournier's gangrene (Courtesy of Dr. Marcello Di Martino, Department of Health Sciences, University of Piemonte Orientale, Novara, Italy).

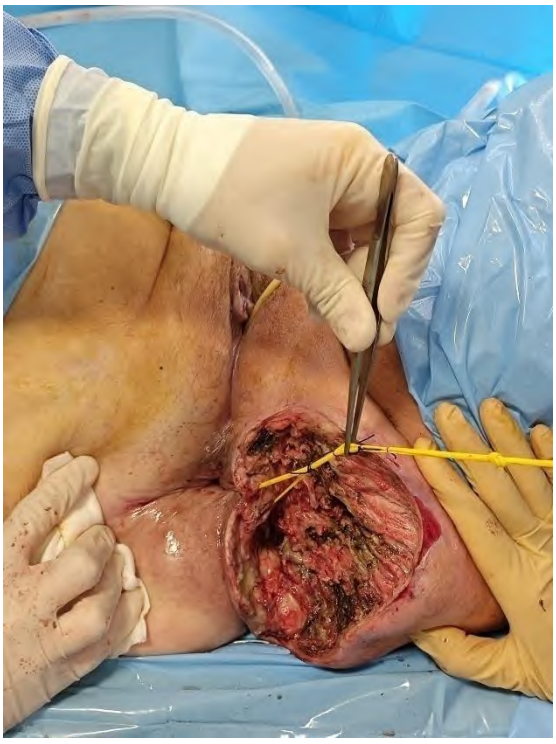

Figure 2. Intraoperative photograph of the previous case, showing the removal of necrotic tissues and the identification of an associated perianal fistula, treated with the placement of a seton (Courtesy of Dr. Marcello Di Martino, Department of Health Sciences, University of Piemonte Orientale, Novara, Italy).

The cornerstone of therapy is surgical drainage. It must be performed in all cases of fluid collection and is also indicated when spontaneous pus discharge has already occurred since the disruption of the skin is often insufficient to allow for adequate drainage and digital breakdown of the septa within the abscess cavity enables a more radical treatment of the pus collection.

The incision should be made as close as possible to the anal margin to minimize the length of the tract in case of evolution in the anal fistula. It is preferable to make the incision parallel to the fibers of the anal sphincter to minimize muscle damage.
The only exceptions to this strategy are: 1) intersphincteric abscesses requiring a small transverse endoanal incision at the level of dentate line and 2) supralevator abscess, if no other collections are detected in the other perianal spaces at imaging, as in this case, the abscess originates from intersphincteric space and a transrectal incision needs to be performed.
The setting in which the procedure is performed depends on the characteristics of the patient and the severity of the presentation. Small simple abscesses in patients without severe comorbidities can be drained in an outpatient setting after infiltration of local anesthetic in Sims' position. However, performing the procedure under spinal anesthesia or sedation facilitates a more efficient surgical intervention, reducing surgical distress for the patient, minimizing the risk of suboptimal treatment (for an inadequately sized incision or incomplete debridement), and allowing for the identification of a fistula or other associated anorectal pathology. Imaging techniques are often unnecessary in such cases. The decision about hospital admission should be based on patient conditions, anesthesia performed and local rules because the outpatient follow-up is sufficient.
In cases with recurrent disease, deep and/or multiple abscesses, perianal Crohn's disease and in immunocompromised patients the drainage is indicated in the operating theatre. In such circumstances, spinal or general anesthesia is preferred to allow adequate relaxation of the sphincters and thus facilitate surgical exploration, which is performed, usually, in the lithotomy position although a prone position is recommended in the abscesses of deep postanal space for a better exposition of the operative field. Imaging techniques, both pre-and intra-operatively are indicated. In most collections, drainage is carried out through the skin plane, but in the case of supralevator or intersphincteric abscess, transrectal drainage may be preferable to reduce the risk of supra-sphincteric or extra-sphincteric fistula formation. In the presence of a horseshoe abscess, it is preferable to make 2 or multiple incisions, to effectively drain the entire collection a put a drain to prevent false closure of the wound due to the premature approximation of the superficial wound edges.
A general principle to reduce the risk of recurrence is to ensure that all internal septa and loculations of the collection are dissected to ensure that all purulent material is drained. The duration of postoperative stay varies according to the patient's condition.
Antibiotic prophylaxis as well as postoperative therapy are not indicated in uncomplicated disease.
Antibiotic treatment must be started at the time of diagnosis and continued after drainage in immunocompromised patients, in Crohn's disease, in cases of cellulitis and/or necrosis, and cases of associated systemic sepsis. It is given empirically and must be active against aerobic and anaerobic bacteria (e.g. metronidazole plus amoxicillin-clavulanic acid/cefazolin or a quinolone) for 5-10 days according to the clinical evolution and wound healing. Only in the most severe cases or immunocompromised patients, the antibiotic treatment may be modified according to the results of culture tests (not routinely practiced) performed at the time of surgery.
The type of microorganisms cultured may also predict the risk of recurrence: while the presence of gut microorganisms suggests a true cryptogenic etiology with a consistent risk of perianal fistula, gram-positive bacteria suggest a different etiopathogenesis (e.g. hidradenitis) with a negligible risk of fistulation.
In patients with prosthetic valves, a history of bacterial endocarditis, congenital heart disease, and heart transplant recipients with valvular disease antibiotic prophylaxis is strongly recommended.
After the pus is drained, the cavity is irrigated with saline and dilute hydrogen peroxide solution and packed with gauze, removed after 24-48 hours. The goal is to achieve healing by secondary intention while minimizing the risk of complications.

In the case of a small collection, drainage alone may be sufficient. In the other cases, a factor that can lead to recurrence is the premature closure of the skin over the cavity. There is no consensus on how to achieve this goal. Repeated gauze packing has been traditionally performed, but it may cause relevant pain without any advantage when compared to no-packing or drain placement strategies. An alternative option is deroofing the overlying skin or, in case of large cavities, inserting a mushroom catheter to perform drainage and irrigation with less discomfort for the patients.
In the majority of cases, the patient can be discharged with instructions for 2-3 daily warm sitz baths, pain management, and periodic outpatient follow-up, as the wound may take 3-8 weeks to heal.
When an internal anal opening is identified during the procedure (by injecting the cavity with a dilute hydrogen peroxide solution or methylene blue to detect any leakage from the anal canal), the placement of a seton may improve local source control in preparation for definitive treatment, which is typically performed after approximately 8 weeks.

Perianal fistula prevention

The perianal fistula occurrence rates after abscess drainage range between 30% and 50%. There are no recommendations for lowering this risk except to perform an effective drainage of the pus collection. In cases where the presence of fistulas is suspected at the time of abscess' drainage, it is preferable to postpone its definitive treatment until a later surgical time, since in the presence of inflammation and oedema of the tissues, locating the passageway can be difficult and the iatrogenic creation of false paths is possible. An immediate fistulotomy in the case of a concomitant superficial fistula may lower future recurrence, but it should be considered in selected patients only by an experienced colorectal surgeon, after a careful evaluation of the patient's comorbidity and past medical history.
There is a close relationship between perianal abscess and perianal fistula, which can be summarized as 'all fistulas are preceded by an abscess, but not all abscesses lead to a fistula'.

Conclusion

In the case of an anorectal abscess, early diagnosis and appropriate surgical management are essential to minimize the duration of symptoms and the risk and severity of sequelae. The cornerstone of treatment is surgical drainage of the collection, with antibiotics reserved for complex cases and/or for fragile patients. The choice of anesthesia should be evaluated based on the type of abscess, the patient's characteristics, and the local healthcare setting. Perioperative antibiotics are suggested in case of systemic sepsis, cellulitis, immunocompromised patients and secondary forms for 5-10 days. Antibiotic prophylaxis is recommended for prosthetic valves, history of bacterial endocarditis, congenital heart disease, and heart transplant recipients with valvular disease.
In the absence of colorectal expertise, research of an associated fistula and its treatment should not be performed due to the risk of sphincter damage and the creation of iatrogenic tracts. Despite advancements in diagnostic and therapeutic techniques, the occurrence of perianal fistulas after abscess treatment is common (30 to 50%) and requires further surgical intervention.

Competing interests

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

References

1. Sahnan K, et al. Perianal abscess. BMJ. 2017;356:j475.
2. Adamo K, et al. Prevalence and recurrence rate of perianal abscess--a population-based study, Sweden 1997-2009. Int J Colorectal Dis. 2016;31:669-673.
3. Gosselink MP, et al. The cryptoglandular theory revisited. Colorectal Dis. 2015;17:1041-1043.
4. Parks AG. Pathogenesis and treatment of fistula-in-ano. Br Med J 1961;18:1.
5. Zabot GP, et al. Modern surgical strategies for perianal Crohn's disease. World J Gastroenterol. 2020;26:6572-6581.
6. Gupta PJ. Ano-perianal tuberculosis--solving a clinical dilemma. Afr Health Sci. 2005;5:345-347.
7. Fry GA, et al. Primary Actinomycosis of the Rectum with Multiple Perianal and Perineal Fistulae. Mayo Clin Proc. 1965;40:296-299.
8. Wei PL, et al. Increased risk of diabetes following perianal abscess: a population-based follow-up study. Int J Colorectal Dis. 2013;28:235-240.
9. El-Tawil AM. Mechanism of non-specific-fistula-in-ano: Hormonal aspects-Review. Pathophysiology. 2012;19:55-59.
10. Seow-Choen F, et al. Histoanatomy of anal glands. Dis Colon Rectum. 1994;37:1215-1218.
11. Amato A, et al. Evaluation and management of perianal abscess and anal fistula: SICCR position statement. Tech Coloproctol. 2020;24:127-143.
12. Sorensen MD, et al. Fournier's Gangrene: Epidemiology and Outcomes in the General US Population. Urol Int. 2016;97:249-259.
13. Barkai O, et al. Characterization of Risk Factors Affecting the Recurrence of Perianal Abscesses and Complications. Isr Med Assoc J. 2024;26:428-433.
14. Ommer A, et al. German S3 guidelines: anal abscess and fistula (second revised version). Langenbecks Arch Surg. 2017;402:191-201.
15. Khati NJ, et al. CT of acute perianal abscesses and infected fistulae: a pictorial essay. Emerg Radiol. 2015;22:329-335.
16. Siddiqui MR, et al. A diagnostic accuracy meta-analysis of endoanal ultrasound and MRI for perianal fistula assessment. Dis Colon Rectum. 2012;55:576-585.
17. Royal College of Surgeons. Emergency surgery: standards for unscheduled surgical care. 2011. Available at: www.rcseng.ac.uk/library-and-publications/college-publications/docs/emergency-surgery-standards-for-unscheduled-care/. Last accessed: 1 September 2024.
18. Gaertner WB, et al. The American Society of Colon and Rectal Surgeons Clinical Practice Guidelines for the Management of Anorectal Abscess, Fistula-in-Ano, and Rectovaginal Fistula. Dis Colon Rectum. 2022;65:964-985.
19. Abcarian H. Anorectal infection: abscess-fistula. Clin Colon Rectal Surg. 2011;24:14-21.
20. Sözener U, et al. Does adjuvant antibiotic treatment after drainage of anorectal abscess prevent development of anal fistulas? A randomized, placebo-controlled, double-blind, multicenter study. Dis Colon Rectum. 2011;54:923-929.
21. Vogel JD, et al. Clinical Practice Guideline for the Management of Anorectal Abscess, Fistula-in-Ano, and Rectovaginal Fistula. Dis Colon Rectum. 2016;59:1117-1133.
22. Grace RH, et al. Anorectal sepsis: microbiology in relation to fistula-in-ano. Br J Surg. 1982;69:401-403.
23. Clark S, et al. Colorectal Surgery Companion to Specialist Surgical Practice, 7 th Ed. Amsterdam, Elsevier; 2023
24. Tarasconi A, et al. Anorectal emergencies: WSES-AAST guidelines. World J Emerg Surg. 2021;16:48.

25. Yano T, et al. Prognostic factors for recurrence following the initial drainage of an anorectal abscess. Int J Colorectal Dis. 2010;25:1495-1498.
26. Zhu DA, et al. Packing versus mushroom catheters following incision and drainage in anorectal abscess. Ir J Med Sci. 2019;188:1343-1348.
27. Newton K, et al. Postoperative Packing of Perianal Abscess Cavities (PPAC2): randomized clinical trial. Br J Surg. 2022;109:951-957.
28. Lohsiriwat V. Anorectal emergencies. World J Gastroenterol 2016;22:5867-5878.
29. Turner SV, et al. Perirectal Abscess. In: StatPearls.Treasure Island (FL): StatPearls Publishing; 2024 Jan-.

Chapter 121

Necrotizing soft tissue infections. Principles of treatment

Jan Ulrych
First Department of Surgery, Department of Abdominal, Thoracic Surgery and Traumatology, First Faculty of Medicine, Charles University and General University Hospital, Prague, Czech Republic.

Vaclava Adamkova
Clinical Microbiology and ATB Centre, Institute of Medical Biochemistry and Laboratory Diagnostics, General University Hospital, Prague, Czech Republic.

Introduction

Necrotizing soft-tissue infections (NSTIs) are life-threatening and rapidly progressive infections, that are characterized by the development of necrosis in soft tissue and associated with severe systemic toxicity. Any or all of the anatomic layers of the soft tissues (skin, subcutaneous tissue, superficial fascia, deep fascia, or muscles) may be involved. The limbs followed by the genitoperineal area (Fournier's gangrene) are the most frequently involved part of the body. NSTIs are caused by a variety of microbes and can be either monomicrobial infections (most caused by group A streptococci, particularly *Streptococcus pyogenes,* or by *Staphylococcus aureus*) and polymicrobial infections (characterised by mixed aerobic-anaerobic infection). Specific pathophysiologic mechanisms in NSTIs are related to the toxins and enzymes produced by involved bacteria. Diagnosis of NSTIs is primarily clinical diagnosis. However cutaneous manifestations may be initially absent, or early local symptoms might be similar to those seen in non-necrotizing infections (cellulitis and erysipelas). So, it is estimated that about 50% of patients with NSTIs are initially misdiagnosed. In the late stage, there are local manifestations (haemorrhagic bullae, cyanotic skin discoloration called ecchymosis, skin anaesthesia, crepitus, skin necrosis and gangrene) and systemic symptoms of toxicity. Radiologic imaging (CT, MRI, US) may be able to provide useful information when the clinical diagnosis is uncertain. Early recognition of NSTIs is a key step in patient management. Treatment of NSTIs has to be prompt and aggressive because any therapy delay causes increased mortality and worse outcomes. The principles of treatment of NSTIs are reviewed here, while epidemiology, risk factors, classification, microbiology, clinical features and diagnostic tools are omitted.

Principles of treatment

NSTIs are life-threatening infections associated with high mortality and severe morbidity. Patient survival is the primary outcome of interest. Initially, early surgical source control, antimicrobial therapy, and (organ) supportive measures are the cornerstone of treatment in patients with NSTIs. Adjunctive treatment options

(intravenous immunoglobulin therapy, hyperbaric oxygen therapy) have been explored to improve outcomes in patients with NSTIs, but the efficacy is conflicting. A multidisciplinary collaboration of surgeons, intensivists and infectious disease (ID) specialists is mandatory for the first-line management of NSTIs. In the post-acute phase long-term management consists of prolonged and complex treatment processes including specialized wound management, reconstruction and plastic surgery, rehabilitation, nutrition support, pain management, etc. A multidisciplinary team approach is fully required.

Surgery

Surgery plays a crucial role in NSTI management, both in diagnosis and treatment. Surgical source control in patients with NSTIs includes two basic surgical procedures – surgical debridement and amputation. In addition to controlling the source of infection, surgery allows to confirm the diagnosis of NSTIs and the need for debridement, to determine the extent of infection, and obtain samples for microbiological examination.

Timing of initial surgery

Prompt recognition of NSTIs and immediate surgery is fundamental because delay in early surgical source control significantly correlate with worse outcomes and higher mortality rates. Delay in treatment consists of two variables including patient delay (interval between the onset of symptoms and the patient seeking medical care), and surgical delay. Patient delay is a problem not easily influenced by medical personnel. The main factors contributing to surgical delay are misdiagnosis, a delayed surgical decision, logistical issues regarding operating room access, and transfer to another health care institution. Awareness of NSTIs is an essential factor for the reduction of a high percentage of initially missed diagnoses because NSTIs are much less frequent than non-necrotizing infections (erysipelas, cellulitis, abscess) and local cutaneous symptoms may be initially absent or non-specific. If the clinical diagnosis of NSTIs is less convincing but there is a high suspicion of necrotizing infection, surgery is warranted. Skin incision should be carried down to the fascia over the centre of the area most involved. Surgical exploration may reveal colliquative necrosis of the fascia and the subcutaneous layer with muddy, dishwater-like fluid, and sometimes the presence of gas. A sensitive clinical sign for necrotizing fasciitis is loss of fascia adherence to the overlying adjoining subcutaneous fat layer allowing the surgeon to easily dissect with a finger along the fascia. Regarding surgical decisions radiologic imaging must neither delay nor deter surgery if the clinical diagnosis of NSTIs is obvious. To avoid treatment delay, the patient should undergo initial surgical debridement at the admitting hospital. Once the first line treatment has been performed including initial surgical debridement, antibiotic therapy, and supportive critical care, the patient may be transferred to a tertiary care institution for further complex therapy. Considering the best timing of surgical source control in patients with NSTIs, the initial surgical debridement should be provided as soon as possible, ideally within 6 hours (at least 12 hours) after admission. Based on the recent systemic review and meta-analysis, early surgical debridement decreases the mortality rate for patients with NSTIs by almost 50%. Surgical treatment within 6 hours after presentation at the hospital resulted in a 19% mortality rate compared to 32% when surgical treatment was delayed over 6 hours after hospital admission.

Surgical source control

Surgical source control includes surgical debridement and limb amputation. Surgical debridement remains a basic surgical skill of the general surgeon, but the initial surgical debridement should be ideally performed by a senior surgeon because the consequences of the surgery can be devastating (large tissue defect, risk of amputation, etc.). Surgical debridement includes complete removal of necrotic skin and devitalized soft

tissue, and removal of infected devices or foreign bodies as well. There are two concepts of surgical debridement – traditional surgical debridement and skin-sparing debridement technique.
Traditional surgical debridement involves large areas of tissue. An extensive initial incision is done, and removal of all non-viable tissue should be accomplished including muscle, fascial layers, subcutaneous tissue, and skin if they are compromised. The incision should be extended until viable bleeding tissue is seen. Healthy overlying skin needs to be removed if there is extensive tissue involvement underneath. The goal of traditional surgical debridement is to create wide opened wound with a well-vascularized bed. However, it can lead to large, difficult-to-treat a complex wound associated with disfigurement, immobility, and chronic pain with often only skin grafting as an option for reconstruction.
Skin-sparing debridement techniques include the removal of just only necrotic deep soft tissue (necrotic subcutaneous fat and fascia), and the perfused overlying skin should be preserved. If the skin viability is questionable, skin preservation and reassessment at the second operation are indicated. Skin perfusion and viability can easily be assessed at re-exploration, and removal at that time is easy if indicated. Complete removal of necrotic deep soft tissue remains essential, so if initial surgical exploration is inadequate incision extension, multiple incisions, counter incisions can be used. Skin-sparing debridement results in significantly more wounds closed completely by delayed primary sutures of existing skin flaps and a significantly lower overall wound percentage closed by skin graft while demonstrating equivalent efficacy of surgical source control and a similar low mortality rate.
In initial surgery, amputation of a limb is usually not necessary. Primary amputation may be indicated as a potentially life-saving intervention that reduces operative time and blood loss in unstable patients. In this case, a guillotine amputation should be performed to remove skin, soft tissue, and bone at an uninvolved level proximal to the area of necrotizing infection. Definitive closure is performed subsequently. Limb amputation may be more often considered in critically ill patients if repeated debridement is unlikely to obtain source control, or when functional outcomes are likely to be obviously better with an amputation compared with a reconstruction.
In necrotizing infection of the perineal, genital, or perianal area ongoing faecal contamination may interfere with effective surgical source control. Therefore, stool diversion should be considered in patients with Fournier's gangrene. The traditional surgical technique used for faecal diversion is the diverting colostomy. Recently, rectal diversion devices have been proposed to avoid morbidity associated with colostomy and its complications.

Second-look surgery
Second-look surgery and subsequent surgical debridement should be scheduled and performed within at least 12-24 hours after initial debridement. Earlier debridement may be necessary if the clinical condition is progressively worsening, and laboratory tests give evidence for ongoing infection. Re-explorations should be repeated until the time when no debridement is required. Usually, more operations (3-4 debridements) are needed till complete elimination of the infection source is achieved.

Wound management
When surgical debridement is no longer necessary, ongoing wound management becomes a very important part of surgical care. Microbial pathogens in the wound contribute to delayed wound healing due to maintaining local inflammatory response and competing with host cells for nutrients and oxygen. The appropriate wound dressings should decrease the burden of microbes and provide an optimal environment for wound healing. Standard wound management includes gentle wound debridement to remove microbial biofilm and the use of topical antiseptic agents. However, it has not been established whether some topical antiseptics

are better than simple moist wound care dressing. Dressing changes can be usually performed at the bedside. Negative pressure wound therapy (NPWT) has become a popular treatment modality for wound management including post-operative wound care in patients with NSTIs after surgical debridement and complete removal of necrosis. NPWT is a wound dressing system that continuously or intermittently applies subatmospheric pressure on the surface of the wound. When the wound bed is clean, NPWT accelerates wound healing by removing excessive exudate fluid, reducing bacteria load, increasing capillary circulation and inflow, and encouraging granulation, vascularity, and epithelial migration. The benefits of traditional NPWT may be augmented by the ability to irrigate the wound with fluid or antiseptic solutions through this system. Negative pressure wound therapy with instillation (NPWTi) has been shown to reduce biofilms present in wounds helping heal clinically infected wounds. NPWT allows for a decreased frequency of dressing changes (every 2-3 days) and reduces related patient discomfort and pain medication. Moreover, it was reported, that NPWTi is associated with higher rates of wound closure without increasing complication rates in patients with NSTIs compared with traditional NPWT. Mostly NPWT device is applied on extremities, but it is very useful and effective in managing perineal areas.

Wound coverage or closure

Definitive coverage or closure of the wound can be considered when the wound bed is covered by clean healthy granulation tissue. However, definitive coverage is not urgent and should be delayed until the patient is physiologically stable. During this period temporary skin coverage may be applied. Temporary skin substitutes include porcine and cadaveric skin (allografts) or artificial dermal substitutes. Except for traditional allografts, some patients may also benefit from the use of artificial dermal substitutes. There are bilayer dermal substitutes (e.g., Integra) and single-layer dermal substitutes (eg, MatriDerm). Based on the used dermal substitutes epidermal autograft application is performed after 2-3 weeks (Integra) or immediately (MatriDerm).

Several options are available for definitive wound closure: healing by secondary intention, delayed primary closure, skin grafting, and flap coverage. Delayed primary closure or healing by secondary intention is used only if the wounds are small with excess subcutaneous tissue. Large skin defects are indicated for skin grafting, particularly in limbs. Skin grafting is one of the simplest and most used reconstructive techniques in patients with NSTIs. There is a split-thickness skin graft (graft that contains the epidermis and a portion of the dermis) and a full-thickness skin graft (consists of the epidermis and entire dermis). Complex skin and soft tissue defects from NSTIs, not amenable to skin grafting, can be more effectively and durably covered using a spectrum of flaps. The choice of flap (pedicled or free flap) usually depends on the anatomy region and wound characteristics. Loco-regional muscle flaps and loco-regional fasciocutaneous flaps are employed more often. Free flaps with revascularization at the reconstructive site using micro-surgical techniques can be performed when local flaps are not available.

Antimicrobial therapy

Antimicrobial treatment must begin as soon as the diagnosis of NSTIs is considered. Initial antibiotic therapy for NSTIs is typically empirical in nature because a patient needs immediate treatment, and microbiological data (culture and antimicrobial susceptibility results) usually require up to 48–72 hours before they are available. When microbial aetiology is identified and susceptibility has been tested, directed antibiotic therapy can be adjusted. The duration of antibiotic therapy is not well defined. Antimicrobial treatment should be administered until surgical source control has been completed, further surgical debridement is no longer necessary, and the patient has improved clinically. It usually lasts approximately 7-10 days in total. Initial antibiotic therapy of NTSIs should be prompt and aggressive. Principles of empirical therapy include (1)

administration of broad-spectrum antibiotics with bactericidal action, (2) administration of antibiotics that reduce toxin production (central role of toxin in the pathophysiology of NSTIs), and finally (3) optimised antibiotic regime and administration modality to achieve appropriate target tissue concentrations of antibiotics.

An initial antibiotic regimen is recommended based on a pragmatic approach. Because clinical examination alone cannot differentiate between monomicrobial and polymicrobial aetiology, aggressive broad-spectrum empiric antimicrobial therapy should be selected to cover Gram-positive, Gram-negative, and anaerobic microbes (**Table 1**). Knowledge of the local epidemiological situation has to be taken into account in the choice of the appropriate antibiotic regimen as well. Empiric antibiotic regimens should always include antibiotics, which cover methicillin-resistant *Staphylococcus aureus* (MRSA), particularly in countries with high incidence of MRSA. In addition, extended coverage for Gram-negative pathogens may be required for NSTIs in abdominal and anogenital locations taking into account the risk of Gram-negative bacteria carrying multi-drug resistance (e.g. extended spectrum β-lactamase-producing *Escherichia coli* or *Klebsiella* spp.). Regarding coverage of anaerobic microbes, clindamycin resistance is frequent among anaerobic bacteria reaching 40% in the *Bacteroides fragilis* group in Europe.

Moreover, antibiotics that inhibit bacterial toxin synthesis should be included in the initial antibiotic regimen. Reduction of toxin production is important, particularly in infections caused by *Streptococcus pyogenes*, *Staphylococcus aureus* (including MRSA) or *Clostridium perfringens*. Examples of antitoxin-active drugs include clindamycin, linezolid, and tedizolid. Empiric clindamycin is currently recommended by guidelines based on clindamycin-related reduction in toxin production and disease severity, reported in group A *streptococcus* infection. Although the antitoxin effect of clindamycin is independent of bacteria strain susceptibility, linezolid could be considered in settings where clindamycin resistance is more prevalent.

In patients with NSTIs, the optimal antibiotic treatment should be established depending on pharmacokinetic/pharmacodynamic antibiotic properties, and patient factors. A well-known problem in patients with sepsis is the “third spacing” phenomenon and hypoalbuminemia. In patients with septic shock, there is global vasodilation, endothelial damage and capillary leakage resulting in extravasation of fluid into the interstitial space (“third spacing” phenomenon). Hydrophilic antibiotics (such as β-lactams, aminoglycosides, and glycopeptides) are extensively distributed from intravascular space into the interstitial space. Low plasma antibiotic levels can contribute to lower-than-expected antibiotic concentrations in the target soft tissues. Hypoalbuminemia affects the increase in the unbound fraction of antibiotics. The unbound fraction of antibiotics escapes from intravascular space and is not available for distribution to the target tissue. Optimal dosing antibiotic regimens are related to the concept of time-dependent *versus* concentration-dependent killing. For example, β-lactams exhibit time-dependent activity. Therefore, high-loading doses, higher frequency dosing, prolonged infusions or continuous infusions of β-lactams have been utilized to achieve maximal antimicrobial effect. Regarding patient factors, renal (nephrotoxic antibiotics, e.g. vancomycin) and hepatic (hepatotoxic antibiotics, e.g. clindamycin) function should be considered for each patient to adjust the antibiotic dosage if necessary.

Directed antimicrobial therapy is optimized for the involved microbes to improve clinical outcomes and reduce antibiotic-associated complications (e.g., allergic reactions, adverse drug events, selection of multi-drug resistance pathogens, *Clostridiodes difficile* infection) (**Table 1**). In patients with NSTIs, it is always advisable to consult an ID specialist about antibiotic therapy.

Table 1. Recommendations for antibiotic therapy of NSTIs.

Initial antibiotic therapy		
Aetiology	**Primary antibiotic regimen**	**Alternative antibiotic regimen**
unknown causative pathogens	Piperacillin/tazobactam + clindamycin	Imipenem/cilastatin + linezolid
Directed antibiotic therapy		
Aetiology	**Primary antibiotic regimen**	**Alternative antibiotic regimen**
Polymicrobial infection (aerobic and anaerobic bacteria)		
peptostreptococci, *Bacteroides* spp., *Enterobacterales*	Piperacillin/tazobactam + clindamycin	Imipenem/cilastatin or ceftazidime/avibactam + metronidazole
+*Pseudomonas aeruginosa*	Piperacillin/tazobactam	Ceftolozane/tazobactam or ceftazidime/avibactam
Monomicrobial infection		
Streptococcus pyogenes (rarely streptococci group C, G)	Penicillin G + clindamycin	Clindamycin or linezolid or ceftaroline
Staphylococcus aureus	Methicillin ± clindamycin	Clindamycin or linezolid or vancomycin or ceftaroline
MRSA	Linezolid	Vancomycin or ceftaroline
Clostridium perfringens *Clostridium septicum*	Penicillin G ± clindamycin	Piperacillin/tazobactam ± linezolid
Marine-associated infection		
Vibrio vulnificus, *Aeromonas hydrophila*	Ciprofloxacin ± cotrimoxazole	Doxycycline or 3rd generation cephalosporins
Fungal infection in immunocompromised patients		
Candida albicans	Fluconazole	Echinocandins
Candida non-*albicans*	Echinocandins	Voriconazole or Isavuconazole or Amphotericin B

Abbreviation. MRSA, methicillin-resistant *Staphylococcus aureus.*

Supportive treatment

The patient's physiological condition has to be optimized prior to surgery, without causing a delay in the timing of the initial surgical debridement. Perioperative intensive care in the ICU is obvious. The physiologic deterioration of patients with NSTIs can be caused by two factors – related sepsis and related extensive surgical wounds. In patients with sepsis or septic shock intensive care for hemodynamic and metabolic support should be performed as soon as possible. Fluid resuscitation and analgesia are the mainstays of support for patients with advanced sepsis, usually combined with vasoactive amines associated with mechanical ventilation and other organ function support, if needed. In addition, patients with NSTIs may lose fluids, proteins, and electrolytes through a large surgical wound.

Adjunctive therapies

Intravenous immunoglobulins

Intravenous immunoglobulin (IVIG) therapy has been frequently proposed as adjuvant therapies for NSTIs. Polyvalent IVIG should neutralize superantigens and improve bacteria elimination by facilitating opsonization of Group A *streptococcus* (GAS) for phagocytosis. However, the clinical evidence is limited (only 2 randomized trials) and clinical results are conflicting. Regarding patients' survival both randomized trials did not demonstrate a significant effect of IVIG on mortality, but the first randomized trial was prematurely terminated due to low patient recruitment, and the second randomized trial included NSTIs caused by polymicrobial aetiologies. In contrast, a recent multicentre prospective study focusing on streptococcal aetiology of NSTIs reported a significantly greater mortality rate in patients with GAS who did not receive IVIG. Regarding sepsis-related

organ failure a significant decrease in the SOFA score at days 2 and 3 was noted in patients receiving IVIG. Taken together, these data suggest that IVIG therapy should be used to improve outcomes in a selected population of patients with GAS-related NSTIs.

Hyperbaric oxygen therapy

Hyperbaric oxygen therapy (HBOT) involves the therapeutic administration of 100% oxygen at pressures above one atmosphere absolute (101.3 kPa). HBOT increases tissue oxygen tension, improves tissue perfusion and has a bacteria-killing effect. Bacteria-killing effect of HBOT is induced by the direct effect of oxygen free radicals on bacteria and by enhancing neutrophil activity, inhibition of anaerobic growth, inhibition of toxin production, and enhancement of antibiotic activity. The role of HBOT as an adjunctive treatment of NSTIs has been debated because relevant clinical evidence is absent (no randomized trials). Based on recent systematic reviews and meta-analyses the use of HBOT in the treatment of NSTIs can significantly reduce the mortality rate, however regarding the rate of amputation and other complications results are conflicting. Moreover, HBOT is not available in all hospitals and the critically ill patient should not be transferred to carry out HBOT. So, HBOT could be considered, if available, but it should not interfere with intensive care in the ICU and delay the standard treatment.

Immunomodulation

The new adjunctive modality mentioned in the treatment of NSTIs is immunomodulation. Reltecimod is a new agent studied for the modulation of inflammation in NSTIs, however further study is warranted to assess its efficacy.

Long-term management

The long-term impact of NSTIs is related to the local and systemic effects of the disease. Extensive and more complex wounds require specialized nursing staff wound care followed by plastic and reconstruction surgery. During this long recovery period intensive nutrition support is essential, and pain management is necessary. To avoid different types of pain related to patients with NSTIs (background pain, breakthrough pain, and procedural pain), the pain management strategy should be regularly adjusted to the phase of care and interventions. The systemic effect involves post-intensive care syndrome including decreased cognitive performance, sleep disturbances, anxiety and depression. This specialized care is similar to burn survivors, and it should be provided in centres. A multidisciplinary team approach should focus not only on survival but also on long-term functional outcomes.

Mortality and outcomes

The mortality rate associated with NSTIs is very high (around 20%-30%), but it remains constant over the last two decades. Despite high mortality, the quality of life is negatively influenced too. Survivors experience long-term physical consequences (mutilating scars and functional deficits), psychological consequences (traumatic stress symptoms, fear of relapse, adjusting to an altered appearance, sexual issues) and social and relational consequences (changes in social contacts, a lack of understanding). The disease also has a major psychological impact on family members, as well as a major financial impact.

Conclusion

Initially, early surgical source control, antimicrobial therapy, and (organ) supportive measures are the cornerstone of treatment in patients with NSTIs. The initial surgical debridement should be provided by the general surgeon at the admitting hospital as soon as possible, ideally within 6 hours (at least 12 hours). Surgical debridement remains the mainstay of therapy, and skin-sparing debridement with the removal of only devitalized/necrotic tissue and preservation of normally perfused skin are suggested. Scheduled re-explorations should be done at least every 12–24 hours after the initial operation until no debridement is required. Antibiotic treatment must be prompt, and the initial empirical antibiotic regimen should cover a broad spectrum of Gram-positive, Gram-negative and anaerobic bacteria. The antibiotic regimen should include an anti-MRSA agent and antibiotics that inhibit bacterial toxin synthesis should be added. The optimal antibiotic treatment should be established depending on pharmacokinetic/pharmacodynamic antibiotic properties, and patient factors. Therefore, it is always advisable to consult an ID specialist about antibiotic therapy. In patients with sepsis or septic shock intensive care for hemodynamic and metabolic support has to be performed immediately. In the post-acute phase, wound management plays a crucial role. NPWT is recommended for wound care after the complete removal of necrosis. Definitive wound coverage or closure is usually facilitated by plastic and reconstruction surgery. In long-term management nutrition support, pain management, rehabilitation and other specialized care are necessary. Patients with NSTI are best cared for at tertiary care institutions that can provide a multidisciplinary team approach to managing their complex care and focusing not only on survival but also on long-term functional outcomes.

Competing interests

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

References

1. Afzal H, et al. Negative Pressure Wound Therapy With and Without Instillation in Necrotizing Soft Tissue Infections. Surg Infect (Larchmt). 2024;25:199-205.
2. Andreoni F, et al. Clindamycin Affects Group A Streptococcus Virulence Factors and Improves Clinical Outcome. J Infect Dis. 2017;215:269-277.
3. Bruun T, et al. Risk Factors and Predictors of Mortality in Streptococcal Necrotizing Soft-tissue Infections: A Multicenter Prospective Study. Clin Infect Dis. 2021;72:293-300.
4. Bulger EM, et al. A Novel Immune Modulator for Patients With Necrotizing Soft Tissue Infections (NSTI): Results of a Multicenter, Phase 3 Randomized Controlled Trial of Reltecimod (AB 103). Ann Surg. 2020;272:469-478.
5. Darenberg J, et al. Intravenous immunoglobulin G therapy in streptococcal toxic shock syndrome: a European randomized, double-blind, placebo-controlled trial. Clin Infect Dis. 2003;37:333-340.
6. Guliyeva G, et al. Practical Review of Necrotizing Fasciitis: Principles and Evidence-based Management. Plast Reconstr Surg Glob Open. 2024;12:e5533.
7. Hirose Y, et al. Streptococcus pyogenes Transcriptome Changes in the Inflammatory Environment of Necrotizing Fasciitis. Appl Environ Microbiol. 2019;85:e01428-19.
8. Hua C, et al. Necrotising soft-tissue infections. Lancet Infect Dis. 2023;23:e81-e94.
9. Huang C, et al. The effect of hyperbaric oxygen therapy on the clinical outcomes of necrotizing soft tissue infections: a systematic review and meta-analysis. World J Emerg Surg. 2023;18:23.

10. Madsen MB, et al. Immunoglobulin G for patients with necrotising soft tissue infection (INSTINCT): a randomised, blinded, placebo-controlled trial. Intensive Care Med. 2017;43:1585-1593.
11. Messa Iv CA, et al. Bilayer wound matrix dermal substitute allows survival of split-thickness skin graft in necrotizing fasciitis defects: A retrospective, uncontrolled case study. J Plast Reconstr Aesthet Surg. 2021;74:1633-1701.
12. Montravers P, et al. Treating necrotizing skin and soft-tissue infections. Intensive Care Med. 2024;50:1342-1345.
13. Nawijn F, et al. Time is of the essence when treating necrotizing soft tissue infections: a systematic review and meta-analysis. World J Emerg Surg. 2020;15:4.
14. Pea F. Practical concept of pharmacokinetics/pharmacodynamics in the management of skin and soft tissue infections. Curr Opin Infect Dis. 2016;29:153-159.
15. Peetermans M, et al. Necrotizing skin and soft-tissue infections in the intensive care unit. Clin Microbiol Infect. 2020;26:8-17.
16. Sartelli M, et al. World Society of Emergency Surgery (WSES) guidelines for management of skin and soft tissue infections. World J Emerg Surg. 2014;9:57.
17. Sartelli M, et al. 2018 WSES/SIS-E consensus conference: recommendations for the management of skin and soft-tissue infections. World J Emerg Surg. 2018;13:58.
18. Sartelli M, et al. WSES/GAIS/WSIS/SIS-E/AAST global clinical pathways for patients with skin and soft tissue infections. World J Emerg Surg. 2022;17:3.
19. Stevens DL, et al. Infectious Diseases Society of America. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. Clin Infect Dis. 2014 Jul;59(2):e10-52.
20. Tessier JM, et al. Necrotizing Soft Tissue Infections: A Focused Review of Pathophysiology, Diagnosis, Operative Management, Antimicrobial Therapy, and Pediatrics. Surg Infect (Larchmt). 2020;21:81-93.
21. Tom LK, et al. Comparison of Traditional and Skin-Sparing Approaches for Surgical Treatment of Necrotizing Soft-Tissue Infections. Surg Infect (Larchmt). 2020;21:363-369.
22. Toppen W, et al. Contemporary national outcomes of hyperbaric oxygen therapy in necrotizing soft tissue infections. PLoS One. 2024;19:e0300738.

Chapter 122

Fournier's gangrene

Konstantinos Stamatis
Department of Critical Care, "Evangelismos" Hospital, Medical School, National and Kapodistrian University of Athens, Athens, Greece.

George Gkiokas
2nd Department of Surgery, "Aretaieio" University Hospital, National and Kapodistrian University of Athens, Athens, Greece.

Introduction

Since 1883, when Jean Alfred Fournier described a fulminant gangrene of idiopathic nature and abrupt onset of the scrotum and penis in otherwise healthy young males, the disease bearing his name remains a challenge for the clinicians involved in the management of those patients. Over the years, it has been referred to by several names, such as "streptococcus gangrene", "synergistic necrotizing cellulitis", and "peri-urethral phlegmon", all of which describe a soft tissue disease that is infective, destructive, and fatal. It is a rare type I (polymicrobial) necrotizing fasciitis of the perineal, perianal or genital areas, comprising less than 0.02% of overall hospital admissions in the United States. However, it still has a high mortality rate, with most modern studies reporting fatality rates that range between 20% and 40%. The polymicrobial nature, the underlying medical comorbidities of the disease population, the extent of soft tissue involvement in an area dense in critical anatomical structures, as well as the potentially rapid advancement of the infection, make the therapeutic management of Fournier's gangrene (FG) a demanding task.
In the text that follows we present the most recent evidence regarding Fournier's gangrene epidemiology, pathophysiology, clinical characteristics and diagnostic investigation. Moreover, we discuss the role of clinical predictive scores, and issues regarding the appropriate approach to antimicrobial agent selection, the emergence of novel therapeutic agents, surgical source control, the role of fecal diversion, hyperbaric oxygen therapy, and negative pressure wound therapy. Furthermore, topics such as the identification of patient survival predictors and the potential establishment of more effective management protocols are being addressed. In addition, we discuss the results of the most recent clinical trials in the context of the latest meta-analyses and systematic reviews, thus aiming to tackle the above-mentioned issues in light of the best available clinical evidence.

Epidemiology

Data from the US State Independent Databases, which include 100% of admissions and discharges from all US civilian hospitals, identified 1,641 males and 39 females with FG in a study population comprising 13 states in 2001 and 21 states in 2004). This represents less than 0.02% of all hospital admissions in the respective

period, with an incidence rate of 1.6 per 100,000, as far as male patients are concerned, and male to female ratio of 10:1. The same study showed a case fatality rate of 7.5%, which is significantly lower when compared to rates of 20%-25% demonstrated by single centers elsewhere. The mean age of male patients presenting with FG is approximately 50 years, with the main comorbidities being obesity and hypertension, whereas patient factors that act as independent mortality predictors include increased age, admission via transfer, and Charlson comorbidity index; specific risks related to increased mortality are heart failure, renal failure, and coagulopathy. A recent systematic review and meta-analysis demonstrated that diabetes, heart disease, renal failure and kidney disease are associated with a higher risk of mortality, with sepsis (76%) and multiorgan failure (66%) being the most common causes of death in patients with FG. In addition, diabetes, chronic alcoholism, infection with the Human Immunodeficiency Virus and Leukemia have been implicated as predisposing factors. As far as the etiology of FG is concerned, anorectal causes have been implicated in 30-50% of cases, urogenital in 20-40% of cases, and a dermatologic source in 20%; overall, a local cause can be identified in approximately 95% of cases. A rare cause of FG can be the use of sodium-glucose cotransporter protein-2 (SGLT-2) inhibitors in patients with type 2 diabetes. 491 such cases were identified by the American Diabetes Association in 2022 with the Food and Drug Administration issuing a safety warning in 2018.

Pathophysiology

A local nidus of infection acts as a portal of entry for different bacteria in the perineum, with the synergistic effect of aerobic and anaerobic bacteria resulting in activation of the coagulation cascade in nutrient vessels, reduced blood supply and tissue hypoxia that leads to further anaerobe growth and activation of enzymes like collagenase, heparinase, hyaluronidase, streptokinase, and streptodornase. This results in the digestion of the underlying fascial barriers with subsequent rapid spread of the infection, tissue necrosis and further coagulation of small vessels. The result is an overwhelming septic response culminating in overt septic shock and multiorgan failure. **Figure 1** gives a comprehensive representation of the overall pathophysiological process and the pathways involved in the development of the infection.

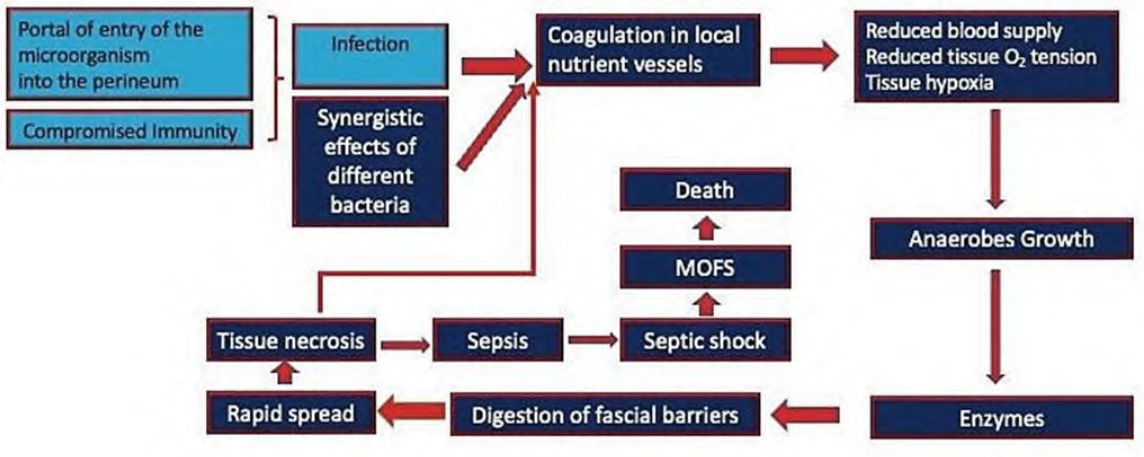

Figure 1. Fournier's gangrene physiopathology.

As far as FG local spreading is concerned, advanced gangrene can extend through the fascial planes ascending as high as the torso and descending to the thigh. The perineal fascia, Colle's fascia, is continuous with Scarpa's fascia of the anterior abdominal wall and Buck's and Dartos's fascia of the penis and scrotum. The rare testicular involvement in patients with FG has been attributed to the non-perineal testes' blood supply. Streptococcal and staphylococcal species, together with *Enterobacteriaceae*, anaerobes and fungi are responsible for the polymicrobial nature of most cases of FG.

Clinical presentation

Usually there is a history of sudden pain and swelling in the perineal and scrotal area in a patient with predisposing factors or a recent local trauma. It is not uncommon for the pain to be out of proportion to the local signs, especially during the early stages of disease progression. Pruritus and fever might also be present, as well as cutaneous manifestations such as erythema, crepitations, and patches of gangrene together with a potential point of entry. A foul odour might be present together with purulence or wound discharge, and the whole area might be tender to palpation. Furthermore, patients may present with symptoms and signs of sepsis, septic shock and multiorgan failure. These can include fever, tachycardia and hypotension, increased respiratory rate progressing to overt respiratory failure, oliguria suggestive of acute kidney injury and altered level of consciousness. Patient might need prompt fluid resuscitation, intubation and mechanical ventilation, hemodynamic support with vasoactive and inotropic agents and renal replacement therapy in the intensive care unit. Mortality can be as high as 42% in cases of FG patients who require critical care admission.

Microbiology

Most cases of FG are polymicrobial NSTI, with deep tissue cultures obtained from the involved regions showing that the most common microorganisms are those native in the perineal and genital regions. Typically, there is a mixed growth of aerobic (*Escherichia coli*, *Klebsiella pneumoniae*) and anaerobic (*Bacteroides fragilis*, *Clostiridium* spp.) organisms. Other species which might be isolated include *Streptococcus* spp., *Staphylococcus* spp., *Vibrio* spp., *Pseudomonas* spp., *Proteus* spp., and *Corynobacterium* spp. Some authors have reported *Staphylococcus aureus* as being the most frequently isolated microorganism in 46.7% of cases, whereas others have found *E. coli*, mostly isolated in both deep tissue and blood cultures (42%), with *Enterococcus* spp. (18%) and *K. pneumoniae* (29%) following in tissue and blood cultures, respectively. These varying results are indicative of the polymicrobial nature of the infection and underscore the necessity for early and aggressive broad-spectrum antibiotic coverage in suspect cases.

Imaging studies of Fournier's gangrene

CT scan is the imaging modality of choice for patients with FG, as it can demonstrate disease extension, can delineate tissue planes accurately, and can show the presence of gas and fluid collections. Thickening and non-enhancing of the fascial planes are suggestive of potential fascial necrosis. What is more, CT findings can assist with the planning of surgical debridement and the potential need for re-exploration. CT scan has a

sensitivity of 88.5% and a specificity of 93.3% for the diagnosis of necrotizing soft tissue infection (NSTI). CT scan should be considered in stable patients suspected of having FG; however, it should not delay surgical intervention and should be avoided in patients who remain unstable after initial resuscitation. MRI scanning provides greater detail, as far as soft tissue disease involvement is concerned, with T2 deep fascia hyperintensity being the most common MRI diagnostic criterion. However, the significantly longer examination time and the limited capacity for patient monitoring and likely intervention during the performance of the examination restrict its potential applications in the context of emergency FG imaging, particularly as far as critically ill patients are concerned. Ultrasound scan is easy to perform, can be used at the bedside and is almost universally available. In addition, it can demonstrate the presence of gas or fluid and can display other causes of scrotal pain, such as testicular torsion, inguinal hernia or epididymo-orchitis; its main drawback is the requirement to apply pressure with the probe to an inflamed and painful area, which is something that is usually not tolerated by patients suffering from FG.

Clinical predictive scores

The Laboratory Risk Indicator for necrotizing infection (LRINEC) score was proposed in 2004 as a diagnostic evaluation system for the presence of necrotizing infection. It comprises six independent variables: C-reactive protein (>150 mg/L), total white blood cell count (<15, 15-25, >25 cells/μL), hemoglobin (>13.5, 11-13.5, <11 g/dL), sodium (>135, <135 mmol/L), creatinine (<1.6, >1.6 mg/dL), and glucose (<180, >180 mg/dL). A score equal to or greater than 8 is supposed to predict a higher than 75% risk for the presence of necrotizing soft tissue infection. In the initial study, an LRINEC score cutoff value of 6 demonstrated a positive predictive value of 92% and a negative predictive value of 96%, with an area under the receiver operating characteristic curve at 0.980 and 0.976 in the developmental and validation groups, respectively. These excellent results have come into question in more recent years, with subsequent meta-analyses and systematic reviews showing worse sensitivity and specificity results for the LRINEC score (cutoff value of 6: sensitivity 68.2%, specificity 84.8%, cutoff value of 8: sensitivity 40.8%, specificity 94.9%).

Fournier's Gangrene Severity Index (FGSI) is a standard score that is derived by a combination of physiological variables at admission. These include temperature, heart rate, respiratory rate, serum K+, serum Na+, serum creatinine, hematocrit, white blood cell count and venous serum bicarbonate. Each of these parameters can take values between 0 and 4. FGSI was initially proposed by employing regression analysis on patient data, in an attempt to clarify factors that influence mortality on FG patients. A score greater than 9 has been shown to be sensitive and specific for predicting mortality in FG patients. Apart from being validated as a mortality predictor in subsequent studies, FGSI has also been shown that it can be used to accurately infer the requirement for repeated surgical interventions, longer hospitalization periods, and the development of systematic sepsis and FG-specific complications. Such results signify that the FGSI can potentially be used as a morbidity predictor as well. However, some authors believe that the FGSI downgrades FG mortality. By using logistic regression analysis, they have added the extent of disease dissemination and the patient's age to derive the Uludag Fournier's Gangrene Severity Index (UFGSI). With a cutoff value of nine points, UFSGI can predict a 91% probability of death and an 84% probability of survival that compares favorably to respective values of 75% and 78% that have been published for the FGSI.

Principles of therapeutic management

The malignant course of the infection calls for prompt diagnosis and treatment. There should be a high index of clinical suspicion, with aggressive resuscitation and likely intensive care unit admission. Surgical source control with extensive debridement should be performed as soon as possible, together with timely commencement of broad-spectrum antibiotic regimens. Fecal diversion should be considered and repeated procedures might be needed to achieve the best outcome.

Antibiotic therapy

Early broad-spectrum antibiotic therapy should be initiated in all suspect cases of FG. The initial empiric therapy should include Gram-positive, Gram-negative, as well as anaerobic coverage. Local hospital guidelines should take into consideration the local incidence of methicillin-resistant *Staphylococcus aureus* (MRSA). However, some authors believe that the initial antibiotic regimen should always provide MRSA coverage, with the additional advantage of providing inhibition of invasive group A *Streptococcus* virulence proteins. The emergence of multi-drug resistance organisms (MDRO), usually MRSA and MDRO *Acinetobacter*, presents additional challenges, as there is evidence that they are associated with increased morbidity and mortality rates. According to the last update by the Infectious Diseases Society of America regarding the practice guidelines for the diagnosis and management of skin and soft tissue infections, the initial empiric broad antibiotic treatment should be vancomycin or linezolid plus piperacillin-tazobactam or a carbapenem; or plus ceftriaxone and metronidazole. According to the same guidelines, documented group A streptococcal necrotizing fasciitis should be treated with penicillin plus clindamycin. The addition of clindamycin to the initial empiric regimen is advocated if there is suspicion of toxin production. When culture results are available, antibiotics should be de-escalated based on results and sensitivities. There is evidence that the duration of antibiotics administration does not have an impact on mortality, primary closure, surgical site infection or increased rates of *C. difficile* infection. An antibiotics course of 14 days is usually adequate; this can be shortened when surgical infection control has been achieved, depending on each case. When applying the above-mentioned recommendations in the individual clinical setting, one has to be careful and take into consideration local factors and each clinical scenario's specific details, as there is an absence of randomized controlled trials on the empirical use of antimicrobials in the context of NSTI.

Novel agents

Reltecimod, a CD-28 T-lymphocyte receptor mimetic that hinders stimulation of T-cells was recently tested in a randomized, double-blind, placebo-controlled trial to assess its efficacy when administered within 6 hours for the treatment of NSTI with organ dysfunction. Although not affecting mortality, reltecimod administration resulted in improved resolution of organ dysfunction and hospital discharge status.

Surgical debridement

Early and extensive surgical debridement is of paramount importance in patients with FG, as it has been shown to lower mortality and decrease the complication rate. A systematic search and meta-analysis of 109 studies with 6051 NSTI patients showed an overall mortality of 21.1%. 33 studies with 2123 were included for quantitative analysis, demonstrating a considerably lower mortality for patients undergoing surgery within 6 hours after presentation compared to patients whose surgery was delayed for more than 6 hours (19% *vs.* 32%, respectively). Interestingly, patients who had surgery within 12 hours from presentation had also lower mortality compared to patients who had surgery after 12 hours. Time passed from the onset of symptoms until hospital presentation or surgery did not have an impact on mortality and mean operating time was inversely related to mortality. Debridement should involve only the tissues involved with the infection; removal of deeper tissues can take place while leaving healthy subcutaneous tissue and skin in place, thus allowing existing skin flaps to be used for delayed primary suture wound closure and avoidance of skin grafting. All necrotic tissue has to be removed, and a multidisciplinary and patient-oriented individualized approach should be adopted to achieve the best outcome. Scheduled re-explorations are suggested every 12-24 hours after the initial surgical debridement, or even earlier if the patient's condition necessitates. Re-explorations can stop when the remaining tissue is viable, granulation tissue is evident, and little or no debridement is required. As far as orchiectomy is concerned, the consensus is that it should not be done prophylactically and that it should be generally avoided. Blood supply of the testes comes separately from the gonadal arteries, making testicular involvement in FG rare. According to one study, only 2.6% of 11,069 FG patients underwent orchidectomy, with pathology reports showing 100% normal testicular histology when orchidectomy was performed based only on the surgeon's judgement.

Fecal diversion

Fecal diversion has historically been used for the management of the difficult-to-control FG, having been shown to improve the overall outcome in various studies. These investigations, however, do not take into account the morbidity associated with the creation of a colostomy and the need for subsequent reversal of the stoma. The rate of bowel diversion in FG patients varies in different studies, with a systematic review and meta-analysis showing a wide range between 7% and 67%, which is suggestive of a lack of clear indications and strong evidence regarding the subgroup of patients who could be benefited the most from fecal diversion. Involvement of the perianal area in the infective process is a more or less clear indication for fecal diversion, which in this case shortens the time required for wound healing and overall hospital length of stay. There is also a lack of strong evidence about the best timing for fecal diversion, with small studies suggesting that in challenging situations with difficult-to-control infection, there should be a consideration for the early creation of a stoma. The creation of a transverse loop colostomy is usually chosen, above the umbilicus and away from the lower abdomen that can be potentially involved in the infective process, as it leads to the formation of relatively solid stools that cause little contamination of the surrounding skin area. Rectal diversion devices have been recently employed in order to protect the surgical wound from fecal contamination and reduce skin breakdown without the need for a stoma creation.

Hyperbaric oxygen therapy

Hyperbaric oxygen therapy (HBOT) is becoming an increasingly attractive treatment option in FG patients and NSTIs in general, as it can promote tissue repair and wound healing, facilitate wound repair mechanisms such as angiogenesis and fibroblast growth, and stimulate anti-inflammatory activity. Several case series and reports have demonstrated improved patient survival when using HBOT for the treatment of necrotizing fasciitis in combination with surgical debridement and antibiotic administration. A systematic review and meta-analysis of 23, mainly retrospective studies, demonstrated a clear survival benefit for NSTI patients treated with HBOT. Other retrospective studies have also shown results favoring the use of HBOT in the context of FG, with a mortality rate of 3.7% in the group treated by HBOT and a mortality rate of 28.8% ($p<0.001$) in the control group. The presence of an untreated pneumothorax is an absolute contraindication for HBOT. The presence of upper respiratory infection, pulmonary emphysema with carbon dioxide retention, high fever and a low threshold for seizures are relative contraindications. In conclusion, HBOT in HBOT-capable centers can be used as an adjunct to conventional therapies for FG patients.

Negative pressure wound therapy

After the conclusion of surgical debridement and the removal of necrotic tissue, the application of negative pressure wound therapy (NPWT) facilitates wound surface reduction, removal of exudate and cell residues, and promotion of granulation. A systematic review of 21 case reports or case series and 7 cohort studies showed that NPWT results in less pain, reduced patient discomfort, increased patient mobility and fewer dressing changes. In addition, early application of NPWT can reduce the requirement for reconstructive surgery in cases of extensive tissue involvement. This advantage does not hold when FG is localized, and one has to always take into consideration the increased cost of the device and the dressings, as well as the longer hospital stay associated with NPWT. It needs to be emphasized that the majority of these studies are retrospective, heterogeneous, have small numbers of patients, and rarely yield statistically significant results. However, the application of NPWT seems intuitive, especially in cases of extensive tissue involvement and in possible combination with HBOT, a concept that needs to be addressed in the context of well-designed trials.

Reconstructive surgery

Various methods have been used for postoperative wound reconstruction in FG patients. These include primary closure, creation of temporary thigh pouches to harbor the testicles, full- and split-thickness skin grafts, as well as scrotal advancement, perforator, scrotal, myocutaneous and fasciocutaneous flaps. Component separation primary wound closure following surgical debridement is a safe approach for relatively small to medium defects with no tension. Large defects require surgical reconstruction with skin grafting, flaps, or testicular transposition. There is no consensus on what is the best approach for successful wound reconstruction and there is also a lack of high-quality evidence.

Conclusion

Despite being a relatively rare clinical entity, FG remains a challenging situation for the team of clinicians involved with its management. A high index of suspicion, especially in the subgroups of patients predicted to have increased morbidity and mortality, will allow for the prompt diagnosis, resuscitation, commencement of appropriate broad-spectrum antibiotics and probable admission to the intensive care unit. CT scan remains the mainstay of diagnosis for patients suspected of having FG, but its performance should not interfere with the timely delivery of surgical treatment. Early and extensive surgical debridement of all the necrotic tissue involved with the infection is the most significant determinant of outcome in FG patients and should be carried out within 6 hours from hospital admission. After the initial surgical source control re-explorations should be repeated until no more necrotic tissue remains to be removed. De-escalation of antibiotics should be based on clinical improvement and culture results from samples obtained at the interface of viable and necrotic tissue. While the above-mentioned therapies are being applied, organ-supportive measures in a critical care environment are of capital importance to increase the chances of achieving a successful outcome. Moreover, HBOT and NPWT can be used as adjunct treatments for improving wound healing. Plastic surgeons should be involved when the necrotic infection has subsided and reconstruction methods are considered. Various types of skin grafting can be employed when the extent and severity of tissue involvement require so. We need to emphasize that there is a paucity of high-quality evidence regarding the optimal management of patients with FG, as there is a lack of well-designed randomized clinical trials addressing issues related to the pharmacological, surgical and overall treatment of those patients. The majority of evidence comes from retrospective, small-volume trials, and is used for the development of guidelines and global clinical pathways that can facilitate the care of FG patients. Further research is needed in this area to improve outcomes and provide a successful evidence-based approach for managing FG patients.

Competing interests

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

References

1. Altomare M, et al. Negative pressure wound therapy for the treatment of Fournier's gangrene: a rare case with rectal fistula and systematic review of the literature. J Pers Med. 2022;12:1695.
2. Attila A, et al. Fournier's Gangrene: Microbiological Profile and Risk Factors for Mortality: Review of 97 Cases. Infect Dis Clin Microbiol. 2023;5:13-22.
3. Bowen D, et al. Fournier's gangrene: a review of predictive scoring systems and practical guide for patient management. Ther Adv Infect Dis. 2024;11:20499361241238521.
4. Bozkurt FT, et al. Predictive factors for mortality in intensive care patients with Fournier's gangrene: five years experience from a single center in Turkey. Eur Rev Med Pharmacol Sci. 2023;27:2326-2331.
5. Bruketa T, et al. Rectal cancer and Fournier's gangrene – current knowledge and therapeutic options. World J Gastroenterol. 2015;21:9002-9020.
6. Bulger EM, et al. A novel immune modulator for patients with necrotizing soft tissue infections (NSTI): results of a multicenter, phase 3 randomized controlled trial of reltecimod (AB 103). Ann Surg 2020;272:469-478.

7. Chalya PL, et al. Fournier's gangrene at a tertiary healthcare facility in northwestern Tanzania: a single center experiences with 84 patients. BMC Res Notes. 2015. 2015:8:481.
8. Chia L, et al. Emergence of multi-drug resistance organisms (MDRO) causing Fournier's gangrene. J Infect 2018;76:38-43.
9. El-Qushayri AE, et al. Fournier's gangrene mortality: a 17-year systematic review and meta-analysis. Int J Infect Dis. 2020;92:218-225.
10. Esposito S, et al. Italian Society of Infectious and Tropical Diseases. Diagnosis and management of skin and soft-tissue infections (SSTI). A literature review and consensus statement: an update. J Chemother. 2017;29:197-214.
11. Feres O, et al. Hyperbaric oxygen therapy decreases mortality duet to Fournier's gangrene: a retrospective comparative study. Med Gas Res. 2023;11:18-23.
12. Fernando SM, et al. Necrotizing Soft Tissue Infection: Diagnostic Accuracy of Physycal Examination, Imaging, and LRINEC Score: A Systematic Review and Meta-Analysis. Ann Surg. 2019;1:58-65.
13. Gupta A, et al. Bilateral testicular gangrene: does it occur in Fournier's gangrene? Int Urol Nephrol. 2007;39:913-915.
14. Huang C, et al. The effect of hyperbaric oxygen therapy on the clinical outcomes of necrotizing soft tissue infections: a systematic review and meta-analysis. World J Emerg Surg. 2023;18:23.
15. Huang S, et al. Role of diverting colostomy and reconstruction in managing Fournier's gangrene – a narrative review. BJU Int. Epub 2024 Apr 16.
16. Huayllani MT, et al. Practical Review of the Current Management of Fournier's Gangrene. Plast Reconstr Surg Glob Open. 2022;10:e4191.
17. Insua-Pereira I, et al. Fournier's gangrene: a review of reconstructive options. Cent European J Urol. 2020;73:74-79.
18. Kwee RM, et al. Diagnostic performance of MRI and CT in diagnosing necrotizing soft tissue infection: a systematic review. Skeletal Rdiol. 2021;51:727-736.
19. Lauerman MH, et al. Less is more? Antibiotic duration and outcomes in Fournier's gangrene. J Trauma Acute Care Surg. 2017;83:443-448.
20. Liu H. Case literature analysis of Fournier's gangrene caused by sodium-glucose protein-2 inhibitors. Front Med (Lausanne) 2024:11:1301105.
21. McCormack M, et al. Fournier's gangrene: a retrospective analysis of 26 cases in a Canadian hospital and literature review. Can Urol Assoc J. 2015;9:E407-E410.
22. Nawijn F, et al. Time is of the essence when treating necrotizing soft tissue infections: a systematic review and meta-analysis. World J Emerg Surg. 2020:15:4.
23. Peetermans M, et al. Necrotizing skin and soft-tissue infections in the intensive care unit. Clin Microbiol Infect; 2020;26:8-17.
24. Sartelli M, et al. WSES/GAIS/WSIS/SIS-E/AAST global clinical pathways for patients with skin and soft tissue infections. World J Emerg Surg. 2022;17:3.
25. Singh A, et al. Fournier's gangrene. A clinical review. Arch Ital Urol Androl. 2016;88:157-164.
26. Sorensen MD, et al. Fournier's Gangrene: Epidemiology and Outcomes in the General US Population. Urol Int. 2016;97:249-259.
27. Sparenborg JD, et al. Fournier's gangrene: a modern analysis of predictors of outcome. Trans Androl Urol. 2019;8:374-378.
28. Stevens DL, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. Clin Infect Dis. 2014;59:e10-52.
29. Tarasconi A, et al. Anorectal emergencies: WSES – AAST guidelines. World J Emerg Surg. 2021;16:48.
30. Wong CH, et al. Th LRINEC (Laboratory Risk Indicator for Necrotizing Fasciitis) score: a tool for distinguishing necrotizing fasciitis from other soft tissue infections. Crit care Med. 2004;32:1535-1541.

Chapter 123

The management of infected meshes

Ines Rubio Perez
Department of General Surgery, La Paz University Hospital, Madrid, Spain.

Maria Heras Garceau
Department of General Surgery, La Paz University Hospital, Madrid, Spain.

Introduction

Ventral hernia repair (VHR) is one of the most common surgical procedures performed globally, with over a million operations performed yearly only in the United States (US). Prosthetic mesh implants have shown a significant benefit over other traditional repair techniques with a significant reduction in recurrence.
Mesh infection has a low incidence but can be a devastating complication; surgeons should be trained in prevention strategies and early detection. A mesh infection may result in significant costs for the patient and the system, additional procedures or admissions and a negative impact on quality of life. If the mesh needs to be explanted, the risk of recurrence will be high, and a new intervention can be complex and associate more complications.

Risk factors for infection

In any patient undergoing a ventral hernia repair, it is important to consider all individual patient risk factors that can increase the risk of infection. A way of classifying them could be:

1. Preoperative: mainly patient's comorbidities and other factors, some of them potentially modifiable, such as smoking, obesity, diabetes, MRSA colonization, and others intrinsic to the patient such as ASA score, immunosuppression, COPD, etc.
2. Intraoperative: surgical technique and/or incidents during the intervention, operative time, type of mesh, increased tissue dissection, etc.
3. Postoperative: wound management, complications, infections, mesh exposure.

Some of these factors can be treated or controlled before the operation, to optimize results. Intraoperative factors such as contamination during surgery, the operative approach, surgical technique or the type of mesh selected, can also be very important to avoid complications.
Another important strategy for prevention is to confirm all institutional protocols of infection prevention practices are carefully applied. Adequate preoperative bathing and skin preparation, antibiotic prophylaxis, normoglycemia and normothermia in the perioperative period are some of the infection prevention measures that should be strictly controlled. Careful intraoperative management of any prosthetic materials,

sterile conditions and glove changes must be observed. Unnecessary wound manipulation and proper wound care and dressings should be complied with on the postoperative period.
However, with the existence of multiple techniques for hernia repair and the different mesh materials available, risk factors and prevention strategies are difficult to generalize.

Classification of complications

The use of mesh can lead to a series of complications that have been classified by the Ventral Hernia Working Group (VHWG) as Surgical Site Occurrences (SSO). These include seromas, hematomas, wound dehiscence, mesh migration, infection or fistulas. The VHWG proposes a classification of risk factors, simplified by Berger *et al.*, in 3 main risk groups:

- Grade 1 (Low risk): low risk of complications. No history of wound infection.
- Grade 2 (Comorbid): obesity, smoking, diabetes, immunosuppression, previous wound infection.
- Grade 3 (Contaminated): A) Clean-contaminated; B) Contaminated; C) Active infection.

There is not a clear definition for specifically reporting mesh infections, as they are usually included as surgical site infections of various origins, and rely on the clinical suspicion of the surgeon. Diagnostic criteria for mesh infection may include a positive culture of periprosthetic fluid, mesh exposure, and/or other signs of infection such as wound dehiscence, local necrosis, fistulas or purulent discharge. Currently, the 'Abdominal Core Health Quality Collaborative' (ACHQC) is the only national registry that specifically captures mesh infection, but it's a voluntary database with a relatively small sample of participating surgeons across the US.
According to different series, the incidence of mesh infection after open VHR can range from 1% to 10.1%, and after minimally invasive repair (MIS) 1% to 3%.
A superficial SSI or wound infection may not necessarily involve the underlying mesh. Surgeons should be trained to identify any initial symptoms early and establish early treatment strategies to avoid further complications. The contamination of the mesh may occur at 3 different stages:

1. At the time of surgery (non-sterile conditions, patient's flora, caregivers).
2. Secondary hematogenous contamination of a residual fluid collection.
3. Contiguous contamination (direct extension from an adjacent focus).

The detection of the infection will depend on these, as intraoperative contamination may present as an early infection, while secondary or contiguous contamination may present later in follow-up, although there can be a wide variability of presentations, some of them insidious, or as wounds that don't heal properly.

Type of mesh

There is a wide variety of prosthetic meshes available that can be selected for repairing abdominal wall defects, but there is no single universal mesh that can be considered a Gold Standard. Synthetic meshes are easy to handle and well tolerated but are more susceptible to bacterial adhesion and biofilm formation. Biological meshes have been associated with better tolerance to infections but a higher recurrence rate of hernias.

When bacteria (i.e. from the patient's flora) adhere to the patient's tissues or a mesh, they change from a free-floating phenotype to a proliferative and accumulative state. Once organized they can secrete a protein polysaccharide matrix known as a biofilm, that surrounds and protects them as they enter a quiescent state, making them less susceptible to antibiotics. Another important issue is that biofilm creates an environment that promotes antibiotic resistance, as bacteria are not reached by the host's immune system and can transfer resistance genes between each other. Biofilms can develop in just hours and this mechanical shielding can make wound cultures unable to detect the infection. *Staphylococcus aureus* (including MRSA) is the most common bacteria associated with mesh infections (up to 70-80%) and other common bacteria such as *Staphylococcus epidermidis* and *Enterobacteriaceae* can also produce biofilms.

Meshes can be classified as polymer-based (synthetic) and natural. Polymers are divided into reticular, laminar, and composite. Some of the most commonly non-absorbable materials include polypropylene (PP), polyester (PE), or polyvinylidenfluoride (PVDF). Among the absorbable materials, polyesters made of lactic acid or glycolic acid, and trimethyl carbonate (TMC) are common. These materials may be woven/knitted, have a mono/multifilament design and have different sized pores. There is evidence supporting that multi-filament meshes (i.e. polyester) have a greater surface area and therefore are more susceptible to biofilm development than monofilament prostheses. Pore size is also an important factor: large pores ('lightweight meshes') are less prone to bacterial colonization than smaller pores ('heavyweight meshes') as they allow for fibroblast migration and host defenses to act if bacteria contaminate the mesh. Non-absorbable laminar composed of simple or expanded polytetrafluoroethylene (PTFE) or expanded PTFE (ePTFE) are generally microporous and have a large surface area susceptible to colonization. Composite meshes are made of two or more materials: a tissue integrating material (reticular, woven or knitted and non-absorbable), commonly PP and an absorbable or non-absorbable barrier (hyaluronic, polyglycolic, etc.). Barrier coatings are designed to prevent adhesions and are usually placed intraperitoneally in MIS approaches. Evidence suggests that if placed in a retromuscular position, they seem to increase the risk of SSO compared with non-coated meshes.

Natural biomaterials (bio-prostheses) can be cross-linked or not, and are decellularized and delipidated tissues rich in collagen, such as dermis and small intestinal submucosa and can be allogenic or xenogenic in origin. There is debate about their use as they are costly, and currently not recommended in contaminated fields.

Mesh position and infection risk

Both mesh composition and positioning play an important role when deciding the best treatment for mesh infections. The onlay position has been demonstrated to have a higher rate of SSO and infections than sublay placements. The 'best' location could be the retro-muscular compartment, as it is well vascularized, promotes integration and decreases the risk of infection. Currently, the retro-muscular placement of a non-coated, macroporous, monofilament polypropylene mesh seems to be ideal for minimizing the risk of infection and mesh explantation and has been demonstrated to be safe even in clean-contaminated or contaminated settings). Minimally invasive approaches have been demonstrated to have a lower rate of infection, but intraperitoneal positioning can make salvage complicated if SSOs occur. Therefore, an adequate selection of mesh, approach and position are essential to avoid complications, especially in recurrent or complex patients.

Treatment options for infected mesh

The management of mesh infections is challenging and always requires an individualized approach. There are no clear guidelines on management, and different salvage techniques have been proposed, but unfortunately, in many cases, surgical removal of the mesh is the only option to resolve the chronic infection. Visceral adhesions and fistula formation are feared complications that can increase morbidity and mortality.

Mesh salvage

Conservative management of mesh infection can consist of different approaches:

1. Percutaneous drainage of pus/fluid collections.
2. Drainage and instillation of saline and/or antiseptics.
3. Opening of the wound with local debridement and wound dressings.
4. Application of different NPWT devices (foam of sponge).

Any attempt of mesh salvage (always in the absence of systemic complications or suspected fistula) begins with antibiotic therapy and expert wound care. Culture samples should be obtained to guide antimicrobial therapy. Physical debridement with scrubbing or irrigation of the wound may be necessary to remove biofilm. Negative Pressure Wound Therapy (NPWT) has been shown to increase blood flow to the wound and improve granulation. Extraperitoneal macroporous monofilament meshes placed in onlay or sublay positions can benefit from this therapy. New NPWT devices that allow continuous instillation of antiseptic or antibiotic fluids can increase the chance for mesh salvage, but need close follow-up and management.

Mesh removal

When conservative measures fail, partial or complete mesh excision may be required. Partial mesh excision will include debridement of all areas of unincorporated mesh, removal of any non-viable tissue, and local wound therapy. Any areas of mesh that are already incorporated will be respected. In cases of recurrent or persistent infections, unfavorable mesh characteristics, intraperitoneal mesh locations, and confirmed or suspected enteric fistula, complete mesh excision should be performed. The most likely types to require complete excision due to their characteristics are laminar PTFE, multifilament polyester and other microporous meshes, as shown in **Figure 1**. In cases of fistula or chronified infections, successful salvage of intraperitoneal mesh is rare. If mesh removal must be performed, it must be ensured that all material and sutures are explanted to avoid recurrence, and this can be technically challenging in some cases.

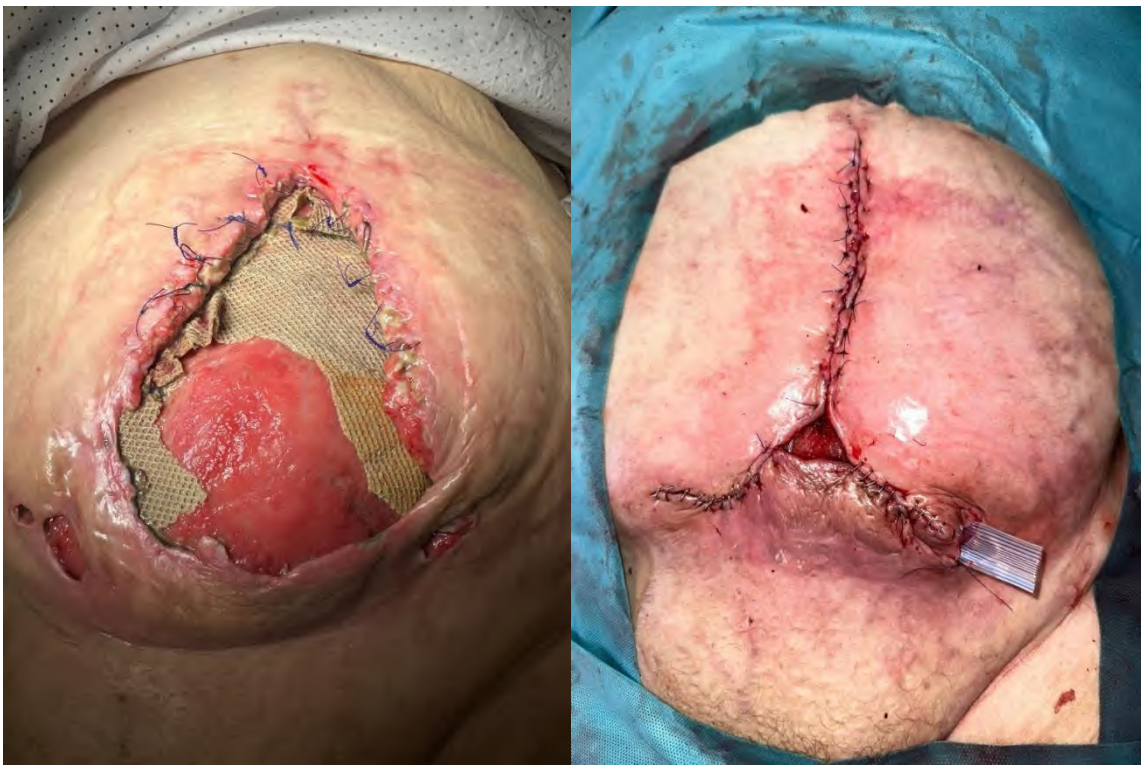

Figure 1A. Patient with severe infection following VHR with contaminated and exposed polyester mesh.
Figure 1B. Mesh explantation, debridement and partial skin closure to allow a second-stage repair.

The WSES global clinical pathways for patients with skin and soft tissue infections contemplate different approaches after mesh removal, that should be individualized: (a) no implant of a new mesh, (b) re-implantation of a new synthetic light-weight, macroporous mesh, and (c) replacement of the infected synthetic by a biological mesh.
In some cases, after the infected mesh removal, a one-stage repair can be achieved if the infection is controlled, and local, and there is enough healthy tissue. Fascial release, component separation and even a new mesh placement in uncontaminated fields can be feasible to achieve fascial closure. In some cases, a staged approach, with a new attempt for repair after 6–9 months is necessary. If the mesh explant is not followed by any repair, the recurrence rate can be very high (20-30%). **Figure 2** shows a proposed algorithm for the management of infected mesh.

Enteric fistula

Mesh infections secondary to enteric fistulization have unique characteristics and management. They are most commonly associated with intraperitoneal meshes, but can also occur following a deep infection or evisceration, and even present chronically as enterocutaneous fistula. These patients must be studied with imaging (CT and/or fistulography) and need surgical treatment, which usually involves resection of the affected bowel and complete removal of the intraperitoneal mesh. For fistulas occurring through a well-incorporated extraperitoneal mesh, partial excision of the affected segment may suffice.

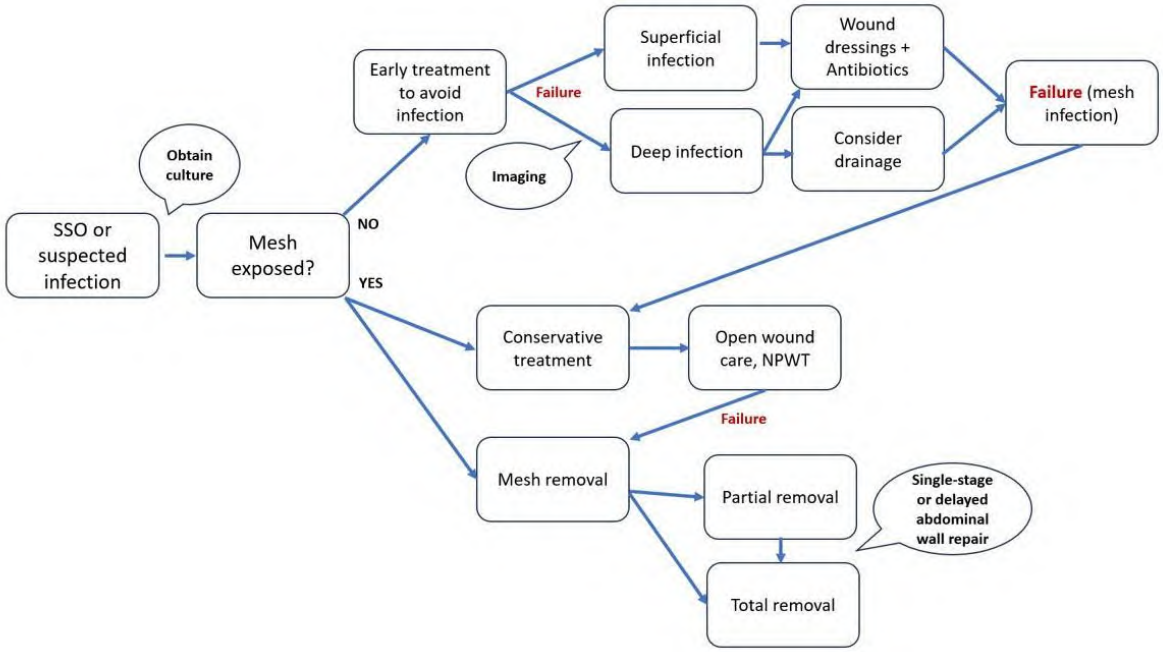

Figure 2. Proposal of a treatment algorithm for the management of mesh infections (Adapted from Sartelli M, *et al.* 2021, Schlosser KA, *et al.* 2023). SSO: Surgical Site Occurrence. NPWT: Negative Pressure Wound Therapy.

Conclusion

Prevention is the best treatment of mesh infection. Selection of operative approach, type of mesh and other perioperative measures significantly affect the incidence and management of mesh infections. Patient optimization for the index intervention is also essential to improve results. There is still no clear guideline for the management of mesh infections, as there is a great heterogeneity of studies and techniques and a lack of standardized reporting. A combination of antibiotic therapy, adequate wound management and NPWT (with/without instillation) can be a first approach. If an enteroprosthetic fistula occurs the patient must be optimized and surgical treatment is warranted. Currently, macroporous, monofilament mesh placed in an extraperitoneal position, with a minimally invasive approach, seems to be ideal for decreasing the incidence of infections and has higher possibilities for mesh salvage. On the contrary, intraperitoneal, microporous, multifilament, and barrier-coated meshes are least amenable to mesh salvage, and will most probably require complete explant followed by a new abdominal wall repair.

Competing interests

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

References

1. Rutkow IM. Demographic and socioeconomic aspects of hernia repair in the United States in 2003. Surg Clin North Am. 2003;83:1045–1051.
2. Quiroga-Centeno AC, et al. Systematic review and meta-analysis of risk factors for Mesh infection following Abdominal Wall Hernia Repair Surgery. Am J Surg. 2022;224:239–46.
3. Mavros MN, et al. Risk factors for mesh-related infections after hernia repair surgery: a meta-analysis of cohort studies. World J Surg. 2011;35:2389–2398.
4. Ventral Hernia Working Group, et al. Incisional ventral hernias: review of the literature and recommendations regarding the grading and technique of repair. Surgery. 2010;148:544–558.
5. Berger RL, et al. Development and validation of a risk-stratification score for surgical site occurrence and surgical site infection after open ventral hernia repair. J Am Coll Surg. 2013;217:974–982.
6. Poulose BK, et al. Design and implementation of the Americas Hernia Society Quality Collaborative (AHSQC): improving value in hernia care. Hernia. 2016;20:177–189.
7. Sartelli M, et al. (Eds.). Chapter 6: The Infected Mesh: How to Treat it. Infections in Surgery, Hot Topics in Acute Care Surgery and Trauma. 2021. Springer Link.
8. Jacombs ASW, et al. Biofilms and effective porosity of hernia mesh: are they silent assassins? Hernia. 2020;24:197–204.
9. Bellon JM. Classification of prosthetic materials used in hernia repair according to their structure and behavior with regard to tissue integration. Rev Hispanoam Hernia. 2014;2:49–57.
10. Thomas JD, et al. Non-coated versus coated mesh for retrorectus ventral hernia repair: a propensity score-matched analysis of the Americas Hernia Society Quality Collaborative (AHSQC). Hernia. 2021;25:665–672.
11. Schlosser KA, et al. Hernia Mesh Complications: Management of Mesh Infections and Enteroprosthetic Fistula. Surg Clin North Am. 2023;103:1029-1042.
12. Baharestani MM, et al. Use of negative pressure wound therapy in the management of infected abdominal wounds containing mesh: an analysis of outcomes. Int Wound J. 2011;8:118–125.
13. Bueno-Lledó J, et al. Mesh Infection After Hernia Repair and Negative Pressure Wound Therapy. A Systematic Review. World J Surg. 2023;47:1495-1502.
14. Dipp Ramos R, et al. Events, care, and outcomes after hernia mesh explantation for infection. Am J Surg 2022;224:174–176.
15. Levy S, et al. Comparison of complete versus partial mesh removal for the treatment of chronic mesh infection after abdominal wall hernia repair. Hernia. 2018;22:773–779.
16. Paton BL, et al. Management of infections of polytetrafluoroethylene-based mesh. Surg Infect. 2007;8:337-341.
17. Hawn MT, et al. Predictors of mesh explantation after incisional hernia repair. Am J Surg. 2011;202:28–33.
18. Sartelli M, et al. 2018 WSES/SIS-E consensus conference: recommendations for the management of skin and soft-tissue infections. World J Emerg Surg. 2018;13:58.
19. Pérez-Köhler B, et al. Mesh Infection and Hernia Repair: A Review. Surg Infect (Larchmt). 2016;17:124-137.
20. Sanchez VM, et al. Mesh infection in ventral incisional hernia repair: incidence, contributing factors, and treatment. Surg Infect. 2011;12:205–210.

Chapter 124

Diagnosis of intra-abdominal infections

Igor A. Kryvoruchko
Kharkiv National Medical University of the Ministry of Health of Ukraine, Kharkiv, Ukraine.

Olexander Yu. Usenko
National Scientific Center of Surgery and Transplantology named after O. O. Shalimov, Kyiv, Ukraine.

Igor A. Lurin
National Academy of Medical Sciences of Ukraine, Kyiv, Ukraine.

Yulia V. Ivanova
Kharkiv National Medical University of the Ministry of Health of Ukraine, Kharkiv, Ukraine.

Introduction

The issue of acute surgical pathology remains a significant concern globally, with persistently high mortality rates and a growing burden on healthcare systems in many countries. The systems of emergency surgical care for patients with intra-abdominal infections (IAI) in many countries of the world differ significantly in their diagnostic and tactical approaches to this category of patients. To facilitate the effective treatment of these patients and to prevent postoperative complications, specialists dealing with these problems must communicate in a common language. In this regard, it is necessary to introduce common concepts at all stages of medical care for this category of patients. Although there is variability in the spectrum of surgical diseases in different countries, the basic concepts of emergency abdominal surgery provide a foundation upon which unified guidelines can be formed. This is particularly evident in the areas of low-income countries, where there are significant deficiencies in the availability of effective surgical care.

The importance of prompt identification of intra-abdominal infections is evident. The primary characteristic of IAI is the rapid progression of endogenous intoxication (EI). In the context of EI, the accumulation of biologically active pathological products – endogenous toxic substances (ETS) – occurs in the tissues and fluids of the body. The sources of ETS are typically as follows: (1) Pathologically functioning organs of the endocrine system; (2) Metabolic products of xenobiotics entering the body from the external environment; (3) Focus of tissue destructive and the areas of ischemia with massive cell death; (4) Primary and secondary infectious-toxic foci; (5) All organs and tissues under hypoic conditions; (6) Endotoxins of microbes when activated in areas of natural vegetation (intestines, etc.); (7) Medications, etc. As a rule, ETS damages all blood cells and tissues of the body, including the endothelium; changes the permeability of cell membranes, and sodium-potassium balance; disrupts vascular tone, and microcirculation of blood, lymph and cerebrospinal fluid; inhibits the function of systems of erythropoiesis, immunity, tissue respiration, synthesis and transport of amino acids; disrupts the function of systems regulating body homeostasis (lipid peroxidation, antioxidant system, etc.). Tension of the abdominal wall muscles indicates the presence of peritonitis. Hypotension and

signs of hypoperfusion, including lactic acidosis, oliguria and acute disturbance of mental status, indicate the onset of sepsis.

The emergency department diagnostic evaluation for patients with intra-abdominal infection consists of the following. The first step in identifying patients with suspected IAI is through a history, physical examination, and laboratory tests. Secondly, patients with inconclusive results in the previous stage of the study, with the presence of central nervous system disorders, and patients with suppressed immunity due to various diseases and treatments with signs of intra-abdominal infection should be considered with emphasis on its confirmation or refutation. Stable patients who have been receiving fluid resuscitation and who cannot have an immediate laparotomy should consider imaging with contrast-enhanced computed tomography as the third option. It is not appropriate to continue with further instrumental diagnosis if there is evidence of diffuse peritonitis requiring emergency laparotomy in patients. Patients with clinical signs of intra-abdominal sepsis should have their severity assessed before surgery based on Sepsis-3 recommendations. Blood cultures do not provide additional clinically relevant information in patients with intra-abdominal infections and are therefore not routinely recommended.

Determination of bacteraemia may be useful in a strategy to determine the duration of antimicrobial therapy when used in conjunction with biomarker studies (procalcitonin, others). Routine Gram staining of infected material in patients with intra-abdominal infection has no proven diagnostic value. In low-resource emergency departments, the diagnosis of intra-abdominal infection is based primarily on clinical findings, supported by basic laboratory tests such as a complete blood count and a differential. Ultrasound, even when available, is not always helpful in diagnosis. Therefore, clinicians must carefully assess each sign and symptom to optimize diagnosis. In recent years, the use of ultrasound has increased and ultrasound scanners have become smaller, more accessible and less expensive. Ultrasound is highly reproducible and easily repeatable but remains highly operator-dependent. In different areas of resource-limited where access to CT is limited, plain radiography and ultrasound are resources that can assist in the diagnosis of emergency abdominal surgical pathology. CT may be useful when the diagnosis is unclear in developed countries, CT has become the gold standard. In instances where abdominal CT and ultrasound do not yield the requisite information, diagnostic peritoneal lavage may be employed as a means of detecting peritonitis. The resulting abdominal contents should be collected for diagnostic studies, with a particular focus on the determination of aerobic and anaerobic bacterial cultures using urgent cytological and bacteriological techniques. Diagnostic laparoscopy is a highly accurate diagnostic test for intra-abdominal pathology and is the recommended diagnostic procedure for patients with abdominal sepsis of unknown origin. It is a widely employed diagnostic procedure for determining the underlying pathology of acute abdominal pain and if surgical pathology is detected, laparoscopic treatment may also be employed. The accuracy of diagnostic laparoscopy is extremely high, with a range of 86-100%. As is well established, all IAIs are categorised as uncomplicated or complicated. It is also known that peritonitis in IAI can be localised or generalised. The occurrence of peritonitis can be attributed to the entry of any microorganism into the abdominal cavity. However, each microorganism exhibits a specific quantitative characteristic and a set of conditions under which peritonitis is likely to occur. This assertion is predicated on the premise that the peritoneum possesses bactericidal and immune properties.

Currently, peritonitis is typically caused by a mixed flora. The etiological features of existing forms of peritonitis are largely associated with differences in the sources of bacterial contamination and stages of the course of peritonitis. About the direct causes of peritonitis, their frequency and structure have remained relatively stable for an extended period. Among surgical pathology, the most common cause of peritonitis is perforation of a hollow organ. This group encompasses patients with abdominal trauma, perforated gastro-duodenal ulcers, perforations of the bowel, and failure of gastrointestinal and inter-intestinal anastomoses. A greater proportion of males are affected (60-70%). The age range of patients is broad, spanning from a few

months to over 80 years of age. Approximately 30% of patients are in the elderly and senile age group. In purulent peritonitis, Gram-negative and anaerobic bacteria, including intestinal flora (*Escherichia coli* and *Klebsiella pneumoniae*), enter the abdominal cavity. The endotoxins produced by Gram-negative bacteria lead to the release of cytokines that trigger cellular and humoral cascades, culminating in cellular damage and, in some patients, infectious shock and multi-organ failure syndrome. In particular, abdominal sepsis is initiated by a component of the outer membrane of Gram-negative microorganisms (e.g. lipopolysaccharide, lipid A, endotoxin) or Gram-positive organisms (e.g. lipoteichoic acid, peptidoglycan), as well as toxins from anaerobic bacteria. This results in the release of pro-inflammatory cytokines, including tumour necrosis factor and interleukins 1, 6, and others. These processes contribute to the formation of toxic mediators, which give rise to a complex, multifactorial syndrome that may manifest in a variety of ways and result in functional impairment of one or more vital organs and systems.

Consequently, in the context of this situation, the patient's condition must be evaluated by the Sepsis-3 criteria. At the initial stage of examination, it is also essential to conduct a differential diagnosis and assess the severity of physiological disorders. This is necessary to determine the necessity for correction of water-electrolyte imbalances, replenishment of fluid deficits to stabilise haemodynamic disorders and other procedures. This assessment is of paramount importance for the implementation of diagnostic procedures, the initiation of antimicrobial therapy, the timing and types of surgical intervention, the choice of open or minimally invasive surgery, the use of tact, and other procedures.

Clinical manifestation of intra-abdominal infections

Acute appendicitis in adults

Approximately 20-30% of cases lack the classic clinical features (history, characteristic physical symptoms, laboratory values) that would otherwise be expected. However, in other cases, acute appendicitis (AA) may 'masquerade' as other diseases, which can significantly complicate the diagnosis of AA, especially in elderly patients and in pregnant women. The diseases with which differential diagnosis of AA is mandatory: perforated gastric or duodenal ulcer; acute pancreatitis; complicated Meckel's diverticulum; torsion of the right appendages, disturbed ectopic pregnancy, ovarian apoplexy, pelvic inflammation; right-sided renal colic and/or urinary infections; intestinal infections. As a rule, the patient complains of pain in the right iliac region, which is constant and moderate in intensity, and does not radiate. The disease manifests abruptly, in the absence of any preceding symptoms and abdominal pain is typically persistent. The localisation of pain is dependent on the anatomical features of the appendix location, including ascending, medial, pelvic, retrocecal or retroperitoneal, and left-sided. In the case of an ascending location, the pain is localised in the right subcostal region and may simulate the symptoms of biliary colic or peptic ulcer disease and it is accompanied by vomiting due to duodenal irritation. The location of the appendix in proximity to extrahepatic bile ducts may result in transient jaundice. In the case of a medial location, the process is displaced to the midline and located closer to the root of the mesentery of the small intestine. In this case, the onset of pain may be accompanied by repeated vomiting, which is associated with reflex irritation of the root of the mesentery and the pain is localised in the vicinity of the navel as a rule. In the pelvic position, the inflamed appendix may contact the bladder wall, which is manifested by dysuria and a lower localisation of pain. In the retrocecal or retroperitoneal position, the symptomatology develops more gradually, which frequently results in delayed hospitalisation. In addition, the affected individual may experience pain in the right thigh and even the right hip joint. A left-sided location of the appendix is an extremely rare occurrence, with a prevalence of only 0.1% of observations. All local symptomatology of AA is found in the left iliac region. Furthermore, the

localisation of pain may be influenced by pregnancy, particularly in the second trimester, when the enlarging uterus shifts upwards and laterally, displacing the ileocecal angle. Consequently, the pain may be localised in the right lateral region or the right subcostal region. The patient typically presents with anorexia and nausea or vomiting. The majority of patients experience vomiting on a single or double occasion. The Rovsing's sign can be identified by palpation of the left lower quadrant of the abdomen with the left hand and simultaneous right-hand pressure on the descending colon. The presence of pain in the right iliac region is indicative of a positive symptom. Kocher's sign is characterised by pain in the epigastrium or wandering pain throughout the abdomen that shifts to the right iliac region within two to four hours. The obturator test, which involves passive internal rotation of the flexed right hip when the patient is on their back, is what is causing pain in cases of pelvic AA. The psoas sign is a diagnostic test performed with the patient in the left side position. The doctor then slowly extends the patient's right hip, thus stretching the iliopsoas muscle. This causes pain, which indicates the presence of an irritated and inflamed appendix near the lumbar muscle. Blumberg's symptom is defined as an increase in pain in the right iliac region when the hand is pulled back sharply from the abdominal wall after pressing on it in the right iliac region.

It is recommended that the likelihood of AA be assessed based on the Alvarado, AIR (Appendicitis Inflammatory Response Score), AAS (Adult Appendicitis Score) and RIPASA (Raja Isteri Pengiran Anak Saleha Appendicitis) scores. The sensitivity and specificity of all these scores are inversely proportional: they are sensitive enough to exclude the disease, but not specific enough to confirm AA. The Alvarado score has insufficient specificity to diagnose AA in adults and does not reliably distinguish between complicated and uncomplicated forms of AA in the elderly, so its use in adults is not recommended. However, a borderline score of less than five is sensitive enough to exclude AA (sensitivity 99%). The AIR and AAS scores are recommended for use in suspected AA cases due to their superior predictive value and ability to reduce the incidence of negative appendectomies and the need for imaging studies in low- and intermediate-risk groups. Given the low probability values associated with the individual clinical data mentioned above for determining the likelihood of AA in an adult patient, an individualised approach is currently recommended, taking into account the probability of disease, gender and age of the patient. Furthermore, the AIR and AAS scores are also recommended as clinical predictors of AA.

A complete blood count is recommended as an increase in the number of leukocytes, and in particular, an increase in the number of polymorphonuclear neutrophils (≥ 75%), is of significant diagnostic value in the context of the clinical signs of AA. It is crucial to highlight that biochemical markers (C-reactive protein, procalcitonin, etc.) represent a promising and reliable diagnostic tool for the detection of both negative cases and complicated AA in adults. Nevertheless, there is currently no evidence of sufficient quality to necessity support their use. It is also recommended that a general urinalysis be performed to exclude urinary system pathology. Patients with a medium probability of AA (according to the AAS/AIR score) should be admitted to the hospital for further observation and monitoring. In patients with an intermediate probability of AA (according to AAS/AIR score), ultrasound is recommended as an essential addition to the physical examination. In patients with an intermediate probability of AA (as assessed by AAS/AIR score) and no ultrasound evidence of AA, CT abdominal imaging with intravenous contrast is recommended. In patients under the age of 40 with a high probability of AA, CT is not recommended (as assessed by AAS/AIR). The primary disadvantage of CT is the exposure to ionising radiation, which necessitates a risk-benefit assessment, particularly in younger patients and women of childbearing age. Nevertheless, the routine use of CT has been demonstrated to reduce the number of unnecessary appendectomies and to enhance the detection of abdominal diseases.

Acute cholecystitis

Acute cholecystitis (AC) is defined as an acute inflammation of the gallbladder, accompanied by a local and systemic inflammatory reaction or the threat of its occurrence. In approximately 90% of cases, AC develops in the context of cholelithiasis, while in 10% of cases, it is designated as acute acalculous cholecystitis, as these patients do not have gallstones. The occurrence of intravesical hypertension is the primary factor in reducing the blood supply to the gallbladder mucosa. A reduction in the perfusion of the wall, particularly in elderly and senile patients, contributes to the disruption of the mucous barrier, the penetration and growth of aerobic and anaerobic microorganisms (*Escherichia coli*, *Klebsiella*, *Enterococcus*, *Streptococcus* species, *Enterobacter* species, *Pseudomonas aeruginosa*), which, in turn, increases the inflammatory exudation into the lumen of the organ. The exudation process results in an increase in intravesical pressure, compression of in-wall vessels, disruption of microcirculation and ischemia in the gallbladder wall, and the release of inflammatory exudate into its lumen. Consequently, a pathophysiological vicious circle is formed, whereby the development of AC is perpetuated.

The clinical manifestations of AC are dependent upon the pathomorphological picture of inflammation of the gallbladder, the presence and extent of peritonitis, as well as concomitant changes in the bile ducts. In the majority of cases, the initial symptom of AC is abdominal pain in the right hypochondrium. The pain may also radiate to the right shoulder or scapula, the lumbar region, or the right shoulder girdle, and in some cases, to the heart (it is a cholecystocardiac syndrome). Nausea is a common symptom, as with biliary colic, but vomiting is more common. Severe vomiting may be indicative of the presence of a stone in the common bile duct, acute pancreatitis, or intestinal obstruction. A loss of appetite and malaise are more commonly observed in patients with AC. Purulent complications of AC are manifested by fever above 37–38°C, tachycardia, chills and jaundice. Murphy's sign is characterised by the patient experiencing sharp pain in the right hypochondrium when the examiner presses the gallbladder at the height of inspiration. Mussy's sign is characterised by tenderness at the point of the phrenic nerve, between the heads of the sternocleidomastoid muscle. Kera's sign is characterised by pain during deep palpation in Ker's point. Blumberg's sign is characterised by the patient experiencing an exacerbation of pain in the right upper quadrant when the examiner sharply withdraws their hand from the abdominal wall after pressing it in the right upper region.

The diagnosis of AC can be established clinically, but laboratory confirmation is of great importance. All patients presenting with clinical manifestations of AC are advised to undergo general and biochemical blood tests, as well as additional examinations in unclear cases, to determine the severity of inflammatory changes and to facilitate a timely diagnosis of cholestasis syndrome and differential diagnosis: right-sided lower lobe pneumonia; myocardial infarction; perforated peptic ulcer; acute pancreatitis; shingles; hepatitis; acute intestinal obstruction; acute appendicitis. In diagnostically challenging cases, where all non-invasive research methods have been exhausted, diagnostic video laparoscopy may be employed. When making the final diagnosis, all patients with AC are recommended to use the classification and diagnostic criteria of the Tokyo Agreement (Tokyo guidelines (2013/2018). The diagnostic criteria for AC as set out in the 2013/2018 Tokyo guidelines are as follows:

A. Local signs of inflammation etc.
   (1) Murphy's sign, (2) RUQ mass/pain/tenderness.
B. Systemic signs of inflammation etc.
   (1) Fever, (2) elevated CRP, (3) elevated WBC count
C. Imaging findings
   Imaging findings characteristic of AC.

Suspected diagnosis: one item in A + one item in B

Definite diagnosis: one item in A + one item in B + C

The severity of AC is determined by the following criteria:

- Grade II (moderate) AC: "Grade II" AC is associated with any one of the following conditions: An elevated white blood cell (WBC) count (greater than 18,000 per microliter) is indicative of the condition. Additionally, a palpable tender mass in the right upper abdominal quadrant, duration of complaints exceeding 72 hours, and marked local inflammation (gangrenous cholecystitis, pericholecystic abscess, hepatic abscess, biliary peritonitis, emphysematous cholecystitis) are also indicative of the condition.
- Grade III (severe) AC: "Grade III" AC is associated with dysfunction of any one of the following organs/systems:
  1. Cardiovascular dysfunction: hypotension requiring treatment with dopamine ≥ 5 μg/kg per min, or any dose of norepinephrine.
  2. Neurological dysfunction: decreased level of consciousness.
  3. Respiratory dysfunction: A PaO_2/FiO_2 ratio of less than 300 indicates.
  4. Renal dysfunction characterized by oliguria and a creatinine level exceeding 2.0 mg/dl.
  5. A PT-INR of greater than 1.5 indicates hepatic dysfunction.
  6. A platelet count of less than 100,000/mm^3 indicates haematological dysfunction.

The Tokyo Guidelines 2013/2018 propose that imaging studies, such as ultrasound, CT and HIDA scans, should be employed to diagnose AC, in conjunction with a comprehensive history, a thorough clinical examination and laboratory tests. Furthermore, it highlighted the value of ultrasound as a diagnostic tool due to its non-ionising, inexpensive, and easy-to-use characteristics. The positive results of bile culture are found in 80-100% of patients with acute cholangitis. In the majority of cases, the causative agents of the biliary infections are microorganisms of the intestinal microflora. These microorganisms include representatives of the *Enterobacteriaceae* family, among which *Escherichia coli* plays a dominant role (50-60%), *Klebsiella* spp. (8-20%), *Serratia* spp., and *Acinetobacter* spp. Gram-positive microorganisms (*Streptococcus* and *Enterococcus*) are identified in 2-30% of cases, while non-spore-forming anaerobes (*Bacteroides*, *Fusobacteria* and *Peptococci*) are found in up to 20% of cases. *Pseudomonas* spp. are present in 2-4% of cases, as reported by Salvador *et al*.

Perforation of hollow organs

Perforation may occur at any level of the gastrointestinal tract, with the contents of the stomach or intestine entering the peritoneal cavity. The causes of this condition are diverse. The clinical symptoms manifest suddenly, with the onset of intense pain and a rapid deterioration in the patient's condition. Diagnosis is typically based on the identification of free gas within the abdominal cavity through the use of radiography.

Esophagus

Esophageal rupture may be iatrogenic during endoscopic procedures or other manipulations or may occur spontaneously (Burhave's syndrome). The patient's condition is severe, with evidence of mediastinitis. The most common site of oesophageal rupture is the distal left oesophagus. Acid and gastric contents cause fulminant mediastinitis and shock. The symptoms of oesophageal rupture include chest and abdominal pain, fever, vomiting, haematemesis, and shock. Approximately 30% of patients present with subcutaneous emphysema. Crepitation, also known as Hammen's symptom, may be heard in the mediastinal region. This is a distinctive crunching or clicking noise that is synchronised with heartbeats. The presence of air in the mediastinum, fluid in the pleural cavity, and widening of the mediastinum, as observed on radiological examination of the chest and abdomen, are indicative of the diagnosis and it is confirmed by esophagography with

water-soluble contrast. A CT scan of the chest reveals the presence of air and fluid in the mediastinum, yet does not provide information regarding the precise location of the rupture.

Peptic ulcer of the stomach and duodenum

The clinical signs of perforative peptic ulcer are as follows: 1. The disease typically manifests acutely, presenting with sharp abdominal pain, akin to a "dagger blow." 2. The abdominal muscles are tensed. 3. Palpation of the abdomen elicits pain. The patient is often positioned with bent knees, and the pain is exacerbated by movement, accompanied by a distressed facial expression, pale skin, cyanotic lips, and dry mucous membranes of the mouth and lips. The patient's blood pressure is often reduced by 5-10%, with a slow pulse and frequent, shallow respiration. Palpation of the anterior abdominal wall reveals a tense appearance. In the initial hours of the disease, sharp pain is experienced in the epigastrium and mesogastrium. Upon percussion of the abdomen, a sharp pain is elicited. The disappearance of hepatic dullness and the appearance of high tympanitis over the liver can be established. In the presence of fluid in the lower and lateral abdomen, a dulling of the percussion sound is determined. The physical examination findings may be contradictory, as it has been observed that symptoms of peritonitis are present in 35% to 50% of patients with perforated peptic ulcers. This is more commonly observed in cases of occluded perforation or patients with atypical localisations. Abdominal pain is less pronounced in perforated ulcers of the posterior wall of the duodenum and the cardia of the stomach when the contents enter the retroperitoneal fascia or omental sac. Localized or generalized peritonitis is a typical manifestation of perforated peptic ulcer, although it may be present in only two-thirds of patients.

Patients with perforated ulcers are advised to undergo a standard set of laboratory tests, including blood, urine, blood chemistry, blood glucose, bilirubin, creatinine, blood amylase, and so forth. However, it should be noted that changes in laboratory parameters in these patients are non-specific, laboratory tests are conducted for differential diagnosis and to ascertain the extent of damage to various organs. All patients are recommended to undergo chest and abdominal radiography to detect free gas under the diaphragm (the diagnostic accuracy of X-ray images in the vertical position and on the left side is the same). If other diagnostic methods are not informative and if technically possible, abdominal CT is recommended. In patients with suspected perforation of a peptic ulcer in the absence of signs of free gas in the abdominal cavity, according to the data of radiological methods of imaging, it is recommended that an oral water-soluble contrast agent be administered with repeated radiological examination. Ultrasound can also reveal free intraperitoneal exploration or free fluid but the role of it in the diagnostic workup of suspected peptic ulcer perforation remains to be determined. The 2020 WSES recommendation suggests the adoption of scoring systems including the BOEY, PULP and ASA scores to stratify patients by risk and predict outcomes. However, these recommendations are weak and based on low-quality evidence. The scoring systems in question are relatively straightforward to use, clinically meaningful, and can be employed to predict postoperative morbidity and mortality. In cases of perforated peptic ulcer with sepsis/septic shock, it is crucial to determine the parameters for assessing the severity of the disease. This entails identifying several symptoms, such as altered mental status and dyspnea, as well as signs, including tachycardia, tachypnea, decreased pulse pressure, and decreased urine output. Additionally, laboratory parameters, such as hyperlactatemia, arterial hypoxemia, increased creatinine, and blood coagulation disorders, must be considered. The systems of organ failure assessment (SOFA) or quick SOFA (qSOFA) are acceptable for assessing disease severity.

Gastric tumour

The occurrence of gastric adenocarcinoma perforation is a rare phenomenon. Patients with perforation of gastric malignancy typically present with a history and symptoms that are similar to those of patients with

benign gastroduodenal or other cavitary perforations. In the context of examining a patient with suspected perforation, it is recommended to pay attention to the sudden and violent onset of symptoms, including diffuse acute abdominal pain, weakness, marked pain on palpation of the anterior abdominal wall, and abdominal muscle tension. It is important to note that changes in laboratory values in perforation are nonspecific. However, physicians must be aware of the presence of leucocytosis and increased amylase levels, which may be observed in gastric perforation. Instrumental methods of examination can reveal characteristic signs of perforation, including free gas in the abdominal cavity, free fluid in the abdominal cavity, and the presence and localisation of the perforation. The diagnostic accuracy of review radiography varies considerably, ranging from 30% to 85%. CT of the abdomen is recommended for all patients with suspected perforation, and if other diagnostic methods are not informative (it has a high diagnostic accuracy of 95-98%). In patients with suspected perforation in the absence of signs of free gas in the abdominal cavity according to the data of radiological methods of investigation, oral administration of water-soluble radiopaque iodine-containing contrast agent with repeated radiological examination is recommended. In all patients with suspected perforation, in the event of a negative radiological examination or the inability to perform a CT scan, it is recommended to perform an ultrasound of the abdominal cavity organs to detect free gas and free fluid (diagnostic accuracy in perforation up to 92%).
Esophagogastroduodenoscopy is indicated for patients with suspected tumour perforation in cases where the clinical and instrumental picture is ambiguous, as well as for the diagnosis of other complications (bleeding, pylori duodenal stenosis), and for biopsy in cases of an unresectable tumour process (allows the presence of a tumour with perforation to be established in 90% of cases). In the absence of free gas in the abdominal cavity, diagnostic laparoscopy is recommended for patients with suspected perforation.

Small bowel (not traumatic)
The clinical picture of intestinal perforation is dependent on a multitude of factors, including the aetiology, age of the patient, localization of the defect, type of perforation, medication, and others. It is important to note that the clinical picture of intestinal perforation develops in the context of any underlying disease, and it is accompanied by the rapid onset of complications such as peritonitis and sepsis. Consequently, it is only possible to speak of specific signs of perforation in the context of a specific etiologically significant pathology. A diagnosis is made based on clinical findings and is then confirmed by instrumental diagnostics, which have different diagnostic values. The most prevalent and distinctive symptom is considered to be abdominal discomfort of varying locations. An examination may reveal abdominal tension and bloating, as well as decreased peristalsis and symptoms of peritoneal irritation. In addition, tachycardia, moderate arterial hypotension, and fever (in the event of peritonitis) may be observed. Moderate dehydration may be evidenced by an increased thirst, a dry tongue, and oliguria. A review of radiography of the abdominal cavity in various positions may reveal the accumulation of free gas in the abdominal cavity. It is recommended that all patients undergo abdominal ultrasound on admission for diagnostic purposes. CT and MRI are considered the "gold standard" for the diagnosis of intestinal perforation, as well as for identifying the causes of perforation. In cases where the diagnosis remains uncertain, laparoscopy is recommended. Laboratory diagnostics lacks highly specific features; therefore, blood, urine, C-reactive protein, and blood biochemical analysis are recommended.

Colon (not traumatic)
Diverticulitis of the colon is defined as inflammation of the diverticulum, which may or may not be accompanied by infection. This may result in phlegmon of the bowel wall, peritonitis, perforation, fistula formation or abscess. The most severe complication of diverticular disease is perforation of the diverticulum, which occurs

in 7-10% of patients with diverticular disease, according to the literature. The outcome of the disease is the formation of an abdominal cavity infiltrate or peritonitis. In the acute form of diverticulitis, the most common symptom is abdominal pain. In the majority of cases, the condition is localized to the lower abdomen on the left side. In some cases, patients may experience symptoms in other locations, including the upper abdomen, the left side, and, on rare occasions, the lower abdomen on the right side. The pain may be continuous or intermittent. In most cases, the pain is not particularly intense and is not accompanied by an increase in body temperature. Other symptoms that are not observed in all patients with intestinal diverticulitis include flatulence, an increased frequency of stools or constipation, nausea, vomiting, and frequent urination. The general condition of patients before the onset of complications remains unaltered. Palpation may reveal a compacted but mobile area of the affected intestine. The symptoms of diverticulitis are more pronounced in cases with a complicated course.

Acute para-intestinal infiltrate

The subsequent phase of acute diverticulitis. The exudate (inflammatory fluid) that forms within the diverticulum soaks the intestinal wall and surrounding tissues, causing them to become inflamed. This subsequently results in an exacerbation of the symptoms. The pain becomes more pronounced. A tumour-like mass with indistinct boundaries may be palpated in the abdomen. Palpation of the abdomen results in the development of pain. The motility of the inflamed intestinal wall is diminished. The symptoms of intoxication also manifest, including weakness and a body temperature above 38 degrees Celsius. In two out of three patients, there is an increase in symptoms associated with impaired intestinal function, including flatulence, abdominal bloating, and changes in the frequency and consistency of stool. In some cases, faecal discharge may be challenging due to compression of the intestine by the infiltrate, yet intestinal obstruction does not develop. The intestinal function is rapidly restored in the context of antibacterial treatment.

Diverticular abscess

An abscess is a localized accumulation of pus. The pain is constant and localised to the area of the purulent cavity. In the majority of cases, the pain is located in the lower abdomen on the left side. The patient's temperature is within the normal range. An increase in body temperature to more than 37.5 degrees Celsius, severe pain, vomiting, and an elevated heart rate typically indicate the breakthrough of the purulent cavity into the abdominal cavity with the development of peritonitis.

Diverticular perforation

Perforative diverticulitis is characterized by the sudden onset of severe abdominal pain. Initially, the pain is localised to a specific area of the abdomen, but subsequently becomes diffuse, lacking a clear localisation. Following the perforation of the colon, the symptoms rapidly intensify, with the onset of high fever and severe intoxication.

Colorectal cancer perforation

Colorectal perforation in colorectal cancer is a less common occurrence. The integrity of the intestinal wall may be violated in cancer as a result of tumour decay or obstruction of the intestinal lumen, pressure of faeces on the intestinal wall, disruption of its blood supply and subsequent necrosis. Furthermore, colon perforation may be observed in the context of non-oncological bowel obstruction, Crohn's disease, ulcerative colitis and toxic megacolon. In certain instances, medical procedures, such as colonoscopy, have been identified as a potential cause of perforation. According to research, the incidence of such complications is approximately 0.2%. The use of immunosuppressants and certain hormonal drugs is associated with an

increased risk of non-traumatic perforation of the colon, regardless of the underlying cause. Colon perforation is defined by the presence of acute abdominal symptoms. Patients typically present with severe abdominal pain, which is often exacerbated by movement and relieved by resting. They often adopt a flexed position on the side or back with bent legs, which may be a result of the pain. The body temperature of patients with intestinal perforation initially exhibits a sub-febrile pattern, followed by a rise to febrile figures. Additionally, patients may exhibit signs of weakness, pallor of the skin, nausea, vomiting, decreased urine output, tachycardia, and respiratory disorders. The abdomen is distended, and the anterior abdominal wall is tense. Palpation reveals an increase in pain, with the greatest discomfort occurring in the area of the perforation. Following the perforation of the colon, the intensity of the pain syndrome gradually decreases as the receptors of the peritoneum adapt to the pathological changes occurring within the abdominal cavity. As peritonitis develops, pain and abdominal wall tension increase in intensity and become more diffuse, affecting all regions of the abdomen. The percussion of the liver in patients with perforation of the colon results in the disappearance of hepatic dullness, indicating the presence of gas in the abdominal cavity. In the low-lying areas of the abdomen, the presence of fluid may result in a dulling of the sound. Auscultation reveals a weakening or disappearance of intestinal noises due to peristaltic disorders. The clinical manifestations of colonic perforation are contingent upon the extent of the perforation, the dimensions of the perforation hole, and the presence or absence of obstruction of the large intestine. In general, the proximal lesion of the colon is more severe due to the rapid dissemination of liquid intestinal contents in the abdominal cavity. The exception to this rule is when the cause of colonic perforation is intestinal obstruction. In such cases, periods of apparent improvement, due to a reduction in the pressure of the contents on the intestinal wall, are more pronounced than usual. On occasion, colonic perforation may be practically asymptomatic due to the small size of the perforation or the proximity of the omentum, which prevents the contents from escaping into the abdominal cavity.

Conclusion

This chapter addresses the clinical question of which diagnostic procedures are appropriate for the initial evaluation of patients with suspected IAI. Intra-abdominal infection is a prevalent clinical issue, and the classification (uncomplicated and complicated IAI) encompasses a spectrum of processes affecting diverse organs. An uncomplicated infection causes intramural inflammation of the digestive tract and has a significant chance of becoming a complicated infection if not treated properly. Complicated intra-abdominal infection is defined as the spread of infection beyond the jejunum into the peritoneal space, which is associated with the formation of an abscess or peritonitis. The necessity for prompt diagnosis and intervention, coupled with the ongoing debate surrounding the optimal procedure to be employed, further complicates the management of these patients. The management of these infections has been significantly advanced by the development of supportive intensive care, diagnostic imaging, minimally invasive interventions, and antimicrobial therapy.

Competing interests

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

References

1. Sartelli M, et al. WSES/GAIS/SIS-E/WSIS/AAST global clinical pathways for patients with intra-abdominal infections. World J Emerg Surg. 2021; 16, 49.
2. Coccolini F, et al. Source control in emergency general surgery: WSES, GAIS, SIS-E, SIS-A guidelines. World J Emerg Surg. 2023; 18, 41.
3. Scott MJ, et al. Consensus Guidelines for Perioperative Care for Emergency Laparotomy Enhanced Recovery After Surgery (ERAS®) Society Recommendations Part 2-Emergency Laparotomy: Intra- and Postoperative Care. World J Surg. 2023 Aug;47(8):1850-1880.
4. Cobianchi L, et al. Time for a paradigm shift in shared decision-making in trauma and emergency surgery? Results from an international survey. World J Emerg Surg. 2023 Feb 17;18(1):14.
5. Sartelli M, et al. It is time to define an organizational model for the prevention and management of infections along the surgical pathway: a worldwide cross-sectional survey. World J Emerg Surg. 2022;17(1):17.
6. Kryvoruchko IA, et al. Association of screening markers of coagulation with the short-term outcome in the small bowel obstruction in adults: a retrospective study. Wiad Lek. 2022;75(9 pt 2):2244-2251.
7. Kryvoruchko IA, et al. Surgical treatment of patients for abdominal sepsis. Klin Khir. 2014;(8):34-38.
8. Di Saverio S, et al. Diagnosis and treatment of acute appendicitis: 2020 update of the WSES Jerusalem guidelines. World J Emerg Surg. 2020; 15, 27.
9. Yokoe M, et al. Tokyo Guidelines 2018: diagnostic criteria and severity grading of acute cholecystitis (with videos). J Hepatobiliary Pancreat Sci. 2018;25(1):41-54.
10. Huang SS, et al. Diagnostic performance of ultrasound in acute cholecystitis: a systematic review and meta-analysis. 2023; World J Emerg Surg: 18(54).
11. Salvador VB, et al. A microbiological and antibiotic susceptibility study of organisms isolated from bile cultures obtained from patients with and without cholangitis at an Asian academic medical centre. Surg Infect (Larchmt). 2011;12(2):105-11.
12. Tarasconi A, et al. Perforated and bleeding peptic ulcer: WSES guidelines. World J Emerg Surg. 2020; 15(3).

Chapter 125

Intra-abdominal infections. Principles of treatment

Andreas Hecker
Department of General and Thoracic Surgery University Hospital of Giessen, Germany.

Martin Reichert
Department of General and Thoracic Surgery University Hospital of Giessen, Germany.

Julia Noll
Department of General and Thoracic Surgery University Hospital of Giessen, Germany.

Jacqueline Braun
Department of General and Thoracic Surgery University Hospital of Giessen, Germany.

Anca-Laura Amati
Department of General and Thoracic Surgery University Hospital of Giessen, Germany.

Markus Weigand
Department of Anesthesiology University Hospital of Heidelberg, Germany.

Introduction

Once diagnosed intra-abdominal infections require a rapid initial source control, accompanied by an adequate antimicrobial and supportive intensive care therapy. These important principles of sepsis therapy, of course, depend on a focus-based diagnosis including clinical examination, laboratory parameters, sepsis scores, and in many cases radiographic imaging, which are not topics of this chapter but are discussed previously in this book.

We have to keep in mind that intra-abdominal infections go in line with clinical signs of peritonitis, which is just a symptom, also caused by disorders other than surgical ones (e.g. diabetes mellitus!).

Table 1 provides a short overview on the different reasons for peritonitis and their classification.

Discussing the therapeutic principles of intra-abdominal infections, we focus on patients with secondary peritonitis due to intestinal perforation or mesenteric ischemia. In contrast, the subgroup of patients with a tertiary or so-called ongoing peritonitis is of the highest interest in modern surgical research: These patients develop an even more complex clinical state, which is characterized by:

- a persistent abdominal infection,
- an altered microbial flora, and
- a progressive or resistant organ dysfunction.

Table 1. The classification of peritonitis as the main symptom of intra-abdominal infection.

Classification	Causes
Primary peritonitis	● Blood-stream infection with peritonitis in the childhood ● Spontaneous bacterial peritonitis in preexisting ● Ascites (e.g. liver cirrhosis) ● Peritonitis in tuberculosis ● Lymphogen or intraluminal bacterial invasion
Secondary peritonitis	● Intestinal perforation, e.g. ○ Acute diverticulitis of the sigmoid ○ Acute cholecystitis ○ Acute appendicitis ○ Toxic megacolon ○ Gastro-duodenal ulcer ● Break-through/transmural migration, e.g. ○ Mesenteric ischemia ○ Toxic megacolon ○ Ileus ● Post-traumatic peritonitis ● Postoperative peritonitis, e.g. ○ Anastomotic leakage ○ Ischemic perforation
Tertiary peritonitis	● Ongoing/persisting peritonitis
Quaternary peritonitis	● Iatrogenic abscess ● CAPD-associated peritonitis

Abbreviation. CAPD: continuous ambulatory peritoneal dialysis.

According to the International Sepsis Forum Definition of Infection in the ICU Consensus Conference from 2005 a tertiary or ongoing peritonitis is defined as a severe recurrent or persistent intra-abdominal infection >48 hours after initially successful and adequate surgical source control of secondary peritonitis. The mortality rate is unacceptably high and ranges between 30 and 65%!

Both for patients with secondary and tertiary/ongoing peritonitis modern intensive care medicine requires: (1) an everyday re-assessment of the intensive care patient, and (2) an interdisciplinary everyday round and discussion of the critical state as essential elements to decide whether these patients require diagnostic or therapeutic interventions.

Treatment of critically-ill patients with secondary or tertiary peritonitis is interdisciplinary!

After reading this book chapter you will:

a. understand the principles of surgical and radiological (e.g. CT-guided drainage) source control;
b. gain an overview of the antimicrobial therapy of intra-abdominal infections;
c. understand the basic supportive intensive care bundles on intra-abdominal infections.

Adequate surgical therapy requires a rapid decision for or against surgical intervention.

After initial hospital admission (secondary peritonitis) and especially after surgical intervention due to abdominal sepsis (persisting/ongoing peritonitis) signs and symptoms of sepsis or an ongoing peritonitis could also be unspecific and missed by clinicians. There is a relevant lack of knowledge on the signs of (intra-abdominal) sepsis and peritonitis especially in non-intensivists. In cases of postoperative peritonitis, it can sometimes be masked and attributed to "normal" postoperative problems like intestinal paralysis, under-resuscitation, postoperative mental deterioration etc.

Signs and symptoms of sepsis are often masked and misinterpreted

Due to the masked clinical symptoms, slight suspicion of a complicated course after initial surgery should lead to radiographic imaging (CT, ultrasound or X-ray). Interdisciplinary everyday rounds include an everyday re-evaluation of the patients with intraabdominal infections concerning the persistence/occurrence of organ dysfunctions, elevated inflammatory parameters, changes in quality of drainage secretion, etc. CT shows the highest sensitivity (97.2%) in cases of secondary peritonitis! As a bedside technique ultrasound allows a rapid examination of the abdomen, but furthermore includes the possibility to drain intra-abdominal fluid collections. CT- or ultrasound-guided drainages are of diagnostic value on the one hand (pus? clear fluid? hematoma? etc.). On the other hand, drainage of intra-abdominal abscesses or biliomas can be one kind of source control with minor morbidity compared to surgery in ongoing peritonitis.

Therapeutic principles in intra-abdominal infections

Once diagnosed e.g. by CT-scan surgeons have to keep in mind the peritonitis management algorithm, which is shown in **Figure 1**.

In principle, the treatment of secondary (or tertiary) peritonitis is based on the three therapeutic columns: surgical source control, antimicrobial therapy, and supportive intensive care medicine. These three therapeutic pathways require and influence each other, which reflects that therapeutic success is only possible in an interdisciplinary setting.

Surgery

Surgical source control is the only causal and life-saving treatment option for patients with secondary peritonitis. The four basic elements of debridement, removal of infected devices, drainage of purulent/infected cavities, and abdominal decompression still summarize the surgical therapy in secondary (and tertiary) peritonitis.

Patients with intra-abdominal sepsis and cardiovascular instability require another surgical approach: In these situations, the four above-mentioned therapeutic principles are used in their purity, but prolonged emergency operation is avoided and the reconstruction is performed 24-48 hours after the initial operation. This goes in line with modern concepts of damage control surgery, which were established for (military) trauma patients first. The indication of this modern damage control approach is the lethal triad of coagulopathy, inflammation and cardiovascular instability. This triad can be used as a landmark for the indication in trauma surgery, but also in patients with persistent or recurrent intra-abdominal infections who dynamically develop this critical health state after initial source control.

The most important independent risk factor for decreased survival in secondary peritonitis is insufficient source control during initial surgery, which emphasizes the importance of damage control surgery in life-threatening intra-abdominal sepsis. A bundle of studies could prove that non-successful inadequate source

control leads to a dramatic increase in mortality. Seiler *et al.* published data from patients (n=258) with diffuse peritonitis. In case of unsuccessful source control (11%) mortality rises from 13 to 27%! In other publications focusing on severe intra-abdominal sepsis even more than 90% of patients died, if source control failed!

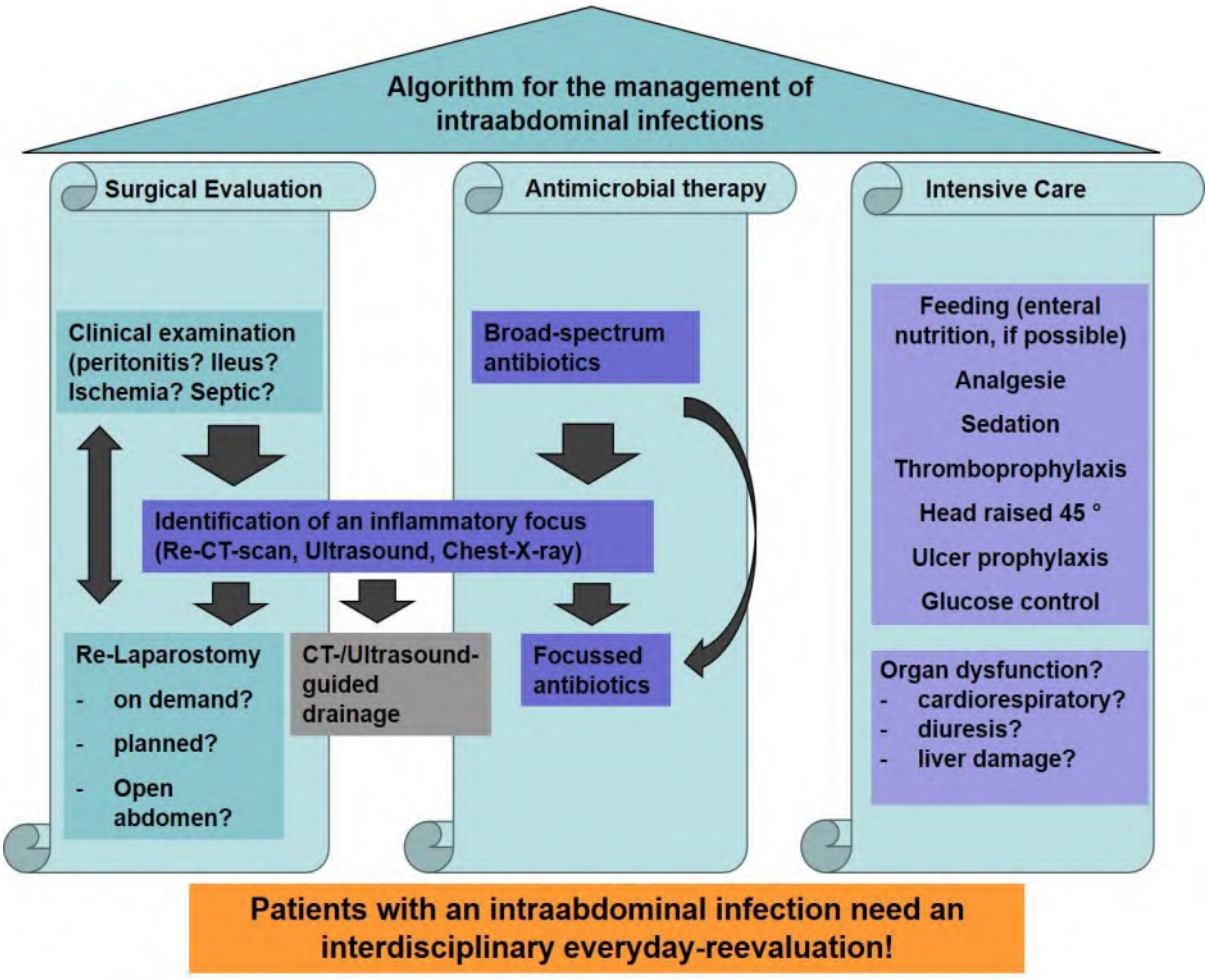

Figure 1. Peritonitis management algorithm.

The influence of the time-to-intervention on patients´ survival

Besides the adequacy of initial source control, the importance of the so-called time-to-intervention (´time between diagnosis to surgery´) is of the highest interest in surgical research. Several trials analyzed the importance of the "time-to-intervention" for the outcome of patients with secondary peritonitis. As an example, Reitz *et al.* published a clear association between time-to-source control and 90-day survival in a high-quality paper in JAMA Surgery recently.

Relaparotomy: planned or on-demand?

The a priori decision to reexplore the abdominal cavity independent from its necessity is defined as planned relaparotomy in the literature. In contrast, the indication for a relaparotomy can be re-evaluated during interdisciplinary everyday rounds of intensive care. In case of deterioration of the critically ill patient, a relaparotomy is performed ´on-demand´.

In a landmark study from Ruler *et al.* a difference between “on demand” (n=116) and “planned” (n=116) laparotomy concerning patients´ mortality (29% on demand, 36% planned) could not be detected. Intervention rates and hospital costs were significantly lower in the “on-demand” study group.
The ´on-demand concept´ requires a continuous clinical view of the patient. In contrast to strong criteria like the lethal triad, the literature reveals that marginal changes in laboratory parameters or clinical signs and symptoms could summit in the decision towards surgical re-exploration.
The complexity of this decision-making process was impressively published by von Ruler *et al.* in 219 cases of patients with secondary peritonitis, who had to undergo a second surgical emergency intervention. Interestingly neither the initial origin of the intra-abdominal focus nor the findings of the surgeon during primary emergency surgery could predict the necessity of a “second look”. Otherwise, the persistence or occurrence of organ failure after surgery were good indicators for early surgical re-exploration.
Once decided, the relook should be performed as soon as possible. 523 patients with secondary peritonitis, who had undergone initial emergency surgery were analyzed. In 105 cases a relaparotomy was necessary and performed. As published by Koperna *et al.* mortality was significantly lower, if surgery was performed within 48 hours after initial emergency surgery.

Are there still indications for a planned relaparotomy or open abdomen strategies?
Although the on-demand laparotomy is the gold standard of care in cases of intra-abdominal infection there are still clear-defined indications for a staged laparotomy like reevaluation of the intestinal viability in cases of mesenteric ischemia with secondary peritonitis.
Furthermore, severe cases of intra-abdominal infection could require open abdomen surgery as the gold standard surgical approach for patients with ongoing peritonitis, who bear the risk of abdominal compartment syndrome (ACS) development.

Intensive care

Every surgical intensive care patient with secondary peritonitis e.g. after sigmoid perforation requires certain key elements such as prophylaxis of ulcers (proton pump inhibitors), lung protective ventilation (acute respiratory distress syndrome, ARDS), hemodynamic stabilization (mean arterial pressure > 65 mmHg, application of ionotropics), adequate blood glucose, etc.
The role of corticosteroids for patients with intra-abdominal infections was controversially discussed in the literature. Today there seems to be a subgroup of critically ill patients with cardiovascular instability and/or septic shock who could profit from corticosteroid application.
For the surgeon visiting intensive care patients, there are some golden rules, which help evaluate the patient. As mentioned above this is crucial to see the positive or negative progress of the patient on the ward.

1. The round should be interdisciplinary! Intensive care patients with intra-abdominal infections require surgeons, intensivists, pneumologists, antibiotic stewards, nurses, and so on. Only in this setting the three columns of sepsis therapy are covered by experts in their field.
2. Give your patients a FAST-HUG. Working on intensive care the simple FAST-HUG concept introduced by Vincent *et al.* helps to monitor key aspects of supportive intensive care therapy: **F**eeding, **A**nalgesia, **S**edation, **T**hromboembolic prophylaxis, **H**ead-of-bed elevation, stress **U**lcer prevention **G**lucose control.

The basic elements of intensive care therapy in sepsis are shown in **Figure 1.**

Antimicrobial therapy

Blood cultures should be collected prior to any antimicrobial treatment! Initial administration of intravenous antimicrobials should be provided within 1 hour after hospital admission! The first choice is a broad-spectrum antibiotic (or a combination) (Tarragona-strategy ´hit hard & early´).

Especially in cases of secondary peritonitis the broad-spectrum antimicrobial therapy can and should be de-escalated and focused according to resistograms from blood culture or another specimen. In ongoing peritonitis, a modification or escalation could be necessary.

If the intra-abdominal infection is not under control the antibiotic therapy has to be critically re-evaluated after 48 hours.

In principle, antimicrobial therapy should be administered as soon as possible. For critical patients with intraabdominal sepsis, a bundle of trials showed a correlation between time-to-antibiotics and patient survival (e.g., 2% per hour of delayed antimicrobial therapy [German Medical Education of Sepsis Source Control and Antibiotics, MEDUSA]). Knowing the importance of efficient antimicrobial therapy the indiscriminate use of broad-spectrum antibiotics resulting in bacterial resistance is a life-threatening problem in modern sepsis therapy. This non-specific use led to increased rates of pulmonary (30%) and urinary (8%) infections in intensive care. The paramount importance of antimicrobial resistance in intra-abdominal infections and emergency surgery is underlined by the World Alliance Against Antibiotic Resistance of the World Society of Emergency Surgery (WSES AGORA). Antibiotic stewardship is gaining more and more importance in modern intensive care. Surveilling the use of antimicrobials is essential to avoiding antibiotic resistance. As shown in the STOP-IT trial a prolonged antimicrobial therapy (8 *vs.* 4 days) is not beneficial for patients with intra-abdominal infections, who had undergone a successful source control (n=518). De Waele *et al.* emphasized that this statement could also be transferred to critically ill patients (APACHE II > 10) if source control was adequate.

Figure 2 reports a schematic overview of the antimicrobial therapy for patients with secondary peritonitis.

Besides antibiotic treatment especially patients with ongoing/tertiary peritonitis often require antimycotic therapy. Fungal isolates are known negative predictors for prolonged ongoing peritonitis. In contrast to patients with candidiasis on normal wards, Bassetti *et al.* were able to show that mortality goes up to 50% in cases of candidiasis in the ICU.

The European Society for clinical microbiology and Infectious Diseases (ESCMID) recommends echinocandins as the first-choice medication for intensive care patients with *Candida* infection. In cases of *Candida parapsilosis* fluconazole could be a rational alternative.

Once initiated antimycotic therapy should be applied up to 14 days after negative culture results.

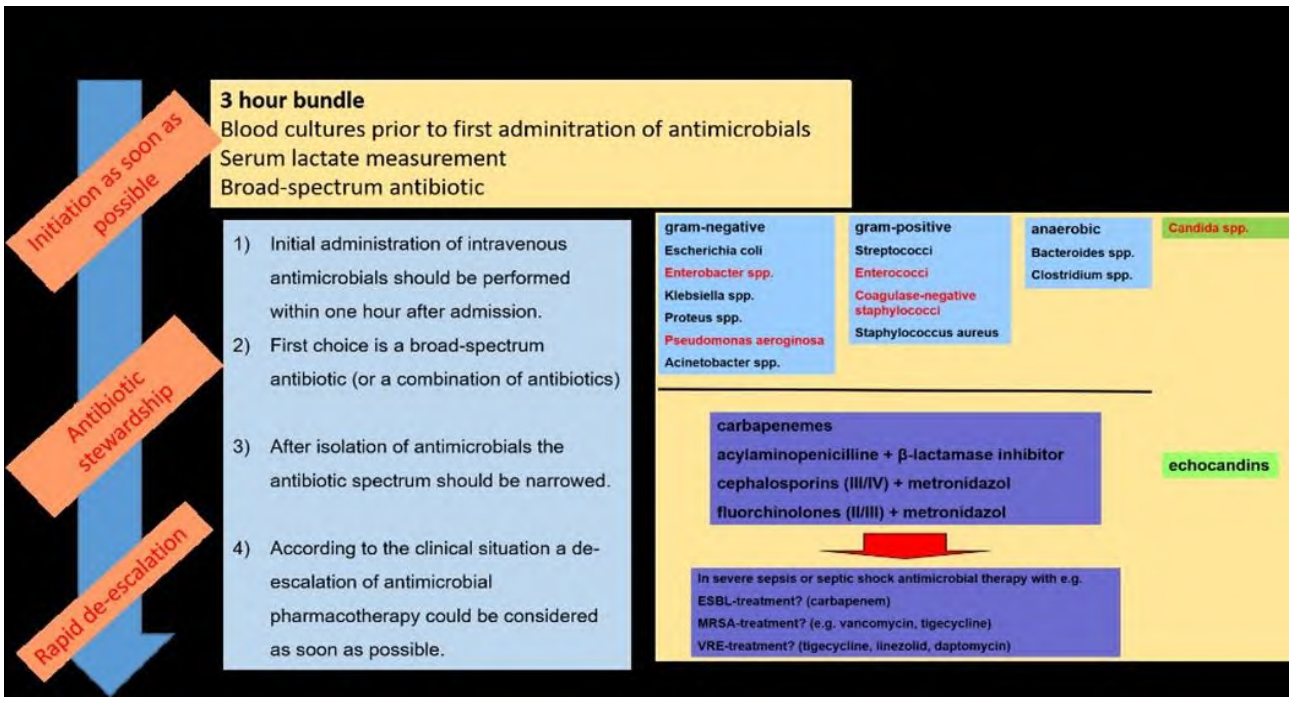

Figure 2. Schematic overview of the antimicrobial therapy for patients with secondary peritonitis.

Conclusion

Therapy of intra-abdominal infections is based on three columns surgery, intensive care medicine, and antimicrobial therapy.
Surgery is able to cure patients from these life-threatening infections by debridement, drainage, and abdominal decompression. In its purity damage control surgery is performed in critically ill patients.
Patients suffering from (secondary or tertiary) peritonitis require an everyday (re-)evaluation from an interdisciplinary team!

Competing interests

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

References

1. De Waele, J.J., Abdominal Sepsis. Curr Infect Dis Rep, 2016. 18(8): p. 23.
2. Hecker, A., et al., Intra-abdominal sepsis: new definitions and current clinical standards. Langenbecks Arch Surg, 2019. 404(3): p. 257-271.
3. Sartelli, M., et al., The role of the open abdomen procedure in managing severe abdominal sepsis: WSES position paper. World J Emerg Surg, 2015. 10: p. 35.
4. Calandra, T., J. Cohen, and I.C.U.C.C. International Sepsis Forum Definition of Infection in the, The international sepsis forum consensus conference on definitions of infection in the intensive care unit. Crit Care Med, 2005. 33(7): p. 1538-48.

5. Poeze, M., et al., An international sepsis survey: a study of doctors' knowledge and perception about sepsis. Crit Care, 2004. 8(6): p. R409-13.
6. Rubulotta, F.M., et al., An international survey: Public awareness and perception of sepsis. Crit Care Med, 2009. 37(1): p. 167-70.
7. Moore, L.J. and F.A. Moore, Early diagnosis and evidence-based care of surgical sepsis. J Intensive Care Med, 2013. 28(2): p. 107-17.
8. Seiler, C.A., et al., Conservative surgical treatment of diffuse peritonitis. Surgery, 2000. 127(2): p. 178-84.
9. Reitz, K.M., et al., Association Between Time to Source Control in Sepsis and 90-Day Mortality. JAMA Surg, 2022. 157(9): p. 817-826.
10. van Ruler, O., et al., Comparison of on-demand vs planned relaparotomy strategy in patients with severe peritonitis: a randomized trial. JAMA, 2007. 298(8): p. 865-72.
11. van Ruler, O., et al., Variables associated with positive findings at relaparotomy in patients with secondary peritonitis. Crit Care Med, 2007. 35(2): p. 468-76.
12. Koperna, T. and F. Schulz, Relaparotomy in peritonitis: prognosis and treatment of patients with persisting intra-abdominal infection. World J Surg, 2000. 24(1): p. 32-7.
13. Vincent, J.L., Give your patient a fast hug (at least) once a day. Crit Care Med, 2005. 33(6): p. 1225-9.
14. Bloos, F., et al., Effect of a multifaceted educational intervention for anti-infectious measures on sepsis mortality: a cluster randomized trial. Intensive Care Med, 2017. 43(11): p. 1602-1612.
15. Sartelli, M., et al., Antimicrobials: a global alliance for optimizing their rational use in intra-abdominal infections (AGORA). World J Emerg Surg, 2016. 11: p. 33.
16. Sawyer, R.G., et al., Trial of short-course antimicrobial therapy for intra-abdominal infection. N Engl J Med, 2015. 372(21): p. 1996-2005.

Chapter 126

Infection or dysbiosis: are uncomplicated abdominal “infections” truly infectious diseases?

Philip S. Barie
Departments of Surgery and Medicine, Weill Cornell Medicine, New York, NY, USA.

Lillian S. Kao
Department of Surgery, UTHealth Houston John P. and Kathrine G. McGovern Medical School, Houston, TX, USA.

Robert G. Sawyer
Department of Surgery, Western Michigan University Homer Stryker M.D. School of Medicine, Kalamazoo, MI, USA.

Introduction

Uncomplicated acute appendicitis (uAA), acute calculous cholecystitis (uACC), and mild acute diverticulitis (umAD) are sometimes treated with antibiotics alone, or source control surgery with short-course antimicrobial therapy for the former two entities. Hypotheses have emerged that such “infections” might be treatable successfully with neither. In order to obtain proof, numerous obstacles to required randomized, controlled trials (RCTs) must be overcome, including unwillingness of patients to be randomized, lack of equipoise regarding preferences for treatment, and biased presentation of treatment options. Diagnosis of diseases under study must be accurate, to avoid inadvertent underpowering by enrollment of ineligible subjects.

Distinguishing inflammation from infection has challenged medical practitioners for more than 150 years. History and physical examination are neither sensitive nor specific. Fever, a salutary host response, is unreliable as it is a marker of both inflammation and infection. Systemic inflammatory response syndrome (SIRS) criteria, (fever or hypothermia, tachycardia, tachypnea or hypocapnia, and leukocytosis or leukopenia) lack diagnostic accuracy but do portend prognosis. Biomarkers such as C-reactive protein and procalcitonin have provided only modest diagnostic improvement.

Imaging of the acute abdomen is ubiquitous, with better diagnostic performance than routine laboratory testing, but is not infallible, even for computed tomography (CT) Difficulty in distinguishing between infection and sterile inflammation using radionuclide pharmaceuticals (nuclear medicine) has led to the development of investigational ^{67}Ga- or ^{99}mTc-labeled antimicrobial agents and peptides. Ensembles of diagnostic tests have been incorporated into various scoring systems and the application of artificial intelligence to clinical diagnostics. The ability to exclude an infectious source, and to withhold antibiotic therapy, is consistent with principles of antimicrobial stewardship, which is increasingly a point of emphasis in surgical practice.

Is uncomplicated acute appendicitis an infectious disease?

Data are scant regarding whether uAA can be treated without antibiotics or surgery. Only recently has the possibility of non-operative management (NOM) of uAA (without surgery) been considered rigorously. It was 1901 when NOM of complicated appendicitis was first broached. Operative mortality was then approximately 15% (**Figure 1**).

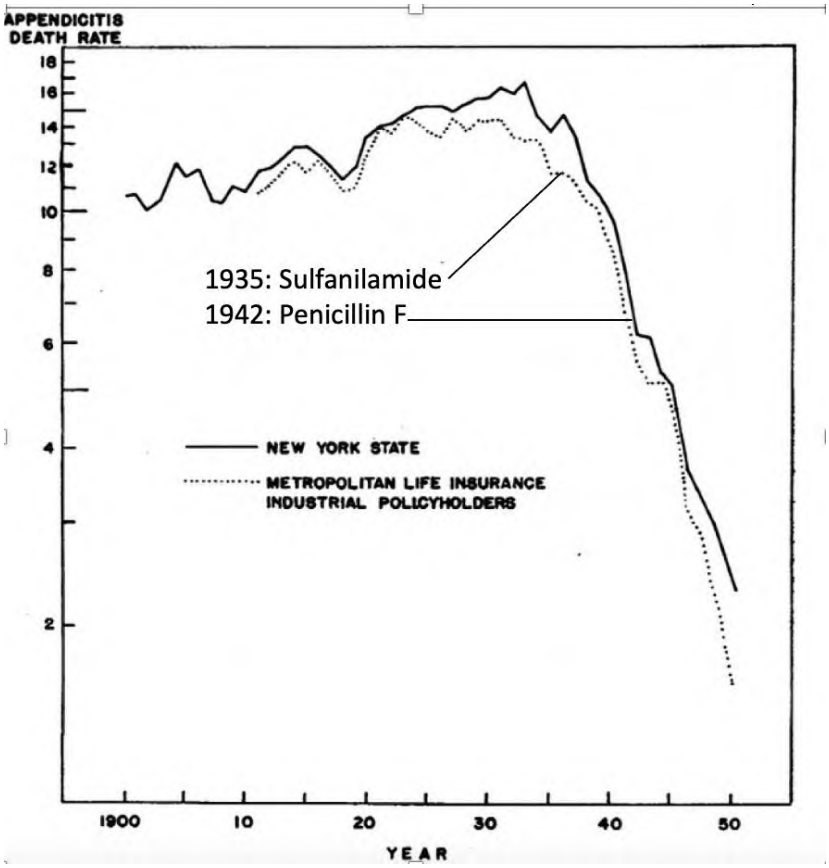

Figure 1. Actuarial data published in 1952 of appendicitis mortality 1900-1950, with clinical introductions of sulfanilamide and penicillin F superimposed. The association of antibiotic treatment with appendicitis mortality is apparent (Adapted from Lembcke PA, 1952).

Not operating on severe cases with poor surgical outcomes resulted in an 80% decrease of operative mortality. The introductions of sulfanilamide in 1935, and D-tubocurarine and penicillin F in 1942, reduced mortality of complicated appendicitis to about 2% (**Figure 1**). The first large series of appendicitis cases, including patients with uAA, treated by NOM with antibiotic therapy was reported in 1956 by Coldrey, who advocated for most cases to be treated by NOM.

The description of laparoscopic appendectomy in 1980 and the description of CT to facilitate accurate diagnosis in 1998 heralded the modern era of appendicitis care. Higher diagnostic confidence of uAA, imparted in particular by contrast-enhanced CT, led to numerous trials and meta-analyses which argue that NOM of appendicitis is non-inferior to laparoscopic appendectomy in the short term (up to 30 d), although ineligible subgroups (e.g., pregnancy, presence of an appendicolith) have been identified, and the 1-year failure rate (meaning appendectomy is required eventually) is ~30%.

The classical theory that AA progresses over time from uAA to complicated disease has been espoused for more than a century, but an alternative hypothesis has emerged that phlegmonous and gangrenous appendicitis are distinct entities, supported by differences in gene expression. The hypothesis that uAA and gangrenous AA are distinct is supported further by the observation that the appendiceal microbiome differs among uAA patients undergoing NOM and those with uAA or complicated appendicitis undergoing appendectomy. uAA may also undergo spontaneous resolution, first observed more than a century ago. The prevalence of spontaneous resolution has been estimated to be 8%-13% based on ultrasound evaluation.

Two small trials have examined whether uAA can be managed with observation and supportive therapy alone (i.e., no antibiotics.) Park *et al.* conducted a prospective, radiologist-blinded, placebo-controlled, RCT of 245 patients with CT-confirmed uAA. Subjects were excluded with appendiceal diameter >11 mm, appendicolith, extraluminal gas, intraperitoneal fluid, abscess, or phlegmon. Patients were randomized to supportive care (i.e., fluid, analgesia, antipyresis) and a 4-d course of cefmetazole plus metronidazole or placebo drug. The median follow-up was 19 months. The primary endpoint was defined as initial treatment failure within 1 month and recurrent appendicitis during a median 19 months follow-up. There was no difference in failure rate (23% *vs.* 21%, p=0.61).

The APPendicitis Acuta III (APPAC III) trial is a placebo-controlled, double-blind, multicenter RCT of adults aged 18-60 years with low-dose CT-confirmed uAA. Hypotheses were two: Antibiotic therapy is NECESSARY for the treatment of uAA, and antibiotic therapy is SUPERIOR to supportive care without antibiotics when the primary endpoint is evaluated at 10 days post-intervention. Exclusion criteria included: Age outside of the range, allergy to antibiotic or contrast medium, chronic kidney disease, diabetes mellitus type 2 treated with metformin, pregnancy/lactation, “severe systemic illness,” and abscess, appendicolith, perforation, or tumor by CT. *Versus* placebo, the APPAC III antibiotic regimen consisted of ertapenem 1 g IV x 3 d in-hospital, followed by levofloxacin 500 mg PO qd and metronidazole 500 mg PO qd for 4 days. The primary endpoint was resolution resulting in hospital discharge within 10 days of study initiation. A 94% success rate was assumed for the antibiotic group. A difference of 15 percentage points was considered “clinically important.” The sample size calculation (power of 0.8, one-sided alpha of 0.05, 10% dropout rate) was 142 patients (71 per group). Only 66 evaluable patients were enrolled despite the 3,783 patients screened, which would have provided adequate statistical power only if the difference between groups was 25 percentage points. The 10-day treatment success rate for antibiotics was 97% (95% confidence interval [CI] 92%-100%) and 87% (95% CI, 75%-99%) for placebo, but the study was underpowered. In summary, data are insufficient to determine the safety and efficacy of non-antibiotic therapy of uAA.

Is uncomplicated acute cholecystitis an infectious disease?

Acute calculous cholecystitis (ACC) ranges in presentation across a spectrum of severity. Although there are several grading systems to describe cholecystitis severity, the Tokyo Guidelines 2018 (TG18) is the only one to include physiologic parameters. According to TG18, severity ranges from Grade I (mild-no evidence of marked local or systemic inflammation) to Grade III (severe-dysfunction of at least one organ system.) Grade I is considered uncomplicated (uACC). In considering whether or not uACC is an infectious disease, two questions should be considered: Do bacteria have a role in pathophysiology? What is the impact of antibiotic use on clinical outcomes?

Regarding pathogenesis, acute cystic duct obstruction occurs initially, leading to gallbladder wall inflammation and edema. Over time, the gallbladder can become hemorrhagic and ischemic and may progress subsequently to gangrene or perforation. Infection is considered a secondary phenomenon. Do bacteria play a role

in uACC, and does failure to treat bactibilia have any clinical consequences? TG18 recommends bile or blood cultures only for patients with Grades II-III cholecystitis, but not uACC. Recent studies reporting culture results in patients with varying grades of acute cholecystitis found bactibilia in 35%-65% of bile cultures, compared with 8%-16% of positive blood cultures. However, the clinical relevance of bactibilia is uncertain.

Although early laparoscopic cholecystectomy is the standard of care for ACC, the World Society of Emergency Surgery (WSES) guidelines state that NOM includes fluids, analgesia, and antibiotics, and recommend antibiotics for patients who are refusing or are not candidates for surgery. However, the evidence quality is low. Mazeh *et al.* compared intravenous amoxicillin-clavulanic acid or ciprofloxacin plus metronidazole to best supportive care in an RCT of 215 patients with uACC, followed by delayed laparoscopic cholecystectomy. All patients were scheduled for surgery, but more patients underwent cholecystectomy (86% *vs*. 62%, *p*=0.02) or percutaneous cholecystostomy (PC, 12% *vs.* 5%, *p*=0.43) after antibiotics. Of note, among the patients who underwent surgery, only 18% had a positive bile culture (*p*=0.50). Thus, contrary to guidelines, the trial does not support antibiotic use in NOM of uACC.

Antibiotic prophylaxis is recommended by the Surgical Infection Society (SIS) for patients undergoing laparoscopic cholecystectomy for acute cholecystitis. Antibiotic prophylaxis is effective in reducing surgical site infections (SSIs) after clean-contaminated (Class II) procedures (e.g., laparoscopic appendectomy or cholecystectomy for uAA or uACC, respectively); the relative risk is consistent across degrees of contamination, implying that the absolute risk reduction with antibiotic prophylaxis increases with the per-procedure baseline risk of SSI.

Disease-specific data have become available. The Perioperative Antibiotic Prophylaxis in the Treatment of Acute Cholecystitis (PEANUTS)-II trial was a multicenter, non-inferiority RCT that randomized patients requiring immediate cholecystectomy for mild-moderate ACC to preoperative cefazolin or no antibiotic. The 30-day infection rates (12.6% *vs.* 7.1%) were not different (absolute difference 5.5%, 95% CI -0.4% to 11.3%). In post-hoc subgroup analyses, there were no differences in treatment effect based either on severity or bile culture results. Based on the trial, antibiotic is indicated for incisional prophylaxis, but not therapeutically prior to laparoscopic cholecystectomy.

There is no role for postoperative antibiotics in patients with uACC after cholecystectomy. Hajibandeh *et al.* performed a systematic review and meta-analysis of "extended postoperative antibiotics" *versus* no postoperative antibiotics in patients undergoing emergency cholecystectomy for ACC. Extended postoperative antibiotics were defined as >3 doses of antibiotic (any type or dose) after emergency cholecystectomy. Based on four RCTs (953 patients,) there were no differences in any infectious or non-infectious complications. In particular, the extended postoperative antibiotic was not associated with decreased odds of SSI (OR 1.13, 95% CI 0.58-2.18) or infectious complications overall (OR 0.94, 95% CI 0.62-1.44). In accord, the SIS guidelines recommend against the use of postoperative antibiotic agents in patients undergoing laparoscopic cholecystectomy for mild-to-moderate acute cholecystitis. This recommendation also holds for patients who undergo conversion from laparoscopic to open cholecystectomy for uACC, even for inadvertent bile spillage.

Does antibiotic use augment the effectiveness of PC? Data are scant. In general, patients with uACC are not treated by PC. However, retrospective data suggest that antibiotic plus PC may be associated with greater short- and long-term treatment success when compared to antibiotic alone for patients with mild-to-moderate ACC not undergoing surgery. Because PC is used primarily in high-risk patients, there are no relevant RCTs of antibiotics *vs.* no antibiotics.

No RCTs compare antibiotics to no antibiotics for uACC treated solely by NOM. A challenge to conducting such a trial is that biliary colic is often difficult to distinguish from uACC, and there may be differences in the degree of inflammation and in the prevalence of bactibilia based on clinical diagnosis alone. Enrollment of

patients with biliary colic but not acute inflammation would increase the sample size requirement of such a trial (given an expected bias towards the null hypothesis.)
In summary, based on pathophysiology, uACC is not primarily an infectious disease. Even with bactibilia, there is no high-quality evidence to suggest that mild disease should be treated with antibiotics. A single dose of preoperative prophylaxis is indicated in uACC patients undergoing cholecystectomy, although the absolute risk reduction in 30-day infectious complications is modest.

Is uncomplicated mild acute diverticulitis an infectious disease?

Diverticulitis coli traditionally has been believed to be an infectious disease that requires treatment with antibiotics in all its manifestations. However, given the recent understanding that alterations of the microbiome may cause inflammation that may not benefit from antibiotic treatment, researchers have questioned whether less-severe forms of diverticulitis should be considered inflammation (i.e., caused by host responses) rather than infectious diseases (e.g., caused by bacterial pathogens). Currently, many episodes of diverticulitis are managed with antibiotics in the United States, but in Europe, there has been a recent move away from the use of antibiotics for milder forms of diverticulitis.
The Canadian surgeon E. John Hinchey first classified diverticulitis in 1978 (**Table 1**). Hinchey Type 1 diverticulitis included small, localized infections. Type 2 included larger abscesses that required local debridement and wide drainage. Type 3 included diverticulitis that was severe enough to have a non-localized infection (macroscopic pus throughout the abdomen, not just limited to the pelvis). Type 4 diverticulitis included feculent peritonitis (frank stool throughout the abdomen). The development of this classification coincided temporally with the introduction of abdominal CT. Over time, Hinchey Type 1 disease has been separated into two categories. Class 1a includes inflammation or a phlegmon of the colon alone, limited largely to the wall but with some extra-colonic extension, including localized extraluminal air but no fluid collections. Class 1b includes smaller abscesses that can be localized by CT.
Further modification of this system was proposed by the WSES (**Table 1**). Stage 0, uncomplicated diverticulitis, includes inflamed diverticula alone with thickening of the colon wall or increased density of peri-colonic fat with no extraluminal extension. Stage 1a diverticulitis includes peri-colic air bubbles or a small amount of fluid within five centimeters of the bowel, without clear abscess formation. Stage 1b disease includes abscesses < 4 cm.
The AVOD (Antibiotika Vid Okomplicerad Divertikulit [Swedish for 'antibiotics in uncomplicated diverticulitis']) RCT was published in 2012. 623 adult patients were randomized with abdominal pain and tenderness, an elevated white blood cell count or C-reactive protein, and a CT diagnosis of mild diverticulitis to intravenous antibiotics (with potential switch to oral agents) for at least 7 days or no antibiotics. There were no differences in outcomes of pain, fever, or tenderness score after antibiotics or not. Complications (including subsequent sigmoid perforation or abscess) were also similar between groups, as was the need for sigmoid resection. Hospital length of stay was 2.9 days in each arm and the rate of recurrent diverticulitis was 16% in each group.
The DIABOLO (DIverticulitis: AntiBiotics Or cLose Observation?) RCT randomized 528 patients with stage 1a or 1b disease to antibiotic (generally amoxicillin-clavulanic acid with potential for oral switch, 10-day minimum) or observation alone. There was no difference in time to recovery. Neither perforation, obstruction, bleeding, or abscess formation, nor the incidences of any intervention differed between groups. The rates of persistent diverticulitis were similar and the rate of recurrent diverticulitis within 6 months was 3% in each group.

Table 1. Original and modified Hinchey classifications (Modified from Fugazzola P, *et al.* 2022).

Stage	Original Hinchey classification	WSES CT-based modification
0	N/A	Diverticula, thickening of the colonic wall or increased density of the pericolonic fat
1a	Pericolic abscess confined to the mesentery of the colon	Pericolic air bubbles or scant pericolic fluid without abscess (within 5 cm from inflamed bowel segment)
1b		Abscess ≤4 cm
2a	Pelvic abscess resulting from local perforation of a pericolic abscess	Abscess >4 cm
2b		Distant air (>5 cm from inflamed bowel segment)
3	Generalized peritonitis resulting from the rupture of either a pericolic or pelvic abscess into the peritoneal cavity	Diffuse fluid without distant free air (no colon perforation)
4	Fecal peritonitis resulting from free perforation of a diverticulum	Diffuse fluid with distant free air (persistent colon perforation)

Abbreviations. CT: computed tomography, N/A: Not applicable. WSES, World Society of Emergency Surgery.

The STAND (Selective Treatment with Antibiotics for Non-complicated Diverticulitis) RCT randomized 178 patients with Hinchey 1a disease to placebo or antibiotics (intravenous/oral) for 7 days. Hospital length of stay was similar (~4 days each.) Time to reduction in white blood cell count and pain score were also similar. The rates of 7- and 30-day readmission were likewise similar.

The question of whether patients with Hinchey 1b diverticulitis behave differently was addressed by a post-hoc analysis of DIABOLO, which showed no differences in meaningful outcomes between patients receiving antibiotics or not. Of the few patients who ultimately required either emergency surgery or percutaneous drainage, all were in the original DIABOLO antibiotic treatment arm.

Long-term results have also been reported for patients in some of the aforementioned trials. Two-year follow-up of DIABOLO found no differences in the rates of recurrent diverticulitis or elective or emergency colectomy between patients who received antibiotics or observation. Ten-year follow-up of AVOD showed no difference in diverticulitis recurrence or complications or a requirement for either emergency or planned surgery for diverticulitis. These long-term results suggest strongly that for umAD, antibiotics are unnecessary.

Meta-analysis of studies comparing antibiotic use to no antibiotics in the management of mild diverticulitis show no differences in outcomes with the use of antimicrobial agents *vs.* placebo for either umAD (Hinchey 1a) or mild complicated (Hinchey 1b) diverticulitis. Consensus guidelines have adopted these findings as recommendations, including those of the American Society of Colon and Rectal Surgeons (ASCRS) and the American Gastroenterological Association (AGA). Although the data regarding non-antibiotic management of umAD are solid, there are still some limitations. Given the propensity to not enroll patients with severe disease in RCTs, it is possible that patients with limited disease by CT might be excluded for a more "worrisome" clinical picture. Second, studies did not require follow-up imaging, so abdominal pain from a non-diverticular cause may have been superimposed on uninflamed diverticulosis coli.

In summary, umAD, generally Hinchey 1a or 1b in current nomenclature, does not benefit from antimicrobial therapy. The implication is that this disease is not an infection, but localized inflammation. More severe disease does require antibiotics and potentially surgical or other forms of intervention.

Synthesis

The evidence is strongest that umAD is not an infectious disease and can be treated without antibiotics, strong but indirect regarding uACC, and lacking for uAA. There is evidence that the gut microbiome is altered in sepsis. Whether causal or consequential, interactions between the microbiome and the inflammasome have been referred to as a vicious cycle. Although uACC is associated with ischemia and prostanoid-mediated inflammation, and bacterial invasion is a secondary phenomenon, recent metagenomic studies have identified a lush biliary microbiome. Alterations of the gut microbiome have been described in both uAA and umAD. Considering umAD, if one accepts that antibiotic therapy does not alter the outcome, one must consider alternative pathophysiology. Diverticulitis is clearly an inflammatory disease that occurs in the setting of diverticulosis coli. Given the immediate presence of the dense, diverse colonic microbiome, bacteria and other micro-organisms are certainly involved, but most likely not initially in the standard paradigm of disease pathogenesis (infection). Considering that umAD generally resolves on its own without antimicrobial therapy, a plausible hypothesis is that the inflammation is related to a disturbance of the normal colonic microbiome, resulting in dysbiosis, which is defined as an imbalance of micro-organisms present in a person's natural microflora, especially that of the gut, believed to contribute to a range of conditions of ill health.

O'Grady *et al.* demonstrated a loss of diversity and other evidence of dysbiosis in patients with diverticulitis compared with healthy controls. Restoration of a normal microbiome could explain the resolution of umAD without antibiotic therapy. One could therefore posit that prebiotics, probiotics, or synbiotics might be effective as prophylaxis or treatment. However, a systematic review of probiotics in the management of diverticular disease was inconclusive. Ojetti *et al.* randomized patients to probiotic therapy with *Limosilactobacillus reuteri* ATCC PTA 4659 or placebo in the treatment of umAD. Resolution of pain occurred within 7 d in both groups, but the group receiving the probiotic had a greater decrease in C-reactive protein.

Are there valid reasons to continue to use antibiotics in umAD? Conceivably, the progression of Hinchey 1a or 1b diverticulitis to more extensive disease could be prevented with antimicrobial therapy. Frailty and medical comorbidities are also common among diverticulitis patients, and, at least according to the AGA guidelines, should receive antibiotics, as should patients with immunocompromise or signs of sepsis. Public perception continues to always expect antimicrobial treatment for diverticulitis, an attitude that will not change rapidly. As a result, it may be impossible to reassure patients sufficiently that antimicrobial agents are not necessary for umAD. Pre- or probiotic therapy is not recommended for either therapy or prevention.

Competing interests

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

References

1. Huston JM, et al. Antibiotics vs. appendectomy for acute uncomplicated appendicitis in adults: Review of the evidence and future directions. Surg Infect (Larchmt). 2017;18:527-535.
2. The CODA Collaborative. A randomized trial comparing antibiotics with appendectomy for appendicitis. N Engl J Med. 2020;383:1907–1919.
3. Hedrick TL, et al. Can we define the ideal duration of antibiotic therapy? Surg Infect (Larchmt). 2006;7:419-432.

4. Sawyer RG, et al. Trial of short-course antimicrobial therapy for intraabdominal infection. N Engl J Med. 2015;372:1996-2005.
5. Barie PS, et al. Infection or inflammation: Are uncomplicated acute appendicitis, acute cholecystitis, and acute diverticulitis infectious diseases? Surg Infect (Larchmt). 2023;24:99-111.
6. Young P, et al. Acetaminophen for fever in critically ill patients with suspected infection. N Engl J Med. 2015;373: 2215-2224.
7. Barie PS, et al. Causes and consequences of fever complicating critical surgical illness. Surg Infect (Larchmt). 2004;5:145-159.
8. Talmor M, et al. Relationship of systemic inflammatory response syndrome to organ dysfunction, length of stay, and mortality in critical surgical illness: Effect of intensive care unit resuscitation. Arch Surg. 1999;134:81-87.
9. Wray CJ, et al. Acute appendicitis: Controversies in diagnosis and management. Curr Probl Surg. 2013;50:54-86.
10. Jeger V, et al. Is there a role for procalcitonin in differentiating uncomplicated and complicated diverticulitis in order to reduce antibiotic therapy? A prospective diagnostic cohort study. Swiss Med Wkly. 2017;147:w14555.
11. Wagner PL, et al. Defining the current negative appendectomy rate: For whom is preoperative computed tomography making an impact? Surgery. 2008;144:276-282.
12. Fleuren LM, et al. Machine learning for the prediction of sepsis: A systematic review and meta-analysis of diagnostic test accuracy. Intensive Care Med. 2020;46:383-400.
13. Delaplain PT, et al.; Scientific Studies Committee of the Surgical Infection Society. Different surgeon, different duration: Lack of consensus on the appropriate duration of antimicrobial prophylaxis and therapy in surgical practice. Surg Infect (Larchmt). 2022;23:232-247.
14. Leeds IL, et al. Treating wisely: The surgeon's role in antibiotic stewardship. Ann Surg. 2017;265:871-873.
15. Sartelli M, et al. Antimicrobial stewardship: A call to action for surgeons. Surg Infect (Larchmt). 2016;17:625-631
16. Barie PS. Non-operative management of appendicitis: Evolution, not revolution. Surg Infect (Larchmt). 2021;22:991-1003.
17. Park HC, et al. Randomized clinical trial of antibiotic therapy for uncomplicated appendicitis. Br J Surg. 2017;104:1785-1790.
18. Salminen P, et al. Antibiotics versus placebo in adults with CT-confirmed uncomplicated acute appendicitis (APPAC III): randomized double-blind superiority trial. Br J Surg. 2022;109:503-509.
19. Colling KP, et al. Surgical Infection Society guidelines for antibiotic use in patients undergoing cholecystectomy for gallbladder disease. Surg Infect (Larchmt). 2022;23:339-350.
20. Fugazzola P, et al. The WSES/SICG/ACOI/SICUT/AcEMC/SIFIPAC guidelines for diagnosis and treatment of acute left colonic diverticulitis in the elderly. World J Emerg Surg. 2022;17:5.
21. Chabok A, et al. Randomized clinical trial of antibiotics in acute uncomplicated diverticulitis. Br J Surg. 2012;99:532-539.
22. Daniels L, et al. Randomized clinical trial of observational versus antibiotic treatment for a first episode of CT-proven uncomplicated acute diverticulitis. Br J Surg. 2017;104:52-61.
23. Jaung R, et al. Antibiotics do not reduce length of hospital stay for uncomplicated diverticulitis in a pragmatic double-blind randomized trial. Clin Gastroenterol Hepatol. 2021;19:503-510.
24. Bolkenstein HE, et al. Conservative treatment in diverticulitis patients with pericolic extraluminal air and the role of antibiotic treatment. J Gastrointest Surg. 2019;23:2269-2276.
25. van Dijk ST, et al. Long-term effects of omitting antibiotics in uncomplicated acute diverticulitis. Am J Gastroenterol. 2018;113:1045-1152.
26. Isacson D, et al. Long-term follow-up of the AVOD randomized trial of antibiotic avoidance in uncomplicated diverticulitis. Br J Surg. 2019;106:1542-1548.
27. van Dijk ST, et al. Observational versus antibiotic treatment for uncomplicated diverticulitis: An individual-patient data meta-analysis. Br J Surg. 2020;107:1062-1069.
28. Hall J, et al. The American Society of Colon and Rectal Surgeons clinical practice guidelines for the treatment of left-sided colonic diverticulitis. Dis Colon Rectum. 2020;63:728-747.

29. Peery AF, et al. AGA clinical practice update on medical management of colonic diverticulitis: Expert review. Gastroenterology. 2021;160:906-911 e1.
30. Lembcke PA. Measuring the quality of medical care through vital statistics based on hospital service areas: 1. Comparative study of appendectomy rates. Am J Public Health. 1952;42:276–286.

Chapter 127

Prognostic scores for intra-abdominal infections. Can they be used in clinical practice?

Vladimir Khokha
General Surgery Unit, Podhalanski Specialized Hospital, Nowy Targ, Poland.

Denis Khokha
Scientific Research Center of Surgery, Transplantology and Hematology, Minsk, Belarus.

Introduction

The surgeons' desire to have a universal scale that can objectively assess the severity of the patient's condition, reliably determine the possible extent of surgery and predict the outcome of the disease is certainly understandable. There is a large number of long-standing, already classical and new scales. Some of them are easy to apply, do not require complex laboratory analyses, and are readily applicable both in developed well-equipped centers and in resource-limited settings. Scales with high accuracy and specificity are usually quite cumbersome and require laboratory test results, and life support device readings, difficult or not feasible in resource-limited hospitals. There are online calculators and phone apps. However, their accuracy and specificity also vary greatly, and it is highest when it comes to monopathology. If it is necessary to apply the scale to a wide range of pathologies, like intra-abdominal infections (IAIs), its effectiveness is significantly lower.

IAIs are a pathology with a high morbidity and mortality rate. When compared to other diseases, IAIs are more frequently associated with septic shock and acute kidney injury.

Patients with IAIs are generally classified into low or high risk. High risk means patients with a high risk for treatment failure and mortality. Early prognostic evaluation of the patient’s risk is the cornerstone for optimization of the diagnostic and treatment plan because increased mortality associated with inappropriate management cannot be reversed by subsequent modifications.

Prognostic scores for intra-abdominal infections

Scoring systems can be roughly divided into two groups: disease-independent scores for evaluation of serious patients requiring care in the intensive care unit (ICU) such as APACHE II and Simplified Acute Physiology Score (SAPS II) and peritonitis-specific scores such as Mannheim Peritonitis Index (MPI).

Although considered a good marker, APACHE II value in peritonitis has been questioned because of the difficulty of evaluating interventions, which might significantly alter many of the physiological variables.

Moreover, it requires appropriate software to be calculated. Pacelli F. *et al.* retrospectively reviewed records of 604 patients who consecutively underwent emergency operations for unequivocal IAIs. Results showed a significant dominance of host-related factors over the type and source of infection on the prognosis of patients with IAIs.

Age, nutritional status, chronic disease, sepsis, organ failure, surgery and antibiotic therapy play an important role in the timely assessment of disease severity and determining prognosis. At the same time, the trial eligibility criteria usually restrict the inclusion of patients with co-morbid diseases that would decrease the death rate of patients with intra-abdominal infections. Furthermore, the development of minimally invasive surgical interventions, the introduction of drainage techniques and adjustments in sepsis target therapy and antibiotic therapy strategies, bring changes in long-existing prognostic scales.

The most often used but none specified for IAIs prognostic scales listed below.

ASA-PS (American Society of Anesthesiologists Physical Status Classification) - a predictor of perioperative mortality and is applicable for use in early inpatient evaluation, has been in use for over 60 years. The purpose of the system is to assess and communicate a patient's pre-anesthesia medical co-morbidities. The classification system alone does not predict the perioperative risks, but when used with other factors (e.g., type of surgery, frailty, level of deconditioning), it can help predict perioperative risks.

ACS-NSQIP (American College of Surgeons Universal Surgical Risk Calculator) is based on preoperative data to predict mortality after different types of operations and can be used in early phases of care. Its calculation requires access to an internet-based portal, which may limit its use in certain environments. ACS-NSQIP calculator requires a specific code for each operation and is not applicable to non-operative patients.

CCI (The Charlson Comorbidity Index) was later modified by Charlson by adding age to the comorbidity index into the Charlson Age-Comorbidity Index (CACI). The CACI combines 19 medical conditions weighted 1–6, with age weighted 1 for every decade past 40 years. The limitation to the use of these scores is cumbersome and time-consuming calculation.

ESAS (The Emergency Surgery Acuity Score) is a preoperative risk stratification system that predicts perioperative mortality in emergency surgery patients. It captures both patient comorbidities and the acute physiology at presentation and includes 3 demographic variables, 10 comorbidities and 9 laboratory variables ESAS was validated using only operative patients.

PMRS (The Perioperative Mortality Risk Score) is based on readily available preoperative and postoperative data; hence, half of these factors cannot be evaluated in the preoperative period. It was derived from a study of surgical patients aged 70 years or older and is not generalizable across the entirety of the surgical population.

POSSUM (The Physiological and Operative Severity Score for the Enumeration of Mortality and Morbidity) is a 12-factor, four-grade, physiological score (ranging from 12 through 88) plus a 6-factor operative severity score (ranging from 6 through 44). P-POSSUM, the refinement of the original scoring system, collects the same 18 physiological and operative parameters; a different calculation formula is employed to determine predicted mortality. POSSUM score overestimates of mortality rates for low-risk procedures; it cannot be used for non-operative cases, as it is based partially on operative data.

SAS (The Surgical Apgar Score) is a 14-point score based on the intraoperative measurements of the heart rate, mean arterial pressure and estimated blood loss and therefore cannot be used in the preoperative setting.

SORT (The Surgical Outcome Risk Tool) is a preoperative risk prediction tool for death within 30 days of surgery in adults, estimating the general risks of the procedure and some information about the patient. It has not been studied in the emergency surgical patient population. In 2020 a new large-scale SORT model, which demonstrates good accuracy in neurological/spinal and cardiothoracic surgery was published.

ALaRMS (The Acute Laboratory Risk of Mortality Score) developed using numeric laboratory data and administrative data from hospital electronic health record systems of 1,428,824 adult discharges from 70 hospitals, demonstrated excellent predictive ability in high-volume admissions, in both medical and surgical patient populations.

The systematic review by Toloui A. *et al.* summarized the literature regarding the prognostic accuracy of the emergency surgery score (ESS). ESS performed excellently in 30-day post-op mortality (AUC 0.84–0.89), and incidence of cardiac arrest (AUC 0.86–0.88), for the prediction of 30-day sepsis/septic shock in emergency general surgeries (AUC 0.75–0.92). Despite the acceptable prognostic accuracy of ESS in 30-day mortality, morbidities, and in-hospital ICU admission in different emergency surgeries, the high number of required variables and the high probability of missing data highlight the need for modifications to this scoring system.

Prognostic scales specified for IAIs.

Sepsis is now defined as “life-threatening organ dysfunction caused by a dysregulated host response to infection”. According to Sepsis III definition, organ dysfunction is measured by the Sequential Organ Failure Assessment (SOFA) score and is deemed “life-threatening” if the score is increased by ≥2 points. Abdominal sepsis is now defined as an increase of the SOFA score of ≥ 2 points due to intra-abdominal infection.

The qSOFA and procalcitonin at presentation to the emergency department in septic patients have a significant correlation with mortality in patients hospitalized with sepsis. Lactate added to SIRS and qSOFA score improves the accuracy of SIRS and qSOFA to predict short-term mortality in older non-severely dependent patients attended for infection. There is no effect in adding the Charlson index.

The PIPAS severity score tool has a superior predictive ability and higher sensitivity for peritonitis in-hospital mortality than the qSOFA score tool although the latter tool is more specific. A prospective cohort study on 136 consecutive peritonitis cases managed surgically in a tertiary hospital. The PIPAS severity score had a significantly better discriminative ability (AUC = 0.893, 95% CI 0.801-0.986) than the qSOFA score (AUC = 0.770, 95% CI 0.620-0.920) for peritonitis mortality (p=0.0443). The best PIPAS severity cut-off score (a score of ≥2) had sensitivity and specificity of 76.5%, and 93.3% respectively, while the corresponding values for the qSOFA criteria (score ≥2), were 58.8% and 98.3% respectively. The PIPAS severity score is recommended as the initial prognostic tool for peritonitis cases in the emergency department.

The MPI is specific for peritonitis and easy to calculate, designed by Wacha and Linder in 1983. The prospective cohort study by Neri A. *et al.* included 143 consecutive patients operated on for perforative peritonitis. The study aimed to assess the prognostic efficacy of the Mannheim Peritonitis Index (MPI) in a population with a significant proportion of older patients and to substantiate advanced age as an independent prognostic factor. In the subgroup of patients with MPI score≥21, the mortality rate was 46.4% for patients older than 80 years old and 38.3% for younger patients (p=0.07); in patients with MPI score<21, the mortality of those aged more than 80 years reached 33.3% compared to 3.4% for younger patients (p=0.001). The authors concluded that the age older than 80 years is strongly related to a major increase in mortality rates.

One thousand and twenty-four patients older than 65 years who required urgent surgical procedures were prospectively recruited from 38 Italian centers participating in the multicentric FRAILESEL (Frailty and Emergency Surgery in the Elderly) study, between December 2016 and May 2017. A univariate analysis was carried out, with the purpose of developing a frailty index in emergency surgery called "EmSFI" and Receiver operating characteristic curve analysis was then performed to test the accuracy of the predictive score. The validated EmSFI represents a reliable and time-sparing tool, despite its discriminative value decreased regarding complications.

Fusario D. *et al.* conducted an observational study on 61 patients to validate the Emergency Surgery Frailty Index (EmSFI), in over 65 years old patients operated on for acute appendicitis. The complication rate was higher in oldest elderly patients over 80 years-(42.9 *vs.* 22.5%; p=0.05) and was mainly related to medical

complications (42.9 *vs.* 12.5%, *p*=0.007). However, intestinal obstruction, periappendicular abscess on preoperative CT, peritonitis and a longer duration of surgery are related to an increased risk of complications in the group of patients under 80 years.

While general symptoms such as fever (or hypothermia), tachycardia, and tachypnea reflect the SIRS (systemic inflammatory response syndrome) criteria, additional signs such as altered mental status, oliguria, change in the skin with elongated capillary refill time, elevated liver enzymes, pathologic coagulation, etc., should be recognized on everyday rounds but especially should lead to further diagnostics.

The World Society of Emergency Surgery (WSES) derived the World Society of Emergency Surgery Sepsis Severity Score (WSESSSS) from data and experience obtained from a global perspective observational study (CIAOW Study) that recruited patients in 132 medical institutions located in 54 countries. Another tool to potentially identify patients with intraabdominal sepsis at a high risk of death is a World Society of Emergency Surgery Sepsis Severity Score of 8 points or more. The most significant variables, adjusted to clinical criteria, were used to create a severity score for patients with complicated intra-abdominal infections (cIAIs) including clinical conditions at admission (severe sepsis/septic shock), the origin of the cIAIs, the delay in source control, the setting of acquisition, and any risk factors such as age and immunosuppression. This predictive system was validated in a different worldwide population, giving great generalizability to the scoring system.

Tolonen M. and colleagues showed that combining the formal SOFA score with the WSESSSS gives a detection rate of sepsis and septic shock of 83.9%. WSESSS is designed to be used early in sepsis and include expanded patient-specific criteria that do not require periods of observation undergoing critical care.

Recently the group, representing the Global Alliance for Infections in Surgery, which includes general and emergency surgeons, intensive care specialists, and specialists in infectious diseases signed the evidence-based position statement, with its main objective being to describe best practices for cIAI management. A typical patient admitted to the emergency department is one with abdominal pain and two or more of fever, tachycardia, tachypnea, and leukocytosis or leukopenia (i.e., SIRS).

Conclusion

Identifying a new clinical score to assess the severity of the cIAIS would be clinically relevant in order to modulate the aggressiveness of treatment according to the type of infection and the clinical characteristics of the patients. However, none of the existing prognostic scores is currently accepted as being ideal for predicting outcomes in complicated IAIs. Based on the currently available data, it can be assumed, that it is possible to increase the accuracy of predicting the severity of the course of IAIs and mortality by combining different prognostic scales. For example, the first screening step can be qSOFA or SOFA. The next step should be a more in-depth assessment of the severity of the patient's condition and prognosis based on more detailed scales such as e.g. WSESSSS. For widespread use of the WSESSSS prognostic scale created a mobile application: https://github.com/DneezK/WSES-Sepsis-Severity-Score.

Competing interests

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

References

1. Sartelli M, et al. The management of intra-abdominal infections from a global perspective: 2017 WSES guidelines for management of intra-abdominal infections. World J Emerg Surg. 2017;12:29.
2. Komatsu S, et al. Prognostic factors and scoring system for survival in colonic perforation. Hepatogastroenterology. 2005;52:761-764.
3. Koperna T, et al. Risk stratification in emergency surgical patients: is the APACHE II score a reliable marker of physiological impairment? Arch Surg. 2001;136:55-59.
4. Pacelli F, et al. Prognosis in intra-abdominal infections. Multivariate analysis on 604 patients. Arch Surg. 1996;131:641-645.
5. Dellinger RP, et al. Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2008. Intens Care Med. 2008;34:17- 60.
6. Sartelli M, et al. Complicated intra-abdominal infections in Europe: a comprehensive review of the CIAO study. World J Emerg Surg. 2012;7:36.
7. Toloui A, et al. Prognostic accuracy of emergency surgery score: a systematic review. Eur J Trauma Emerg Surg. 2024;50:723-739.
8. Singer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315:801-810.
9. Shankar-Hari M, et al. Developing a new definition and assessing new clinical criteria for septic shock. JAMA. 2016;315:775-787.
10. Parrey AH, et al. Procalcitonin and qSOFA as a Marker of Mortality in Sepsis. Rev Recent Clin Trials. 2024 Apr 19.
11. Iranya RN, et al. Comparison of the PIPAS severity score tool and the QSOFA criteria for predicting in-hospital mortality of peritonitis in a tertiary hospital in Uganda: a prospective cohort study. BMC Surg. 2022;22:291.
12. Wacha H, et al. Mannheim peritonitis index – prediction of risk of death from peritonitis: construction of a statistical and validation of an empirically based index. Theor Surg. 1987;1:169-177.
13. Neri A, et al. Re-evaluation of Mannheim prognostic index in perforative peritonitis: prognostic role of advanced age. A prospective cohort study. Int J Surg. 2015;13:54-59.
14. Costa G, et al. The Emergency Surgery Frailty Index (EmSFI): development and internal validation of a novel simple bedside risk score for elderly patients undergoing emergency surgery. Aging Clin Exp Res. 2021;33:2191-2201.
15. Fusario D, et al. The Emergency Surgery Frailty Index (EmSFI) in Elderly Patients with Acute Appendicitis: An External Validation of Prognostic Score. World J Surg. 2023;47:1713-1720.
16. Sartelli M, et al. Complicated intra-abdominal infections in Europe: a comprehensive review of the CIAO study. World J Emerg Surg. 2012;7:36.
17. Sartelli M, et al. Global validation of the WSES Sepsis Severity Score for patients with complicated intra-abdominal infections: a prospective multicentre study (WISS Study). World J Emerg Surg. 2015;10:61.
18. Tolonen M, et al. From the Closed Or Open after Laparotomy (COOL) for Source Control in Severe Complicated Intra-Abdominal Sepsis Investigators. Getting the invite list right: a discussion of sepsis severity scoring systems in severe complicated intra-abdominal sepsis and randomized trial inclusion criteria. World J Emerg Surg. 2018;13:17.
19. Sartelli M, et al. Intra-abdominal infections survival guide: a position statement by the Global Alliance For Infections In Surgery. World J Emerg Surg. 2024;19:22.

Chapter 128

Antimicrobial resistance in intra-abdominal infections

Philippe Montravers
Department of Anaesthesiology and Surgical Intensive Care, DMU PARABOL, APHP, Hôpital Bichat, Paris, France;
UFR Paris Nord, Université Paris Cité, Paris, France;
Université Paris Cité, INSERM UMR 1152 PHERE, Paris, France.

Kevin Boussion
Department of Anaesthesiology and Surgical Intensive Care, DMU PARABOL, APHP, Hôpital Bichat, Paris, France;
UFR Paris Nord, Université Paris Cité, Paris, France.

Gaelle Fouque
Department of Anaesthesiology and Surgical Intensive Care, DMU PARABOL, APHP, Hôpital Bichat, Paris, France;
UFR Paris Nord, Université Paris Cité, Paris, France.

Nathalie Zappella
Department of Anaesthesiology and Surgical Intensive Care, DMU PARABOL, APHP, Hôpital Bichat, Paris, France.

Introduction

Intra-abdominal infections (IAIs) are among the most common types of abdominal emergencies. Antimicrobial resistance (AMR) is a major public health problem in IAIs, leading to the inefficacy of antibiotics against bacteria and infections that become difficult or impossible to treat. The incidence of inappropriate anti-infective treatments increases with resistance rates. AMR can impact various antimicrobial agents. The most threatening condition is multidrug resistance (MDR), which is usually defined as the presence of Gram-negative bacilli (GNB) (*Enterobacterales* and non-fermenting GNB) or Gram-positive cocci (GPC) (enterococci and staphylococci) that are nonsusceptible to at least one agent in three or more antimicrobial categories.
Conventional microbiology techniques identify bacteria and their susceptibility profile in a minimum of 36 to 48 hours, during which time the adequacy of empirical antibiotic therapy can be critical, and partial or total inefficacy can be problematic. In recent decades, an increasing number of observations of multidrug-resistant bacteria (MDRB) have been reported in community-acquired (CA) or hospital-acquired (HA) IAIs. The risk factors for AMR are well known and include previous antimicrobial therapy, diabetes mellitus, severe underlying diseases, and healthcare-associated infections.

This chapter summarizes the recent trends in AMR in CA and HA-IAIs reported in the literature worldwide. The epidemiological data vary greatly from one country to another and over time, especially in low- and middle-income countries. Publications are often more than ten years old, which limits their relevance in the context of rapid changes in resistance patterns. In addition, these analyses are generally restricted to adults. Several websites provide epidemiological information on AMR, but the anatomical origin of the samples and the setting of infection acquisition are often not clearly assessed. The lack of infrastructure and microbiology laboratories explains the fragmentary information in many countries and the limited data focused on HA-IAIs, especially postoperative infections.

Methodology of investigation

To ensure the relevance of information on resistance, we selected manuscripts written in English and published over the last ten years that address the issue of AMR in adult patients. HA-IAIs were defined as infections diagnosed in patients hospitalized >48 hours during the preceding 90 days or acquired in chronic care settings within the previous 30 days, either postoperatively or not. The source (with or without anatomical disruption, localized or diffuse) of the IAI and its location were not detailed. We have indicated the proportions of resistance to the main antibiotics when these data were available, but we have not extensively detailed the mechanisms of resistance, as most manuscripts do not provide this information. We also collected relevant information on the susceptibility profiles of microorganisms isolated from intensive care unit (ICU) patients admitted for both CA and HA-IAIs.

To complete the picture, we collected the results from the Study for Monitoring Antimicrobial Resistance Trends (SMART) database (https://globalsmartsite.com), a worldwide (192 sites in 54 countries in Europe, Africa, Asia, the Middle East, North/Central/South America, and South Pacific) surveillance program of antimicrobial resistance initiated at the turn of the century to monitor the *in vitro* susceptibility of clinical isolates collected from IAIs. Due to the predominance of MDR *Enterobacterales* in the published literature, we have focused this approach on these organisms, without being able to specify the enzymatic mechanisms of resistance. We used the following filters for the database search: data collected between 2020 and 2022; IAIs; geographic region; specific country; all hospital wards except paediatric units; community-acquired/hospital-acquired infection (hospital stay <48/≥48 hours); antibacterial agents (piperacillin-tazobactam (PTZ), ceftriaxone (CRO), ceftazidime-avibactam (CAZ/AVI), ceftolozane-tazobactam (TOL/TAZ), imipenem-cilastatin (IMI), meropenem-vaborbactam (MER/VEB), imipenem-relebactam (IMI/REL), amikacin (AMK), levofloxacin (LEV), colistin (COL)); *Enterobacterales*; and microorganisms resistant to the evaluated drug according to the CLSI-2024 (M100-ED34) criteria.

Expression of antimicrobial resistance and microbiological identification of resistance

Among patients treated for IAIs, aerobic bacteria (GNB and GPC) are the most common microorganisms involved in AMR. *Enterobacterales* (mainly *Escherichia coli*, *Klebsiella* spp., *Enterobacter* spp., etc.) are the most common resistant GNB pathogens. Enzymes inactivating penicillins and cephalosporins (extended-spectrum-beta-lactamase (ESBL) and AmpC-hyperproducing cephalosporinase) are the key mechanisms of multidrug resistance in *Enterobacterales* and usually combine with other mechanisms to inactivate various agents,

including fluoroquinolones or aminoglycosides. More recently, carbapenemase-producing *Enterobacterales* (mainly *Klebsiella pneumoniae*) harbouring enzymes inactivating all betalactams, including carbapenems, have been described. These MDR strains are usually resistant to most antibiotics, including fluoroquinolones and aminoglycosides, whereas colistin remains relatively active and is frequently the last available option. MDR non-fermenting Gram-negative bacilli (*Pseudomonas aeruginosa*, *Acinetobacter baumannii*, etc.) are also known to target beta-lactams through various mechanisms (enzymes, porins, efflux, mutations of targets, etc.) that are usually combined with other mechanisms that inactivate many antibiotic agents, including fluoroquinolones or aminoglycosides. *Acinetobacter* spp. isolates can also be resistant to all antibiotics, except colistin. Gram-positive cocci (GPCs), including enterococci and methicillin-resistant *Staphylococcus aureus* (MRSA), remain a source of concern but at a relatively lower level. Enterococci are frequently resistant to glycopeptides (especially vancomycin), penicillin (through mutations of the protein-binding penicillin) or aminoglycosides, whereas MRSA strains are resistant to most beta-lactams, which usually combine with other mechanisms to inactivate various agents, including fluoroquinolones or aminoglycosides.

Major recent advances in molecular biology have led to the development of rapid diagnostic and identification techniques. Genomic analysis techniques using multiplex polymerase chain reaction (PCR) allow the identification of pathogens and the presence of certain resistance genes within a few hours, enabling antibiotic treatment to be adapted at an early stage. A multiplex PCR rapid diagnostic platform registered for IAI was used to assess the predictive value for identifying the most common germs, including aerobic GNB (*Enterobacterales*, *P. aeruginosa*, *A. baumannii*) and aerobic GPC (streptococci, staphylococci and enterococci). Some antibiotic resistance genes were identified in the same sequence, including those encoding certain ESBLs (CTX-M-type ESBLs) and carbapenemase enzymes. A multicentre study (involving 4 microbiology laboratories) assessed the value of this platform on 300 clinical samples from patients with intra-abdominal infections. The overall sensitivity was 89.3%, the specificity was 99.5%, the positive predictive value was 96%, and the negative predictive value was 98.6%. Compared with conventional microbiology, identification time was reduced by an average of approximately 17 hours and by 41 hours for antibiotic sensitivity profiles. The most frequently detected resistance markers were mecA/mecC (n=25), aacA4 (n=20), and blaCTX-M (n=17), and nine carbapenemase-producing strains were identified.

Community-acquired IAIs

Distribution of resistance in the bowel flora

The incidence of AMR in CA-IAIs is closely linked to the spread of resistance within the population. Reports of the community distribution of resistance in faecal flora would be highly relevant for planning the most adequate empirical drugs for patients with CA-IAI diagnoses. Unfortunately, these analyses are still limited, however the limited results are already a major source of concern. In Ethiopia, 290 stool samples were collected from asymptomatic food handlers at University Cafeteria, with an overall MDR-*Enterobacterales* rate of 42.3%, with 21.7% of the samples positive for ESBL-producing strains and 2.4% of the samples positive for carbapenemase-producing organisms. High resistance rates involving ESBL-producing *Enterobacterales* have also been reported among hospitalized adult patients in another Ethiopian district, illustrating the high relevance of these ecological data. In a study addressing the incidence of ESBL-producing *Enterobacterales* in the bowel flora of 3,600 patients planned for elective colorectal surgery in 3 institutions, the authors reported a prevalence of 12% in Switzerland, 9.4% in Serbia and 28.8% in Israel. The issue of resistance was also

addressed in a French study that showed a non-zero probability of MDRB in IAI isolates in the absence of risk factors for resistance: 21.1% of MDRB in the presence of risk factors and 12.8% without risk factors.

Incidence of MDRB in community-acquired IAIs

In two multicentre CIAO (Europe) and CIAOW (Worldwide) studies that included 1,954 patients who underwent surgery for CA-IAIs (2012-2013) at 136 institutions, 9.2% of isolates were MDRB. The predominant MDRBs were ESBL-producing *Enterobacterales*, which were mainly represented by *E. coli* and *K. pneumoniae* resistant to third-generation cephalosporins (3-GCS) (10.1 and 14.6% of the strains, respectively). The proportion of carbapenem-resistant strains was very low, mainly related to nonfermenting GNB (*P. aeruginosa* and *A. baumannii* for a total of 12 isolates). The authors reported that the risk of isolation of MDRBs, including ESBL-producing strains, was greater in patients from the Eastern Mediterranean and Southeast Asian regions than in patients from other geographic regions. In two subanalyses focusing on community-acquired acute appendicitis and acute cholecystitis, the authors reported 6.8% and 7.8% resistant bacteria in 3.3% and 3.1% of the patients, respectively. A predominance of ESBL-producing *E. coli* was observed, accounting for 77.8% and 64.7% of the MDRB for appendicitis and cholecystitis, respectively.

African region

Studies in West Africa and French-speaking Maghreb countries report a worrying increase in the beta-lactam resistance rate, whereas carbapenem and colistin activity remained stable. More recently, in a single-centre study from Tanzania conducted in 2014-2015, 97 patients with IAIs were analysed, including 56 microbiologically confirmed infections, leading to 60 isolates. The authors reported that 53 *Enterobacterales*, including 25 (47.2%) ESBL producers, were related mainly to *E. coli* (28%), *Klebsiella* spp. (20%) and *Citrobacter* spp. (16%). The 25 ESBL-producing isolates exhibited resistance to penicillin-A (100%), 3-GCS (100%), trimethoprim-sulfamethoxazole (96%), gentamicin (16%), and ciprofloxacin (16.0%), but all the isolates were susceptible to meropenem.

In a multicentric study involving 3 tertiary centres in Egypt, the authors analysed the beta-lactam resistance profile of 181 MDRBs (*E. coli* 45.9%, *Klebsiella pneumoniae* 52.5%) collected from IAIs in 2015-2016. ESBL production was reported in 96.2% of the isolates, which was related mainly to CTX-M-15 and TEM-OSBL, and AmpC resistance genes were noted in 9.7% of the isolates, whereas carbapenemase production was observed in 45.3% of the isolates, with a predominance of OXA-48 (40.6%) and metallo-beta-lactamases (NDM-1 23.7%) for *Klebsiella* spp. and OXA-type (6.0%) and metallo-beta-lactamases (NDM-5 9.6%) for *E. coli*. Overall, the most active drugs against *E. coli* were colistin (100%), AMK (91.6%), ertapenem, and IMI (84.3% and 86.7%, respectively), whereas the most active drugs against *K. pneumoniae* were colistin (93.7%), AMK (76.5%), ertapenem, and IMI (74.5% and 58.2%, respectively).

Latin America region

Authors from Argentina reported that 38% of MDR Gram-negative organisms were collected from CA-IAIs and from patients with appendicitis. They discouraged the use of fluroquinolones and ampicillin/sulbactam, while aminoglycoside-based regimens were preserved. At the time of the studies (2010-2012 and 2014-2015), no resistance to carbapenems was reported. In Peru, Rego *et al.* reported ESBL-producing strains among 43.5% of *E. coli* and 21.2% of *Klebsiella* spp. isolated from IAIs, and high rates of resistance (>50%) against fluoroquinolones were also observed. In Columbia, in a multicentre study analysing samples collected from CA-IAIs in 2012-2014, the authors reported that only 6% of the samples were ESBL-producing *Enterobacterales*. In another multicentre study from Columbia, among surgical samples collected between 2014 and 2018, the authors reported 31% multidrug-resistant *Enterobacterales* (including 5% ESBL-producing strains and 10% carbapenem-resistant strains), 28% multidrug-resistant *P. aeruginosa*, and 31% carbapenem-

resistant *P. aeruginosa*. In this cohort, the authors reported nonsusceptibility to LEV, PTZ, and meropenem in 28%, 24%, and 12% of the *Enterobacterales* isolates and 37%, 36%, and 42% of the *P. aeruginosa* isolates, respectively. Finally, in a multicentre study (2009-2015) from Mexico, 25% of *E. coli* and 15% of *K. pneumoniae* isolates cultured from CA-IAIs were ESBL-producing strains. The authors reported that the susceptibility of *E. coli* and *K. pneumoniae* strains to LEV, PTZ, and IMI was 35%, 86%, and 99%, and 84%, 85%, and 99%, respectively.

Asian region

In a large epidemiological study from 2014-2018, community-acquired samples were collected from Hong Kong, India, Malaysia, the Philippines, Singapore, South Korea, Taiwan, Thailand, and Vietnam. Regional variations were observed as well as changes over time, with a downward susceptibility trend involving fluoroquinolones, 3-GCS, and PTZ. The lowest susceptibility rates were observed for LEV in India (25.9%) and Thailand (34.7%) and for CRO in India (28.7%) and Vietnam (35%). The susceptibility rates of AMK and IMI remained >97% in all the countries except India (91.4% and 87.9%, respectively). In a multicentre study from China (2012-2014), 34.1% of the isolates were ESBL-producing strains, including 54% of the *E. coli* strains and 28.5% of the *K. pneumoniae* strains. The lowest susceptibility rates were reported for CRO (0.75% and 0%), ampicillin-sulbactam (5.7% and 2.5%), and ciprofloxacin (18.4% and 33.3%) for *E. coli* and *K. pneumoniae* ESBL-producing strains, respectively. In contrast, the susceptibility rates remained high for AMK (89.5% and 80.2%) and IMI (96.7% and 80.2%) for ESBL-producing *E. coli* and *K. pneumoniae* strains.

In a single-centre study from Pakistan (2013-2014), the authors reported a decreased susceptibility of *Enterobacterales* (32.6% and 73% for CRO and PTZ towards *E. coli*, respectively) and a dramatic decrease in the susceptibility rate of non-fermenting GNB (66.7 and 0% for IMI for *P. aeruginosa* and *Acinetobacter* spp. with polymyxin-B being the only active drug in 100% of the cases).

European, North American, and Oceanian regions

Unfortunately, in the last decade, no publication from these regions has detailed the epidemiology of resistance during CA-IAIs.

MDRB in ICU patients admitted for community-acquired IAIs

Few recent studies have described the susceptibility profile of bacteria cultured from intensive care unit (ICU) patients operated on for CA-IAIs. In a multicentre study carried out in 309 ICUs worldwide, Blot and colleagues analysed 664 critically ill patients. Antimicrobial resistance for GNB was defined as ESBL-producing strains, carbapenem resistance strains, or fluoroquinolone resistance strains. The authors also identified "difficult-to-treat" resistance for GNB as combination resistance to all tested carbapenem, beta-lactam, and fluoroquinolone agents. The authors reported an incidence of 26.5% of patients with MDRB, mainly aerobic GNB with a predominance of ESBL-producing and fluoroquinolone-resistant strains, whereas carbapenem-resistant organisms were less frequently observed (17.2%, 16.0% and 7.4%, respectively). In contrast, Gram-positive MDRBs were cultured in only a small number of cases (MRSA, 1.1%; vancomycin-resistant enterococci (VREs), 2.3%). However, the incidence of MDRB varies dramatically according to geographical location. The authors reported 7.8% MDRB in CA-IAIs in Western Europe (France, Belgium, the Netherlands, and the United Kingdom), 21.4% in Central Europe (Denmark, Czech Republic, Germany, Poland, and Switzerland), 26.5% in Southern Europe (Greece, Italy, Portugal, and Spain) and 52.1% in Eastern and Southeastern Europe (Croatia, Romania, Russia, and Serbia). The highest rates of resistance were observed in Eastern and Southeastern Europe. ESBL-producing and carbapenem-resistant GNB were detected in 35.4% and 22.9% of the patients, respectively.

Relevant data were also obtained from North Africa and the Middle East (MENA), Middle and South America and the Caribbean (LATAM), and Asia-Pacific. In line with observations in Europe, the authors reported a low incidence of MDR GPC (1–2.5% of the patients) and a majority of MDR GNB, with a predominance of ESBL-producing strains. Overall, the authors reported MDRB incidences of 49.4%, 41.5% and 25% per patient for the MENA, LATAM and Asia–Pacific regions, respectively. Unfortunately, the number of cases collected from North American and sub-Saharan African countries was too limited for any relevance.

Another multicentre retrospective study from China (2013-2018) focused on carbapenem-resistant *Enterobacterales* cultured from IAI samples collected from critically ill patients. Among the 503 patients with CA-IAIs, carbapenem-resistant bacteria were reported in 18.7% of all GNB, and the highest proportions were represented by *Klebsiella* spp. (14.6%) for *Enterobacterales* and *A. baumannii* (37%) for non-fermenting GNB.

Incidence of MDRB in community-acquired IAIs from the SMART database

Table 1 shows the 2020–2022 worldwide resistance rates of *Enterobacterales* to the antibiotics most commonly used in CA-IAIs. High variability in susceptibility profiles has been reported among countries with increased resistance rates compared to the previously published data. A lower incidence of MDRB seems to be reported in several high-income countries than in low- and middle-income countries.

Table 1. Proportions of resistance among *Enterobacterales* strains collected from community-acquired IAIs (Year 2020-2022) according to the CLSI-2024 (M100-ED34) criteria (Adapted from: the SMART database [https://globalsmart-site.com], Version website 5 April 2023. Accessed: 9 August 2024).

	Nb isolates	PTZ	CRO	CAZ/AVI	TOL/TAZ	IMI	MER/VEB	IMI/REL	AMK	LEV	COL
Europe											
Belgium	44	2.27	22.22	0	2.27	0	0	0	0	6.67	15.91
Bulgaria*	29	10.34	31.03	0	3.45	0	0	0	3.45	13.79	10.34
Croatia	111	6.31	10.81	0.9	2.7	2.7	0	2.2	0	15.32	26.13
Czech Rep	77	0	1.3	0	0	1.3	0	0	0	6.49	9.09
France	301	9.3	14.62	0	2.33	0.33	0	0	0.33	6.98	10.63
Georgia*	7	28.57	28.57	0	14.29	28.57	14.29	14.29	14.29	28.57	28.57
Germany	284	4.93	7.75	0	2.11	3.87	0	0	0.7	8.1	15.85
Greece*	19	10.53	15.79	0	5.26	10.53	0	0	0	10.53	10.53
Hungary	63	7.94	30.16	1.59	1.59	4.76	0	0	1.59	20.63	22.22
Italy	103	10.68	19.23	0	6.8	7.69	0	0	2.91	18.27	25.24
Latvia	54	3.7	20.37	0	0	0	0	0	0	11.11	7.41
Lithuania	124	4.84	11.29	0	2.42	0.81	0	0	0	10.48	10.48
Norway	50	4	4	0	0	2	0	0	0	0	6
Poland	88	6.82	12.5	1.14	3.41	3.41	0	1.2	0	10.23	12.5
Portugal	128	6.25	7.81	0	3.91	3.13	0	0	1.56	11.72	14.84
Romania	43	6.98	13.95	2.33	9.3	6.98	2.33	2.5	6.98	23.26	9.3
Serbia	125	20	28.8	6.4	17.6	18.4	12	12.84	10.4	33.6	23.2
Slovenia	35	2.86	11.43	0	0	0	0	0	0	8.57	11.43
Spain	310	7.1	9.94	0.32	2.26	1.6	0.32	0.34	0.32	15.38	10.32
Sweden	83	15.66	16.87	0	4.82	1.2	0	0	0	16.87	10.84
Switzerland	59	11.86	15.25	0	6.78	5.08	0	0	0	5.08	18.64
Turkey	125	13.6	35.71	2.4	9.6	7.94	6.4	5.74	4	27.78	6.4
Ukraine*	7	28.57	28.57	0	28.57	14.29	14.29	20	0	42.86	28.57
United Kingdom	125	5.6	8	0.8	0.8	1.6	0.8	0.85	2.4	11.2	8

(cont.)

Table 1. Proportions of resistance among *Enterobacterales* strains collected from community-acquired IAIs (Year 2020-2022) according to the CLSI-2024 (M100-ED34) criteria (Adapted from: the SMART database [https://globalsmart-site.com], Version website 5 April 2023. Accessed: 9 August 2024) *(cont.)*

	Nb isolates	PTZ	CRO	CAZ /AVI	TOL /TAZ	IMI	MER /VEB	IMI /REL	AMK	LEV	COL
Africa											
Kenya	58	17.24	58.06	6.9	15.52	8.06	6.9	9.09	1.72	33.87	10.34
Morocco	107	7.48	13.89	1.87	3.74	2.78	0.93	1.98	0.93	18.52	4.67
South Africa	250	13.6	22.4	2	8	4.4	1.6	2.67	2.4	19.6	11.6
Tunisia	70	14.29	21.43	7.14	12.86	7.14	7.14	7.46	10	21.43	5.71
Asia											
China	143	21.68	47.55	7.69	15.38	11.89	6.29	7.35	9.79	52.45	11.89
Hong Kong	215	6.98	19.07	0.93	1.86	5.12	0.93	1.01	0.47	21.86	11.16
India	131	28.24	60.31	6.87	25.95	18.32	12.98	14.75	16.03	61.07	10.69
Japan	387	4.39	12.14	0	1.81	1.29	0	0	0.26	12.4	11.89
Kazakhstan*	5	20	40	0	20	0	0	0	0	40	0
Korea, South	228	10.09	28.07	0	7.46	3.07	0	0.45	1.75	25	5.7
Malaysia	159	7.55	32.08	0	5.66	2.5	0	0.65	1.89	17.5	8.18
Philippines	167	9.58	21.56	2.4	4.79	7.78	1.8	2.6	1.2	28.14	14.97
Taiwan	263	7.6	23.95	0	4.18	3.42	0	0	0.76	16.35	7.98
Thailand	347	14.41	46.26	3.17	9.51	6.61	3.46	3.89	4.9	40.23	7.2
Vietnam	174	10.34	49.43	4.02	8.62	8.62	4.6	5.36	6.9	41.95	8.62
Middle East											
Israel	185	3.78	22.7	0	1.62	2.16	0	0	0.54	15.68	14.59
Jordan	79	17.72	53.75	2.53	7.59	6.25	2.53	2.67	5.06	41.25	8.86
Kuwait	45	15.56	33.33	4.44	11.11	4.44	2.22	2.7	6.67	28.89	22.22
Lebanon	84	21.43	45.24	7.14	15.48	8.33	7.14	7.5	3.57	40.48	4.76
Oman*	3	0	100	0	0	0	0	0	0	100	0
Qatar	35	2.86	45.71	0	0	2.86	0	3.03	0	40	11.43
United Arab Emirates	35	8.57	27.78	5.71	5.71	5.56	2.86	5.88	2.86	30.56	5.71
North America											
Canada	326	8.28	18.1	0	4.29	3.68	0	0	1.23	16.87	11.35
United States	995	8.74	13.83	0.3	3.22	5.01	0.1	0.33	1.81	13.73	11.36
Central and South America											
Argentina	176	12.5	23.3	1.7	6.25	7.95	1.7	2.37	5.68	28.41	9.09
Brazil	210	10.95	26.19	1.43	8.1	8.57	1.43	1.53	2.86	26.19	12.86
Chile	96	7.29	20.83	0	3.13	3.13	0	0	2.08	25	9.38
Colombia	207	17.39	20.19	1.45	8.21	14.08	0.48	1.59	3.38	13.62	13.04
Ecuador	192	11.46	35.42	0	8.33	7.81	0	0.56	9.9	44.27	13.54
Guatemala	223	17.94	44.64	5.38	12.11	6.7	5.38	5.53	5.38	33.93	7.17
Mexico	213	19.25	55.61	1.88	12.68	6.07	1.41	2.56	6.57	45.33	8.92
Panama	84	4.76	12.64	0	2.38	4.6	0	0	2.38	17.24	17.86
Puerto Rico	133	9.02	13.43	0.75	4.51	5.97	0.75	0.79	4.51	18.66	9.02
Venezuela	35	20	20	14.29	17.14	22.86	2.86	6.67*	2.86	33.93	71.43
Oceania											
Australia	390	3.08	8.72	0	1.03	2.56	0	0	1.28	5.9	11.03
New-Zealand	154	9.74	13.64	0	3.25	0.65	0	0	0	7.14	4.55

*: Value less than 30 isolates. Wards: Emergency room; General unspecified ICU; Medicine general; Medicine ICU; Surgery general; Surgery ICU. *Abbreviations*. PTZ: piperacillin-tazobactam, CRO: ceftriaxone, CAZ/AVI: ceftazidime-avibactam, TOL/TAZ: ceftolozane-tazobactam, IMI: imipenem-cilastatin, MER/VEB: meropenem-vaborbactam, IMI/REL: imipenem-relebactam, AMK: amikacin, LEV: levofloxacin, COL: colistin.

Frequency of resistance	
< 10%	
10 - 20%	
20 - 30%	
> 30%	

Hospital-acquired IAIs

Reports of the faecal distribution of resistance are also highly relevant in planning the most adequate empirical drugs for patients with a diagnosis of HA-IAIs or postoperative IAIs. The importance of the carriage of MDRB has been demonstrated for ESBL-producing *Enterobacterales* in patients undergoing colorectal surgery. In patients categorised as ESBL carriers before scheduled surgery, the risk of deep surgical site infection (SSI) more than doubles, and a 4.2-fold increase in the incidence of SSI due to ESBL-producing *Enterobacterales* has been reported.

Incidence of MDRB in patients treated for hospital-acquired IAIs

In the two CIAO and CIAOW studies that included 575 patients with a diagnosis of HA-IAIs, 24.4% of MDRB were isolated. Compared with that in CA-IAIs, the frequency of MDRB in patients treated for HA-IAIs was greater. The predominant MDRBs were ESBL-producing *Enterobacterales*, which were mainly *E. coli* and *K. pneumoniae* resistant to 3-GCS (23.5% and 46.3% of the strains, respectively). The proportion of carbapenem-resistant strains remained low, mainly involving non-fermenting GNB (predominance of *A. baumannii*) and some *K. pneumoniae* strains. In GPC, the frequency of MDR microorganisms was greater than that in CA-IAIs, mainly represented by enterococci resistant to glycopeptides (11% and 15% of the isolates of *Enterococcus faecalis* and *E. faecium*, respectively) and MRSA (39% of the *S. aureus* isolates). In two subanalyses focusing on health care-associated acute appendicitis and acute cholecystitis, the authors reported 6.8% and 7.8% resistant bacteria in 2 (11.8%) and 3 (14.3%) patients, respectively. Two strains resistant to carbapenems (*Acinetobacter* spp. and *Pseudomonas* spp.) were observed in patients with appendicitis, whereas two ESBL-producing *Enterobacterales* (*E. coli* and *K. pneumoniae*) and two strains resistant to carbapenems (*Acinetobacter* spp. and *K. pneumoniae*) were identified in patients with cholecystitis.

In a study from South Korea (2009-2013), the authors analysed 143 patients with anastomotic leakage after colorectal surgery. Overall, 32% of patients had positive microbiological cultures yielding MDR bacteria with a predominance of GPC: *Enterococcus* spp. (n=31), *Enterobacter* spp. (n=9), *P. aeruginosa* (n=4), ESBL-producing *E. coli* (n=4), *Acinetobacter* spp. (n=3), and MRSA (n=1).

In a multicentre study from China (2010-2014), the authors reported majorly increased proportions of *Enterobacterales* among HA-IAIs compared with CA-IAIs. The proportion of ESBL-producing strains, however, was quite similar in HA-IAI and CA-IAI patients.

In a US database analysis of 4,453 patients (2013-2017) hospitalized with IAIs treated with carbapenems (29% of healthcare-associated IAIs and 13% of HA-IAIs), resistance to 3-GCS and carbapenem among GNB isolates was 7.6% and 2.2%, respectively, and *A. baumannii* reached the highest level of resistance, 21% for each.

Incidence of MDRB in patients admitted to the ICU for hospital-acquired IAIs

The susceptibility profile of bacteria cultured from ICU patients operated on for hospital-acquired IAIs was recently analysed in a multicentre study mentioned above. The authors assessed the susceptibility profile of 482 patients treated for early-onset hospital-acquired infection (≤7 days from hospital admission) and 836 patients with late-onset hospital-acquired IAI (>7 days from hospital admission). The authors reported an incidence of MDRB in 29% and 24.6% of patients (early- and late-onset hospital-acquired IAIs), with a predominance of ESBL-producing and fluoroquinolone-resistant GNB. Carbapenem-resistant organisms were less frequently observed (18.0%, 19.3%, and 9.8%, respectively, for early-onset cases) (15.0%, 16.7%, and 5.9%, respectively, for late-onset IAIs). MDR Gram-positive bacteria were cultured in only a small number of cases (MRSA 1.5% and VRE 3.7% for early-onset cases and MRSA 0.7% and VRE 2.8% for late-onset cases). Major differences in the incidence of MDRB have been reported across geographical areas. The authors reported an incidence during early-onset hospital-acquired IAIs of MDRB of 15.4% in Western Europe (France, Belgium, Netherlands, and United Kingdom; 9.8% for late-onset cases), 18.2% in Central Europe (Denmark, Czech Republic, Germany, Poland, and Switzerland; 22.9% for late-onset cases), and 28.5% in Southern Europe (Greece, Italy, Portugal, and Spain; 27.3% for late-onset cases). The highest incidences of resistance (46.8%; 32.1% for late-onset cases) were observed in Eastern and Southeastern Europe (Hungary, Romania, Serbia, and Russia). ESBL-producing and carbapenem-resistant GNB were detected in 25.5% and 23.4% of the patients, respectively, but only 14.3% and 13.2% of the patients had late-onset hospital-acquired infections, respectively.

In a multicentre retrospective study from China (2013-2018) involving 521 patients treated for HA-IAIs, carbapenem-resistant bacteria were reported in 31.7% of all GNB, with *Klebsiella* spp. (27.4%) and *A. baumannii* (61.8%) being the most common carbapenem-resistant strains for *Enterobacterales* and non-fermenting GNB, respectively.

In a multicentre prospective trial analysing the duration of antibiotic therapy in 249 patients treated for postoperative peritonitis, the predominant MDRBs cultured from surgical samples were ESBL- and AmpC-hyperproducing *Enterobacterales*, accounting for 51% and 46% of the isolates, respectively. In this study, the emergence of MDRB related to ESBL- and AmpC-hyperproducing *Enterobacterales* (51% and 46%), MRSA (21%), *P. aeruginosa* (14%) and *A. baumannii* and *S. maltophilia* (13%) was reported in subsequent clinical isolates from 37% of patients. The emergence of AMR has also been documented in a cohort of ICU patients who underwent repeated surgery for persistent peritonitis, in which resistance was assessed via peritoneal fluid cultures at the first, second, and third reoperations. A progressive shift in the peritoneal flora was observed with an increasing number of reoperations, resulting in the extinction of susceptible strains and the emergence of MDR strains (*Enterobacterales*, non-fermenting GNB, including *P. aeruginosa* and enterococci). The proportion of patients harbouring MDR strains increased from 41% at index surgery to 49% at the first reoperation, 54% at the second reoperation (p=0.037) and 76% at the third reoperation (p=0.003 *versus* index surgery). According to multivariate analysis, the only risk factor for the emergence of MDR strains was the time to reoperation (OR 1.19 per day, p=0.0006).

The temporal changes in the incidence of MDRB have rarely been assessed in IAIs. In a retrospective monocentric study (1999-2019) analysing the proportions of MDRB, the authors reported 45% of all patients with MDRB among 422 ICU patients treated for postoperative peritonitis without any change in the yearly incidence. However, increasing proportions of MDR *Enterobacterales*, including ESBL-producing *Enterobacterales*, were observed over time (p=0.016).

Incidence of MDRB in hospital-acquired IAIs from the SMART database

Table 2 shows the 2020–2022 worldwide resistance rates of *Enterobacterales* to the antibiotics most commonly used in HA-IAIs. High variability in susceptibility profiles has been reported among countries. In several high-income countries, a higher incidence of resistance seems to be observed in HA-IAIs than in CA-IAIs, particularly for beta-lactams (**Table 1**), whereas the proportions of resistance seem quite similar in low- and middle-income countries.

Table 2. Proportions of resistance among *Enterobacterales* strains collected from hospital-acquired (≥48 hours) IAIs (Year 2020-2022) according to the CLSI-2022 criteria (Adapted from: the SMART database [https://globalsmart-site.com], Version website 5 April 2023. Accessed: 9 August 2024.

	Nb isolates	PTZ	CRO	CAZ /AVI	TOL /TAZ	IMI	MER /VEB	IMI /REL	AMK	LEV	COL
Europe											
Belgium	135	20	26.41	1.48	6.67	2.94	1.48	1.56	2.96	14.71	12.59
Bulgaria*	16	12.5	18.75	0	6.25	6.25	6.25	6.25	6.25	12.5	18.75
Croatia	115	9.57	24.35	4.35	8.7	9.57	3.48	4.95	3.48	32.17	17.39
Czech Rep	55	12.73	9.09	0	0	0	0	0	0	7.27	18.18
France	202	20.3	20.3	0	6.44	0.99	0	0	0.5	11.39	13.86
Georgia	48	2.08	27.08	0	2.08	8.33	0	0	8.33	29.17	50
Germany	327	17.74	23.85	0.31	6.12	3.67	0.31	0.66	1.53	10.4	12.54
Greece	160	15.63	24.38	2.5	11.25	10.63	1.25	2.72	8.75	31.25	15
Hungary	176	11.93	28.25	0	7.39	3.95	0	0	1.14	25.99	17.05
Italy	310	22.9	32.37	0.97	15.81	12.82	0.65	0.68	8.06	30.13	8.71
Latvia	75	14.67	29.33	0	6.67	1.33	0	0	1.33	18.67	10.67
Lithuania	101	16.83	29.7	0	5.94	2.97	0	0	3.96	14.85	13.86
Poland	120	23.33	34.17	0	15	3.33	0	0	0.83	23.33	13.33
Portugal	184	32.07	30.27	0	13.04	8.11	0	0	1.09	19.46	10.33
Romania*	26	15.38	34.62	11.54	11.54	15.38	7.69	13.64	11.54	19.23	15.38
Serbia	84	32.14	46.43	9.52	33.33	20.24	17.86	14.67	20.24	52.38	28.57
Slovenia	91	14.29	18.68	0	3.3	6.59	0	1.27	3.3	8.79	17.58
Spain	339	17.11	20.94	0.59	6.49	2.95	0.88	0.94	0.88	22.12	10.91
Sweden*	1	0	0	0	0	0	0	0	0	0	0
Switzerland	66	22.73	24.24	0	7.58	4.55	0	0	1.52	15.15	18.18
Turkey	305	31.8	43.93	3.28	14.75	13.44	4.26	4.26	5.9	43.28	14.43
Ukraine	223	27.8	47.98	6.73	23.32	15.25	11.21	12.14	9.42	42.15	12.56
United Kingdom	183	8.2	12.02	1.09	3.28	4.37	0.55	1.17	1.64	8.2	8.74
Africa											
Kenya	35	22.86	34.29	5.71	17.14	11.43	5.71	6.45	5.71	25.71	14.29
Morocco	137	17.52	37.68	5.11	10.22	7.25	2.92	6.15	3.65	43.48	8.03
South Africa	100	17	18	2	10	10	8	7.87	3	18	18
Tunisia	122	16.39	30.33	7.38	12.3	9.02	6.56	6.25	6.56	22.95	13.93
Asia											
China	690	28.12	54.7	3.91	20.72	14.04	3.19	4.19	16.67	48.63	6.81
Hong Kong	107	14.95	27.1	0.93	7.48	8.41	0.93	4	1.87	26.17	8.41
India	282	40.43	60.7	19.5	37.23	31.23	26.95	30.24	31.91	63.86	16.31
Japan	223	8.97	15.25	0	3.59	4.04	0	0.92	0	10.76	13.9
Kazakhstan*	29	13.79	34.48	6.9	13.79	10.34	10.34	11.11	6.9	31.03	10.34
Korea, South	463	22.46	43.84	1.51	14.25	5.83	1.51	1.74	2.16	35.21	3.02
Malaysia	183	9.29	32.43	1.09	6.01	3.24	1.09	1.14	1.09	23.78	8.2
Philippines	119	20.17	29.41	6.72	16.81	12.61	7.56	7.83	0.84	39.5	6.72
Taiwan	634	22.08	41.04	1.1	16.4	8.49	0.79	1.97	2.21	26.73	9.46
Thailand	233	27.9	62.23	8.58	23.18	14.16	9.01	10.45	6.44	48.07	10.73
Vietnam	136	30.15	68.38	6.62	24.26	18.38	11.03	12.12	11.03	63.97	5.15

(cont.)

Table 2. Proportions of resistance among *Enterobacterales* strains collected from hospital-acquired (≥48 hours) IAIs (Year 2020-2022) according to the CLSI-2022 criteria (Adapted from: the SMART database [https://globalsmart-site.com], Version website 5 April 2023. Accessed: 9 August 2024 *(cont.)*

	Nb isolates	PTZ	CRO	CAZ /AVI	TOL /TAZ	IMI	MER /VEB	IMI /REL	AMK	LEV	COL
Middle East											
Israel	146	13.01	31.51	2.74	6.85	4.79	0.68	0.72	4.11	23.29	13.7
Jordan	42	33.33	61.9	7.14	23.81	11.9	11.9	12.2	4.76	50	9.52
Kuwait	150	6.67	34	4	4.67	5.33	3.33	4.76	2.67	33.33	22
Lebanon*	11	18.18	54.55	0	9.09	0	0	0	0	18.18	18.18
Oman*	8	37.5	50	0	37.5	12.5	12.5	14.29	25	50	12.5
Qatar	77	9.09	32.91	2.6	6.49	3.8	2.6	2.7	3.9	20.25	9.09
United Arab Emirates	42	9.52	30.95	2.38	7.14	4.76	2.38	2.44	2.38	23.81	7.14
North America											
Canada	332	16.57	25.53	0.3	9.94	2.7	0.6	0.95	1.51	18.32	10.84
United States	552	14.49	25.72	0.36	7.61	3.99	0.18	0.38	1.27	17.39	9.96
Central and South America											
Argentina	194	23.2	32.99	3.09	14.43	12.89	3.09	3.33	9.28	28.35	14.43
Brazil	189	32.8	47.37	4.23	24.87	19.47	3.7	5.52	11.11	31.05	17.99
Chile	266	37.22	52.26	0.38	27.07	7.89	0.38	0.83	7.52	40.23	13.16
Colombia	253	22.13	30.83	3.16	12.25	14.62	3.16	5.19	5.93	25.69	12.65
Ecuador	116	22.41	41.38	2.59	16.38	18.97	0.86	1.9	12.07	37.93	27.59
Guatemala	40	2.5	42.5	0	2.5	2.5	0	0	0	45	2.5
Mexico	330	16.06	54.82	1.21	8.18	4.82	0.91	1.6	4.85	46.08	6.36
Panama	144	15.97	28.47	3.47	6.25	6.25	2.78	2.34	2.78	39.58	16.67
Puerto-Rico*	12	8.33	16.67	0	0	0	0	0	0	41.67	25
Venezuela	36	13.89	27.78	5.56	11.11	5.56	2.78	3.57*	8.33	47.22	27.78
Oceania											
Australia	314	10.51	20.38	0.32	5.73	3.5	0.32	0.34	0.32	7.96	11.78
New Zealand	117	10.26	19.33	0.85	5.13	3.36	0.85	0	1.71	10.08	3.42

*: Value less than 30 isolates. Wards: Emergency room; General unspecified ICU; Medicine general; Medicine ICU; Surgery general; Surgery ICU. Abbreviations. PTZ: piperacillin-tazobactam. CRO: ceftriaxone. CAZ/AVI: ceftazidime-avibactam. TOL/TAZ: ceftolozane-tazobactam. IMI: imipenem-cilastatin. MER/VEB: meropenem-vaborbactam. IMI/REL: imipenem-relebactam. AMK: amikacin. LEV: levofloxacin. COL: colistin.

Frequency of resistance
< 10%
10 - 20%
20 - 30%
> 30%

Clinical consequences of MDRB

Numerous studies have demonstrated the deleterious role of AMR in patients treated for IAIs. This factor has been less evaluated in community-acquired infections than in HA-IAIs. Compared with patients without MDRB, Labricciosa *et al.* reported that patients with MDRB had 2.7 times more inadequate empirical antimicrobial therapy, 1.36 times more admissions to the ICU, 1.74 times more reoperations, a hospital length of stay 2.33 times longer, and 1.76 times more frequent death. These features could be related to the delayed efficacy of antibiotic therapy in patients with MDRB. Lee *et al.* reported that the proportion of adequate empirical antibiotic therapy within 3 days was 2.16 times lower in patients with MDRB. The relevance of these observations may change depending on the extent of bacterial resistance. In the case of carbapenem-resistant strains, where therapeutic options are very limited or even nonexistent, the prognosis is even worse. In cases of IAIs involving carbapenem-resistant *Enterobacterales*, Liu *et al.* reported a 3.7-fold increased death rate on Day 28 and a 6-fold increase in in-hospital mortality via multivariate analysis. The cost of hospitalization may also increase as a result of prolonged anti-infective therapies or the use of more expensive molecules.

Conclusion

AMR is a major threat to the management of patients with IAIs, especially those associated with *Enterobacterales*. The global spread of AMR through faecal carriage is dramatically underestimated in the population. More accurately identifying the risk factors for AMR can reduce the likelihood of inappropriate empirical antimicrobial therapy. Regularly updated knowledge of local, regional, and national AMR could enable the development of improved antibiotic protocols and recommendations. In microbiology laboratories, the use of rapid diagnostic tests based on genetic analysis of resistance could, in the near future, provide prescribers with valuable information on difficult-to-treat bacterial infections and accelerate the adequacy of antibiotic therapy.

Competing interests

PM has received honoraria for lectures, presentations, data safety monitoring boards and advisory boards from Berlin Chemie, Curetis, MSD, Menarini, Mundipharma, Pfizer, Shionogi, Viatris. The other authors have no competing interests to disclose. The other authors have no financial and non-financial competing interests to declare.

References

1. Labricciosa FM, et al. Epidemiology and risk factors for isolation of multi-drug-resistant organisms in patients with complicated intra-abdominal infections. Surg Infect (Larchmt). 2018;19:264-272.
2. Magiorakos AP, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect. 2012;18:268-281.

3. Lee DS, et al. Risk factors for acquisition of multidrug-resistant bacteria in patients with anastomotic leakage after colorectal cancer surgery. Int J Colorectal Dis. 2015;30:497-504.
4. Blot S, et al. Epidemiology of intra-abdominal infection and sepsis in critically ill patients: "AbSeS", a multinational observational cohort study and ESICM Trials Group Project. Intensive Care Med. 2019;45:1703-1717.
5. Liu J, et al. Risk factors and molecular epidemiology of complicated intra-abdominal infections with carbapenem-resistant Enterobacteriaceae: A Multicenter Study in China. J Infect Dis. 2020;221:S156-s163.
6. Cantón R, et al. Antimicrobial surveillance: A 20-year history of the SMART approach to addressing global antimicrobial resistance into the future. Int J Antimicrob Agents. 2023;62:107014.
7. Zilberberg MD, et al. Carbapenem treatment and outcomes among patients with culture-positive complicated intra-abdominal infections in US hospitals: A retrospective cohort study. Open Forum Infect Dis. 2019;6:ofz504.
8. Ciesielczuk H, et al. Multicenter performance evaluation of the Unyvero IAI cartridge for detection of intra-abdominal infections. Eur J Clin Microbiol Infect Dis. 2018;37:2107-2115.
9. Amare A, et al. High prevalence of fecal carriage of Extended-Spectrum Beta-Lactamase and carbapenemase-producing Enterobacteriaceae among food handlers at the University of Gondar, Northwest Ethiopia. PLoS One. 2022;17:e0264818.
10. Shenkute D, et al. High magnitude of fecal carriage of Extended-Spectrum Beta-Lactamase-Producing Enterobacteriaceae at Debre Berhan Comprehensive Specialized Hospital, Ethiopia. Infect Drug Resist. 2022;15:2445-2458.
11. Dubinsky-Pertzov B, et al. Carriage of Extended-spectrum Beta-lactamase-producing Enterobacteriaceae and the risk of surgical site infection after colorectal surgery: A prospective cohort study. Clin Infect Dis. 2019;68:1699-1704.
12. Guilbart M, et al. Compliance with an empirical antimicrobial protocol improves the outcome of complicated intra-abdominal infections: a prospective observational study. Br J Anaesth. 2016;117:66-72.
13. Coccolini F, et al. Antibiotic resistance evaluation and clinical analysis of acute appendicitis; report of 1431 consecutive worldwide patients: A cohort study. Int J Surg. 2016;26:6-11.
14. Coccolini F, et al. Antibiotic resistance pattern and clinical outcomes in acute cholecystitis: 567 consecutive worldwide patients in a prospective cohort study. Int J Surg. 2015;21:32-37.
15. Seni J, et al. Comparison of antimicrobial resistance patterns of ESBL and non ESBL bacterial isolates among patients with secondary peritonitis at Bugando Medical Centre, Mwanza - Tanzania. BMC Emerg Med. 2016;16:41.
16. El-Kholy AA, et al. Molecular characterization of multidrug-resistant Gram-negative pathogens in three tertiary hospitals in Cairo, Egypt. Eur J Clin Microbiol Infect Dis. 2020;39:987-992.
17. Morganti L, et al. Antimicrobial susceptibility of Gram-negative bacilli of community acquired intra-abdominal infections in a hospital at Buenos Aires, Argentina. Rev Esp Quimioter. 2016;29:202-205.
18. Scapellato PG, et al. Aerobic etiology of acute appendicitis in adults. Multicenter study of abdominal sepsis in Argentina. Medicina (B Aires). 2017;77:121-124.
19. Revoredo Rego F, et al. Microbiological and resistance profiles of community acquired and nosocomial intra abdominal infections in surgery of National Hospital Guillermo Almenara, Lima, Peru. Rev Gastroenterol Peru. 2016;36:115-122.
20. Vallejo M, et al. Clinical and microbiological characteristics of complicated intra-abdominal infection in Colombia: a multicenter study. Rev Chilena Infectol. 2016;33:261-267.
21. Lemos-Luengas EV, et al. In vitro activity of ceftazidime-avibactam against Gram-negative strains in patients with complicated urinary tract infection and complicated intra-abdominal infection in Colombia 2014-2018. Braz J Infect Dis. 2022;26:102369.
22. Ponce-de-Leon A, et al. Antimicrobial susceptibility of Gram-negative bacilli isolated from intra-abdominal and urinary-tract infections in Mexico from 2009 to 2015: Results from the Study for Monitoring Antimicrobial Resistance Trends (SMART). PLoS One. 2018;13:e0198621.
23. Tsai CH, et al. Antimicrobial susceptibility of E. coli isolates from intra-abdominal infections in the Asia-Pacific Region: Trends in ciprofloxacin, ceftriaxone, cefepime, and piperacillin/tazobactam susceptibility. Infect Drug Resist. 2023;16:5599-5611.

24. Zhang H, et al. Update of incidence and antimicrobial susceptibility trends of Escherichia coli and Klebsiella pneumoniae isolates from Chinese intra-abdominal infection patients. BMC Infect Dis. 2017; 17:776.
25. Saad U, et al. Antimicrobial susceptibility of intra-abdominal infection isolates from a tertiary care hospital in Karachi. J Ayub Med Coll Abbottabad. 2016;28:568-571.
26. Liu L, et al. Antimicrobial susceptibilities of specific syndromes created with organ-specific weighted incidence antibiograms (OSWIA) in patients with intra-abdominal infections. BMC Infect Dis. 2018;18:584.
27. Montravers P, et al. Short-course antibiotic therapy for critically ill patients treated for postoperative intra-abdominal infection: the DURAPOP randomised clinical trial. Intensive Care Med. 2018;44:300-310.
28. Montravers P, et al. Dynamic changes of microbial flora and therapeutic consequences in persistent peritonitis. Crit Care. 2015;19:70.
29. Montravers P, et al. Microbiological profile of patients treated for postoperative peritonitis: temporal trends 1999-2019. World J Emerg Surg. 2023;18:58.
30. De Pascale G, et al. Risk factors for mortality and cost implications of complicated intra-abdominal infections in critically ill patients. J Crit Care. 2019;50:169-176.

Chapter 129

Intra-abdominal infections in the immunocompromised

Erin E. Devine
Section of Acute Care Surgery, Department of General Surgery, Stanford University, Stanford, CA, USA.

Joseph D. Forrester
Section of Acute Care Surgery, Department of General Surgery, Stanford University, Stanford, CA, USA.

Introduction

Immunocompromised patients with intra-abdominal infections (IAIs) are challenging to care for due to the broad spectrum of pathogens and increased risk of complications. Immunocompromised groups include HIV/AIDS, congenital immunodeficiencies, solid organ transplant recipients, leukemia/lymphoma, solid malignancy, chemotherapy, immunosuppression for rheumatologic or inflammatory disease, diabetes, chronic liver disease and malnutrition. The severity of immunocompromise varies across, and within, these groups resulting in heterogeneity of presentation, progression, and outcomes of patients with IAIs.
In immunocompromised patients, IAIs often present atypically, complicating early diagnosis. Depending on the etiology of immune compromise, the inflammatory response can be blunted and typical symptoms such as pain and signs such as abdominal tenderness or peritonitis are absent or reduced. Leukocytosis may or may not be present, and often cross-sectional imaging is required to make a diagnosis. Therefore, a high index of suspicion is required to diagnose IAIs in immunocompromised patients. Moreover, pathophysiology and microbiology can differ, often involving a broader spectrum of pathogens, including opportunistic and multidrug-resistant organisms (MDROs). This complexity requires a nuanced approach to diagnosis, management, and treatment, balancing the need for aggressive antimicrobial therapy and surgical intervention, when indicated, with the potential for adverse drug effects, further risk of MDROs, and surgical or procedural complications.

Pathogenesis

Immunocompromised patients are heterogenous in etiology and severity. Some studies have grouped them into mild-moderate (elderly, malnourished, diabetic, burns, trauma, active malignancy not on chemotherapy, HIV with CD4+ > 200, splenectomy) and severe (AIDS, HIV+ with CD4+ <200, transplant on immunosuppression, high-dose steroids, malignancy on chemotherapy, neutrophil count <1000/uL). Understanding mechanisms of immune compromise is important in the presentation, work-up, and management of these unique groups.

HIV/AIDS

HIV (Human Immunodeficiency Virus) targets CD4+ T-cells, which are crucial in coordinating the adaptive immune response. As the CD4+ count falls, the immune system becomes compromised, leading to AIDS (acquired immunodeficiency syndrome), usually defined as <200 cells/μL. The patient then becomes more susceptible to opportunistic infections (e.g., *Pneumocystis* pneumonia, cytomegalovirus) and certain malignancies (e.g., Kaposi's sarcoma, non-Hodgkin lymphoma).

Leukemia/Lymphoma

Leukemia and lymphoma are cancers of the hematopoietic and lymphoid tissues resulting in overproduction of abnormal white blood cells that lack normal immune function, making patients susceptible to infections. Chemotherapy and radiation further exacerbate pathologic immunosuppression which predisposes patients to intra-abdominal infections and can have consequences for post-operative healing.

Liver disease

Chronic liver disease impairs the immune system through multiple mechanisms. The liver is a key site for immune surveillance, producing immune cells (e.g., Kupffer cells, natural killer cells) and proteins (e.g., complement proteins). Cirrhosis can lead to impaired hepatic immune function and reduced production of complement proteins. Additionally, there is reduced microbiome diversity and damage to gut-associated lymphoid tissue with portal hypertension. These patients are more prone to bacterial infections such as spontaneous bacterial peritonitis, particularly as liver disease progresses to the end stages.

Diabetes

Diabetes mellitus is associated with impaired innate and adaptive immune responses. Hyperglycemia hinders neutrophil function, depresses antioxidant systems and impairs cytokine production. It also leads to microvascular damage, reducing the delivery of immune cells to sites of infection. Poor glycemic control reduces effectiveness in immune responses. As a result, diabetic patients are more susceptible to bacterial infections and have higher rates of complications from infections.

Malnutrition

Malnutrition leads to immunodeficiency by impairing both innate and adaptive immune responses, as well as modulation of the inflammatory response. Protein-energy malnutrition affects the production of immunoglobulins and the function of T-cells and macrophages. Micronutrient deficiencies, such as vitamin A, zinc, and iron, can disrupt the integrity of mucosal barriers and diminish the function of immune cells. Malnourished individuals are at increased risk for infections due to a weakened immune defense, reduced skin barrier function, and impaired gut mucosal immunity.

Congenital immunodeficiency

Congenital immunodeficiency refers to a group of disorders caused by genetic defects that impair the development, function, or regulation of the immune system. These conditions are typically present from birth and may manifest in infancy or early childhood, although some can present later in life. Pathogenesis varies widely depending on the specific genetic mutation involved.

See **Table 1** for a summary.

Table 1. Congenital immunodeficiencies (Adapted from Sindt JE, *et al.* 2023).

Deficiency	Example	Mutation	Effect	Pathogens
B-Cell	X-linked Agammaglobulinemia (XLA)	BTK (Bruton's tyrosine kinase)	Absence of mature B cells, a significant reduction in all antibody classes, and humoral deficiency. Patients with B-cell deficiencies are highly susceptible to encapsulate bacterial infections.	*Streptococcus pneumoniae* and *Haemophilus influenzae*
T-Cell	DiGeorge Syndrome	22q11.2 Deletion	Altered development of the thymus and parathyroid glands resulting in impaired T-cell maturation. T-cell deficiencies predispose patients to viral, fungal, and opportunistic infections, as well as impaired antibody production.	*Pneumocystis jirovecii*
Combined	Severe Combined Immunodeficiency (SCID)	IL2RG ADA RAG1/2	Profound defects in both T and B lymphocyte development leading to a lack of both cellular and humoral immunity. Patients are susceptible to severe infections.	Viral, bacterial and fungal susceptibility
Phagocytic	Chronic Granulomatous Disease (CGD)	NADPH oxidase complex	Impaired ability of neutrophils and macrophages to kill ingested pathogens, leading to recurrent bacterial and fungal infections. Patients often present with granuloma formation due to chronic inflammation.	*Staphylococcus aureus, Aspergillus, Nocardia*
Complement	C3 Deficiency		Deficiency in C3 leads to impaired opsonization and phagocytosis of pathogens, making individuals more prone to infections with encapsulated bacteria. Complement deficiencies can also predispose to autoimmune diseases due to impaired clearance of immune complexes.	*Neisseria meningitidis, Streptococcus pneumoniae*
Innate Immune	Toll-like Receptor (TLR)	Encoding TLRs MyD88 IRAK4	Disrupted innate immune response to microbial pathogens. These patients may exhibit an impaired ability to respond to certain bacterial infections, such as invasive pneumococcal disease, due to defective recognition and signaling by innate immune cells.	Strep Pneumococcus

Drug-induced

Drugs for cancer therapy (chemotherapy and monoclonal antibiotics), organ transplantation, rheumatologic disease, and inflammatory and autoimmune conditions cause immune suppression by intent or by side effects.

See **Table 2** for drug mechanisms and considerations for surgery.

Table 2. Commonly used immunosuppressive drugs, their mechanisms of action, their impact on wound healing, and recommendations for holding them before surgery (Adapted from Coccolini F, *et al.* 2021; Home - UpToDate® Lexidrug™. Rezaieyazdi Z, *et al.* 2019; Mellor JD, *et al.* 2011; Boyce M, *et al.* 2020; Lanas A, *et al.* 2017).

Drug	Mechanism of action	Impact on wound healing	Indications	Recommendation before surgery
Corticosteroids	Inhibit phospholipase A2, reduce cytokine production, and suppress immune response.	Impaired collagen synthesis, decreased fibroblast activity, increased risk of infection.	Autoimmune diseases, organ transplant	Ideally tapered weeks before surgery, but acute use might not need to be held. May need stress dose if steroid dependent.
Belatacept	Inhibits T-cell co-stimulation (CD80/CD86)	Potential for impaired wound healing	Organ transplant	Usually continued, but consult transplant team
Azathioprine	Inhibits purine synthesis, which reduces lymphocyte proliferation.	May delay wound healing and increase infection risk.	Organ transplant, RA, SLE, autoimmune hepatitis, myasthenia gravis, vasculitis, MS.	Hold 1-2 weeks before major surgery.
Methotrexate	Inhibits dihydrofolate reductase, affecting DNA synthesis in rapidly dividing cells.	Can impair wound healing due to effects on cell proliferation.	Rheumatoid arthritis, psoriasis, Leukemia, lymphoma, osteosarcoma	Hold 1-2 weeks prior to surgery, depending on patient risk.
Mycophenolate Mofetil	Inhibits inosine monophosphate dehydrogenase, reducing T and B cell proliferation.	May delay wound healing and increase infection risk.	Organ transplant	Hold 1 week before surgery, resume post-op once stable, consult transplant team.
Cyclosporine	Inhibits calcineurin, reducing T-cell activation.	Variable impact; some studies show impaired healing, others minimal effect.	Organ transplant, autoimmune diseases	Generally, continue through minor surgeries; hold for 1-2 days before major surgeries.
Tacrolimus	Similar to cyclosporine; inhibits calcineurin, reducing T-cell activation.	Similar to cyclosporine; potential risk of impaired healing.	Organ transplant, autoimmune diseases	May be held 24-48 hours before major surgery, check with transplant team.
Sirolimus (Rapamycin)	Inhibits mTOR, affecting T and B cell proliferation and response to IL-2.	Strongly associated with delayed wound healing and increased risk of wound complications.	Organ transplant	Hold 1 week before surgery and resume 1-2 weeks post-op.

(cont.)

Table 2. Commonly used immunosuppressive drugs, their mechanisms of action, their impact on wound healing, and recommendations for holding them before surgery (Adapted from Coccolini F, *et al.* 2021; Home - UpToDate® Lexi-drug™. Rezaieyazdi Z, *et al.* 2019; Mellor JD, *et al.* 2011; Boyce M, *et al.* 2020; Lanas A, *et al.* 2017). *(cont.)*

Drug	Mechanism of action	Impact on wound healing	Indications	Recommendation before surgery
Cyclophosphamide	Alkylating agent that crosslinks DNA, leading to cell death, especially in rapidly dividing cells.	Significant delay in wound healing due to cytotoxic effects on fibroblasts and endothelial cells.	Autoimmune diseases, Breast cancer, lymphoma, leukemia	Hold at least 1 week before surgery.
JAK Inhibitors (e.g., Tofacitinib, Baricitinib)	Inhibit Janus kinase, reducing signaling for immune response.	May impair wound healing and increase infection risk.	GVHD, polycythemia Vera, eczema, RA, UC, psoriasis	Hold 1 week before surgery.
Doxorubicin	Intercalates DNA, inhibiting topoisomerase II, and generates free radicals.	Delays wound healing, causes cell death, and may increase infection risk.	Breast cancer, lymphoma, sarcomas	Hold at least 1-2 weeks before surgery, resume after adequate wound healing.
Cisplatin	Crosslinks DNA, causing apoptosis in rapidly dividing cells.	Can impair wound healing and increase the risk of infection.	Testicular, ovarian, bladder, lung cancers	Hold 1 week before surgery, monitor renal function post-op.
5-Fluorouracil (5-FU)	Inhibits thymidylate synthase, leading to impaired DNA synthesis.	Delays wound healing, particularly when used continuously.	Colorectal, breast, head and neck cancers	Hold 1-2 weeks before surgery; timing depends on dose and schedule.
Paclitaxel (Taxol)	Stabilizes microtubules, preventing cell division.	May impair wound healing due to effects on cell division and blood vessels.	Breast, ovarian, lung cancers	Hold 1-2 weeks before surgery, resume post-op after assessing wound healing.
Docetaxel	Similar to paclitaxel; stabilizes microtubules and prevents cell division.	Impairs wound healing; risk of skin toxicity.	Breast, prostate, lung cancers	Hold 1-2 weeks before surgery, resume once stable post-op.

Abbreviations. DNA: deoxyribonucleic acid. GHVD: graft-versus-host disease.

Common microbiology and empiric antibiotic regimens

Most IAIs are polymicrobial, including Gram-negative rods (e.g. *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter*), Gram-positive organisms (e.g. *Enterococcus* species), and anaerobes (e.g. *Bacteroides* and *Clostridium* species). In addition, immunocompromised patients have the risk for opportunistic and nosocomial infections with MDROs and atypical organisms. These include *Pseudomonas aeruginosa*, *Acinetobacter, Staphylococcus aureus*, *Candida, Aspergillis* species. Other molds such as Mucorales can be seen with profound neutropenia, which is associated with 100% mortality for intra-abdominal infections. Although less common, parasitic infections such as those caused by *Cryptosporidium* and *Strongyloides* can lead to gastrointestinal and biliary tract infections in severely immunocompromised individuals.

Empiric broad-spectrum antibiotics are initiated based on the likely pathogens, local resistance patterns, and the patient's previous microbiological history. Recommended regimens include cefepime and metronidazole, imipenem-cilastatin, meropenem, or piperacillin-tazobactam in high-risk patients. Other options should be reserved for high-risk patients with a history of resistant organisms. Antibiotics should be continued for 4 days after source control or 8 days in critically ill patients. Empiric antifungal coverage with echinocandins is not recommended unless there is high suspicion or documentation of fungal infection. In addition to treating polymicrobial infections from gastrointestinal perforation or translocation, underlying infections such as cytomegalovirus (CMV), *Mycobacterium tuberculosis*, *Helicobacter pylori*, or fungal infections should also be treated.

Foregut: gastric and duodenal perforations

Duodenal and gastric perforations are surgical emergencies, especially in immunocompromised patients, who have a higher risk of complications and mortality due to their impaired immune response. Though not common, gastric and duodenal perforations in immunocompromised patients can be caused by infections (e.g. (*Cytomegalovirus*, tuberculosis, fungal), malignancy (lymphoma, adenocarcinoma), use of immunosuppressive medications (e.g. steroids), chemotherapy, radiation therapy, and underlying diseases along with typical causes such as peptic ulcer disease, *Helicobacter pylori* and non-steroidal anti-inflammatory (NSAID) use.

Classic symptoms of foregut perforation include acute onset abdominal pain, peritonitis, and signs of sepsis. A high index of suspicion is critical for early diagnosis and management of more vague presentations seen in immunocompromised patients.

Management

First, resuscitate patients with intravenous fluids (IVF), empiric broad-spectrum antibiotics, proton pump inhibitors, and pressors, if needed. In select cases of small, contained perforations, non-operative management might be considered. However, given the unpredictable course of some immunocompromised patients, surgery remains the mainstay treatment. A trial of non-operative management should have clear criteria for failure to avoid delays in definitive surgical care since mortality increases with each hour delay in operative management.

Surgical options include primary repair (with or without an omental patch), resection, or bypass procedures, depending on the perforation size, location, and patient condition. Resections in the acute setting have largely been abandoned. The choice of open *versus* laparoscopic surgery depends on resources, patient

condition, and surgeon experience. A jejunostomy distal to the perforation or intraoperative placement of a soft nasojejunal feeding tube should be considered. Patients on high-dose steroids or other drugs are at high risk of leak from a repair or anastomosis and may require distal enteral access for nutrition.
Postoperatively, many of these patients require monitoring in the ICU. Broad-spectrum antibiotics should be continued and narrowed if possible. There is no strong evidence for antifungal coverage in the general population. Evidence is limited in the immunocompromised population, though some available literature suggests that high-risk groups like solid organ transplantation may benefit from echinocandins. Early enteral nutrition should be started.
The overall mortality of perforated peptic ulcer disease is reported anywhere from 3-10% in the literature, 50-60% of which is accounted for by persistent septic shock and multi-organ failure. Immunocompromised patients are at a higher risk of complications and mortality due to their impaired immune response and often comorbid conditions. While studies specific to gastric or duodenal perforation in immunocompromised patients are lacking, studies looking at high-risk co-morbidities including liver disease, malignancy, steroid use, old age, and diabetes, which cause mild immunocompromise, report up to 66-72% morality in these groups and increased relative risk ratios of 1.5-3.2. Impaired wound healing can lead to dehiscence, fistula formation, or incisional hernias. Continued immunosuppression or untreated underlying infections may result in recurrent ulceration and potential re-perforation.

Biliary: acute cholecystitis, cholangitis, liver abscess

Acute cholecystitis is inflammation or infection of the gallbladder that is often caused by gallstones but can be caused by ischemia, infection, or other obstructive process. It is most common in patients with lung and heart transplants. It may present with right upper quadrant pain, fever, possible jaundice and leukocytosis. Immunocompromised patients may present at later stages of the disease and can exhibit hypotension, mental status changes, or sepsis as the first manifestations.
Cholangitis is an ascending infection of the bile ducts that is typically caused by obstruction from stones, strictures or malignancy, but can also be caused by opportunistic microbes. It can progress rapidly and be life-threatening, characterized by the triad of fever, jaundice, and right upper quadrant pain or the pentad including hypotension and altered mental status. Cholangitis in immunocompromised patients often progresses rapidly to septic shock.
A liver abscess is a purulent cavity in the liver caused by seeding from bacteremia, or less commonly from direct extension, parasites or fungi. There is more diversity in pathogens than is seen in immunocompetent individuals due to impaired immune response. Liver abscesses can present with fever, chills, abdominal pain, and hepatomegaly. Jaundice is less common. The presentation may be insidious, with vague symptoms such as fatigue and weight loss, which can delay diagnosis.
Right upper quadrant ultrasound can be diagnostic of acute cholecystitis, cholangitis and liver abscess. Cross-sectional imaging with computed tomography (CT) or magnetic resonance imaging (MRI) (e.g. Magnetic resonance cholangiopancreatography (MRCP)) can augment the diagnosis.

Management
Management of biliary infections in immunocompromised patients involves a combination of antimicrobial therapy, supportive care, and often, surgical, endoscopic, or radiologic intervention. IVF, broad-spectrum antibiotics, and hemodynamic support are critical, and these patients often require intensive care evaluation or admission.

Source control is crucial. For acute cholecystitis, cholecystectomy (often laparoscopic) is the treatment of choice and safe in many immunocompromised patients; however, in critically ill and high-risk patients, percutaneous cholecystostomy may be preferred for moderate or severe cholecystitis that does not improve with supportive care. For cholangitis, endoscopic retrograde cholangiopancreatography (ERCP) with biliary drainage can relieve obstruction. The cause of obstruction should then be addressed (laparoscopic cholecystectomy for choledocholithiasis, stenting for stricture, surgery for obstructing malignancy). Liver abscesses may require percutaneous drainage under imaging guidance or surgical drainage, depending on size, location, and response to initial therapy.
Uncontrolled infection and persistent sepsis may lead to acute kidney injury, respiratory failure, and disseminated intravascular coagulation (DIC). Additionally, recurrent episodes of cholangitis can lead to biliary strictures, chronic inflammation, and biliary cirrhosis. Mortality for cholecystitis overall in immunocompromised patients is reported up to 44%, however, the majority of causes of death were from the underlying conditions rather than cholecystitis. Overall post-op mortality for acute cholecystitis is 2%, however, it rises to 29% in the acute post-transplant period.

Small bowel

Small bowel perforation in immunocompromised can be caused by adhesive obstruction, inflammatory bowel disease complications, malignancy, hernia, tuberculosis, and typhoid fever. Prior surgery or inflammatory conditions can cause adhesions to form, which can cause obstruction and subsequent small bowel perforation or ischemia. Similarly, hernias (inguinal, ventral, internal) can cause obstruction or strangulation leading to ischemia and/or perforation. Immunocompromised patients are at higher risk of complications due to their blunted inflammatory response and often later presentation.
Infectious diseases such as typhoid and tuberculosis can also cause small bowel perforation. Typhoid fever is caused by *Salmonella typhi* and can lead to necrosis of Peyer's patches in the small intestine, resulting in perforation. It is most commonly seen in endemic areas and can pose a significant risk in immunocompromised individuals.
Gastrointestinal tuberculosis is one of the most common causes of intra-abdominal infections, especially in low-resource settings. It is caused by *Mycobacterium tuberculii* and leads to ulceration and perforation of the small bowel. The terminal ileum is the most common site, though TB can involve any intra-abdominal organ. Abdominal TB accounts for approximately 6% of TB cases in the US. The most common reasons for surgical intervention are perforation or obstruction. Abdominal TB has an 11% mortality rate in the US, somewhat lower than that reported globally of 13-52%.
Patients may present with abdominal pain, distension, nausea, vomiting, constipation or obstipation, peritonitis, rigidity and guarding. In patients with TB or malignant obstruction, acute symptoms might also be accompanied by distension, cachexia and weight loss. Intra-abdominal TB infection without perforation, however, has non-specific symptoms of fever, abdominal pain and weight loss. It can present as ascites, plastic (causing obstruction), glandular, or affect other structures and up to 85% of abdominal TB patients do not have pulmonary disease. Typhoid fever may present additionally with prolonged febrile illness, hepatosplenomegaly and rose spots rash before acute presentation with abdominal pain and signs of perforation
Abdominal X-ray can detect large-volume pneumoperitoneum and dilated bowel, however, cross-sectional imaging with CT is more sensitive. If there is suspicion of malignancy, a biopsy should be obtained. Infectious disease testing (HIV, TB, Typhoid) should be ordered for patients with clinical presentations or risk factors.

Management

Patients should be started on IVF, broad-spectrum antibiotics, bowel rest and have an NG tube placed. They should be closely monitored and evaluated by the ICU if unstable.

Again, in select patients with small, contained perforations, a trial of non-operative management with or without IR drainage can be considered with clear failure criteria. However, surgery is the most definite option for obtaining source control. Minimally invasive and open surgery are both appropriate depending on patient's condition, resources, and surgeon experience. A small perforation with healthy-appearing edges can be closed transversely, however, the majority of small bowel perforations require resection and anastomosis. In a patient with distal perforation and very poor tissue quality an end ileostomy can be considered. Additionally, in a hemodynamically unstable patient, a damage control operation with a planned second look can be a safe option.

In patients with malignant obstruction, the decision to operate depends on the patient's overall condition, cancer stage, and prognosis. Options include surgical resection, palliative stenting, or bypass surgery.

Any underlying infection should be treated in addition to management of the perforation. Treatment of intestinal TB involves a combination of antitubercular therapy for a minimum of six months, as well as management of co-existing HIV or other immunocompromising conditions. Typhoid fever is treated with antibiotics (e.g. ceftriaxone, azithromycin, or fluoroquinolones) and similarly only managed with surgery and bowel resection in the setting of perforation.

Complications of small bowel perforation include abscess, anastomotic leak, fistula, stricture, malnutrition, bacteremia, multi-organ failure, and poor wound healing. Immunocompromised patients are at higher risk of complications.

Appendicitis

The etiology and incidence of appendicitis in immunocompromised patients mirror the general population, involving obstruction of the appendiceal lumen, bacterial overgrowth and infection. It represents about 5% of intra-abdominal infections among the immunocompromised. Classic symptoms include right lower quadrant pain, nausea, vomiting, and fever, though in the immunocompromised these can be vague or absent. Ultrasound can be used to assess and is low-risk and inexpensive, but CT remains the most sensitive diagnostic tool for detecting appendicitis, especially in immunocompromised patients.

Management

Initially, patients should be NPO and started on broad-spectrum antibiotics. Surgery remains the definitive treatment given the high risk of recurrence, subtle symptoms, and increased risk of morbidity. Non-operative management is appropriate in patients who cannot tolerate surgery or in whom operative risk might be significantly reduced by waiting (e.g. neutrophil counts recover). One systematic review found that non-operative strategies are successful in approximately 57% of patients and so can be considered. However, given the failure rate of approximately 43%, upfront laparoscopic appendectomy should be offered to those who would tolerate the procedure to prevent future complications, especially if they have obstructive or complicated appendicitis. In uncomplicated appendicitis, no further antibiotics are needed. They are continued in patients with perforation or abscess.

Complications in immunocompromised patients include perforation, abscess formation, generalized peritonitis, sepsis, and postoperative wound infections. The risk of complications is higher due to delayed diagnosis and a more severe course of illness. However, patients often do quite well with surgery.

Colon: colitis

Colitis is the most common intra-abdominal infection in immunocompromised patients. Neutropenic, CMV and *Clostridioides difficile* (CDI) colitis can range from mild to severe and cause sepsis by bacterial translocation or perforation. All types of colitis present with nonspecific gastrointestinal symptoms such as diarrhea, abdominal pain, rectal bleeding, and fever. In severe cases, patients may develop colonic ulcers, which can lead to perforation.

Neutropenic colitis is associated with profound neutropenia and causes sepsis by translocation of bowel flora across a damaged mucosal barrier. Typically, patients present with neutropenia, fever, bowel wall thickening (on US or CT), diarrhea, and/or abdominal pain. In severe cases, patients may present with signs of septic shock and peritonitis. Neutropenic colitis can occur in up to 7% of neutropenic patients and accounts for 7% of cancer-related ICU admissions. Neutropenia occurs 2-3 weeks after initiation of chemotherapy. Neutropenia can also occur in patients with leukemia and following bone marrow transplant. The exact mechanism is not well understood but is thought to be the combination of mucosal injury and severe neutropenia. This leads to mucosal edema and susceptibility to bacterial intramural invasion.

CMV colitis is caused by cytomegalovirus (CMV) and occurs when the virus reactivates, often in the context of severe immunosuppression, such as HIV/AIDS, organ transplantation, or chemotherapy. The virus directly invades the colonic mucosa, causing vasculitis, ischemia, ulceration, inflammation, and bowel wall necrosis which can lead to translocation of bacteria. CMV colitis may be accompanied by weight loss, colonic ulcers, and disseminated disease in severely immunocompromised patients, though typically the symptoms are non-specific CMV diagnosis is made by immunohistochemistry on biopsy. Endoscopy shows ulcerations with a well-defined, punched-out appearance in 80% of patients. CT scan is typically non-specific with bowel wall thickening, however, small bowel wall thickening may be present and is specific to CMV colitis.

CDI can result in similar colonic mucosal inflammation and translocation of bacteria from the toxin produced by *Clostridium difficile*. Immunocompromised patients are at increased risk due to frequent antibiotic exposure, which disrupts normal gut flora, facilitating *C. difficile* colonization. *C. difficile* infection is typically preceded by exposure to high-risk antibiotics like antipseudomonal penicillin, fourth-generation cephalosporin, carbapenems, fluoroquinolones and clindamycin. CT shows colon wall thickening, typically pan colonic. More severe cases may present with pseudomembranous colitis, characterized by marked abdominal pain, distention, and systemic toxicity.

Management

CMV colitis is treated with ganciclovir or valganciclovir for 2-3 weeks. Intravenous ganciclovir is preferred for severe cases. In addition, supportive care, including fluid management and nutritional support, is essential. If colonic perforation or massive bleeding occurs, surgical intervention may be required. When required, there is some debate over total colectomy *versus* partial colectomy of clinically involved segments. In the severely ill immunocompromised patients with CMV colitis mortality is reported up to 70%.

Neutropenic colitis management includes bowel rest, broad-spectrum antibiotics, and supportive care. Granulocyte colony-stimulating factor (G-CSF) may be administered to reduce the duration of neutropenia. Of those without bowel wall thickening, 100% were recovered in 4 days. Of those with bowel wall thickening, up to 70% are recovered in 8 days. Bowel wall thickening > 10 mm was associated with higher mortality (60% compared to 4%). Surgery is reserved for cases with perforation, necrosis, or persistent bleeding given the increased risk of mortality with surgery. Neutropenic enterocolitis requiring emergency surgery had a mortality of 22% for patients not on chemotherapy within the prior 30 days. This rises to 44% in patients with recent chemotherapy.

CDI management includes discontinuation of the inciting antibiotic, if possible, and starting specific therapy. Oral fidaxomicin is preferred. In severe cases, combination therapy with intravenous metronidazole and oral vancomycin may be needed. Surgery is reserved for patients with toxic megacolon and the operation indicated is subtotal colectomy, though there has been some success with diverting loop ileostomy and colon antibiotic lavage as an alternative. Mortality rates in CDI patients who require surgery are reported up to 35%.

Colon: acute diverticulitis

Acute diverticulitis is a common gastrointestinal condition characterized by inflammation of the diverticula, which are small pouches in the wall of the colon. It is more common in the immunocompromised population and the most common intra-abdominal infection in liver and kidney transplant patients. Transplanted patients are up to 22x more likely to have complicated acute diverticulitis than the general population.
Typical symptoms, when present, include left lower quadrant abdominal pain, fever, constipation or diarrhea and nausea. Atypical symptoms include generalized abdominal pain and confusion. Immunocompromised patients were found to have more frequently diffuse peritonitis as compared to immune-competent patients who had more localized peritonitis. The blunted immune response and subtle symptoms often lead to immunocompromised patients presenting with complicated diseases, such as abscess, perforation, or fistula.

Management
If caught early, the mainstay of management is bowel rest and broad-spectrum antibiotics. In cases where resistant organisms or fungi are suspected, broader coverage or antifungal agents may be required. For patients with abscesses, percutaneous drainage can provide adequate source control until the patient can be recovered and optimized for surgery. However, there should be a low threshold for surgical intervention if unstable or they do not improve with nonoperative management. If urgent surgery is necessary, options include laparoscopic or open sigmoidectomy with end colostomy or primary anastomosis with or without a diverting loop ileostomy. Given their high risk of morbidity and mortality, if the decision is made to do an anastomosis, it is favored to divert with a loop ileostomy. Also, for this reason, immunocompromised patients are more likely to undergo surgery, have open surgery, and have a Hartmann's (65-70% *vs.* 37-42%).
Diverticulitis in immunocompromised patients has higher morbidity and mortality. In patients with complicated diverticulitis requiring emergency surgery, mortality was reported as 23-29% compared to 1-6% for the general population. Immunocompromised patients also had higher rates of surgical management of 40% compared to 15-29% in the general population. They also had a higher risk of complications (51-67% *vs.* 22-24%), and need for ICU stay (22% *vs.* 10%), than immunocompetent patients. Complications include abscess formation, perforation, fistula, sepsis, major organ failure, and recurrent diverticulitis. Neutropenic patients who recover their counts following chemotherapy can have a delayed sepsis response and become quite sick as they recover their counts.

Conclusion

Immunocompromised patients with intra-abdominal infections are a challenging population to manage because of the heterogeneity of the immunocompromised populations and the varying presentation of

infections. Key takeaways are the following: 1) have a high index of suspicion for intra-abdominal infection despite vague symptoms, normal exam and normal labs- strongly consider cross-sectional imaging; 2) cover broadly with empiric antibiotics and when appropriate, antifungals or antivirals; 3) though non-operative strategies can be successful and these patients often have higher surgical risks, surgery can be safely done and is often the most definitive management- patients undergoing a non-operative trial should have close observation and clear failure criteria to avoid unnecessary delays to the operating room when indicated.

Competing interests

The authors have no financial and non-financial competing interests to declare for this work product. Other disclosures: JDF-unrestricted research funding from Varian and Pacira for an investigator-initiated trial, and funding from Eclipse Regenysis for an industry-sponsored clinical trial.

References

1. Coccolini F, et al. Acute abdomen in the immunocompromised patient: WSES, SIS-E, WSIS, AAST, and GAIS guidelines. World J Emerg Surg. 2021;16:40.
2. Maseda E, et al. Critically ill patients with community-onset intraabdominal infections: Influence of healthcare exposure on resistance rates and mortality. PLoS One. 2019;14:e0223092.
3. Cao S, et al. Infection with Two Multi-Drug-Resistant Organisms in Solid Organ Transplant Patients Is Associated with Increased Mortality and Prolonged Hospitalization. Surg Infect (Larchmt). 2022;23:394-399
4. Scott-Conner CE, et al. Gastrointestinal problems in the immunocompromised host. A review for surgeons. Surg Endosc. 1996;10:959-964.
5. Bhagwanjee S, et al. Does HIV status influence the outcome of patients admitted to a surgical intensive care unit? A prospective double blind study. BMJ. 1997;314:1077-1081;discussion 1081-1084.
6. Green S, et al. The effect of HIV status on clinical outcomes of surgical sepsis in KwaZulu-Natal Province, South Africa. S Afr Med J. 2017;107:702-705.
7. Rodriguez-Abreu D, et al. Epidemiology of hematological malignancies. Ann Oncol. 2007;18 Suppl 1:i3-i8.
8. Ilgen JS, et al. Cancer emergencies: the acute abdomen. Emerg Med Clin North Am. 2009;27:381-399.
9. Caronna R, et al. Gastrointestinal surgical emergencies in patients treated for hemathological malignancies. Suppl Tumori. 2005;4:S141-S145.
10. Gallaher CE, et al. Management of Multidrug-Resistant Infections in Cirrhosis. Semin Liver Dis. 2022;42:173-187.
11. Joshi N, et al. Infections in patients with diabetes mellitus. N Engl J Med. 1999;341:1906-1912.
12. Demling RH. Nutrition, anabolism, and the wound healing process: an overview. Eplasty. 2009;9:e9.
13. Cunningham-Rundles S, et al. Nutrition and the immune system of the gut. Nutrition. 1998;14:573-579.
14. Primary and Secondary Immunodeficiency. (n.d.). Available at: https://link-springer-com.laneproxy.stanford.edu/book/10.1007/978-3-030-57157-3. Last accessed: 18 September 2024.
15. Sindt JE, et al. Antiplatelet and Wound Healing Implications of Immunotherapy and Targeted Cancer Therapies in the Perioperative Period. Anesthesiology. 2023;139:511-522.
16. Home - UpToDate® Lexidrug™. (n.d.). Available at: http://online.lexi.com.laneproxy.stanford.edu/lco/action/home. Last accessed: 19 September 2024.
17. Rezaieyazdi Z, et al. Preoperative Evaluation and Management of Patients Receiving Biologic Therapies. Arch Bone Jt Surg. 2019;7:220-228.
18. Mellor JD, et al. Clinical guidance on the perioperative use of targeted agents in solid tumor oncology. Asia Pac J Clin Oncol. 2011;7:106-113.

19. Boyce M, et al. Practical Guidance in Perioperative Management of Immunosuppressive Therapy for Rheumatology Patients Undergoing Elective Surgery. Can J Hosp Pharm. 2020;73:218-224.
20. Lanas A, et al. Peptic ulcer disease. Lancet. 2017;390:613-624.
21. Ogawa L, et al. Risk Factors and Outcomes of Mucorales Infection in a Modern Cohort of Solid Organ Transplant, Hematopoietic Cell Transplant, and Chimeric Antigen Receptor T-cell Therapy Recipients. Transplant Proc. 2024;56:1683-1690.
22. Alam AM, et al. Strongyloides stercoralis infection in the UK: A systematic review and meta-analysis of published cases. Clin Med (Lond). 2024;24:100227.
23. Huston JM, et al. The Surgical Infection Society Guidelines on the Management of Intra-Abdominal Infection: 2024 Update. Surg Infect (Larchmt). 2024;25:419-435.
24. Murray JG, et al. Cytomegalovirus colitis in AIDS: CT features. AJR Am J Roentgenol. 1995;165:67-71.
25. Freeman HJ. Spontaneous free perforation of the small intestine in adults. World J Gastroenterol. 2014;20:9990-7.
26. Karasuno T, et al. Invasive candidiasis leading to gastric perforation in an immunocompromised patient. IDCases. 2019;18:e00627.
27. Kwok M, et al. Gastrointestinal mucormycosis in an immunocompromised host. ANZ J Surg. 2019;89:E26-E27.
28. Wang A, et al. Surgical management of peptic ulcer disease. Curr Probl Surg. 2020;57:100728.
29. Søreide K, et al. Perforated peptic ulcer. Lancet. 2015;386:1288-1298.
30. Horn CB, et al. Pre-Operative Anti-Fungal Therapy Does Not Improve Outcomes in Perforated Peptic Ulcers. Surg Infect (Larchmt). 2018;19:587-592.
31. Li WS, et al. Antifungal therapy did not improve outcomes including 30-day all-cause mortality in patients suffering community-acquired perforated peptic ulcer-associated peritonitis with Candida species isolated from their peritoneal fluid. J Microbiol Immunol Infect. 2017;50:370-376.
32. Berg DM, et al. Current Utilization of Antifungal Agents for Intra-abdominal Infections Categorized by Patient Risk Factors During Surgical Procedures: A Literature Review. J Pharm Pract. 2023;36:1232-1243.
33. Imhof M, et al. Duration of survival after peptic ulcer perforation. World J Surg. 2008;32:408-412.
34. George J, et al. Biliary Disease in Immunocompromised Patients: a Single-Center Retrospective Analysis. J Gastrointest Surg. 2019;23:1589-1592.
35. Okamoto K, et al. Tokyo Guidelines 2018: flowchart for the management of acute cholecystitis. J Hepatobiliary Pancreat Sci. 2018;25:55-72.
36. White MG, et al. Gastrointestinal Surgical Emergencies in the Neutropenic Immunocompromised Patient. J Gastrointest Surg. 2021;25:3258-3264.
37. Gupta D, et al. Management of biliary tract disease in heart and lung transplant patients. Surgery. 2000;128:641–649.
38. Kilic A, et al. Outcomes of cholecystectomy in US heart transplant recipients. Ann Surg. 2013;258:312-317.
39. Forrester JD, et al. Mortality After General Surgery Among Hospitalized Patients With Hematologic Malignancy. J Surg Res. 2020;256:502-511.
40. Sharma MP, et al. Abdominal tuberculosis. Indian J Med Res. 2004;120:305-315.
41. Aston NO. Abdominal tuberculosis. World J Surg. 1997;21:492-499.
42. Stewart CL, et al. Cholecystectomy in patients with hematologic malignancies. Am J Surg. 2022;223:1157-1161.
43. Aguado JM, et al. Tuberculous peritonitis: a study comparing cirrhotic and noncirrhotic patients. J Clin Gastroenterol. 1990;12:550-554.
44. Tonolini M, et al. Acute HIV-related gastrointestinal disorders and complications in the antiretroviral era: spectrum of cross-sectional imaging findings. Abdom Imaging. 2013;38:994-1004.
45. Hughes H, et al. Bowel Emergencies in Patients With Cancer. Can Assoc Radiol J. 2024:8465371241252035.
46. Kasprzycki T, et al. Appendicitis in the Neutropenic Patient: A Systematic Review. Am Surg. 2024:31348241265136.
47. Jamtani I, et al. Acute appendicitis after liver transplantation: A single center experience and review of the literature. Ann Hepatobiliary Pancreat Surg. 2020;24:44-51.

48. Cartoni C, et al. Neutropenic enterocolitis in patients with acute leukemia: prognostic significance of bowel wall thickening detected by ultrasonography. J Clin Oncol. 2001;19:756-761.
49. Gorschlüter M, et al. Abdominal infections in patients with acute leukaemia: a prospective study applying ultrasonography and microbiology. Br J Haematol. 2002;117:351-358.
50. Gorschlüter M, et al. Neutropenic enterocolitis in adults: systematic analysis of evidence quality. Eur J Haematol. 2005;75:1-13.
51. Yucel N, et al. Characteristics of the admissions of cancer patients to emergency department. J BUON. 2012;17:174-179.
52. Soares M, et al. Characteristics and outcomes of patients with cancer requiring admission to intensive care units: a prospective multicenter study. Crit Care Med. 2010;38:9-15.
53. Hohenberger P, et al. Surgical interventions in patients with hematologic malignancies. Crit Rev Oncol Hematol. 2005;55:83-91.
54. Rodrigues FG, et al. Neutropenic enterocolitis. World J Gastroenterol. 2017;23:42-47.
55. Yerushalmy-Feler A, et al. Diagnosis and Management of CMV Colitis. Curr Infect Dis Rep. 2019;21:5.
56. Ko JH, et al. Clinical presentation and risk factors for cytomegalovirus colitis in immunocompetent adult patients. Clin Infect Dis. 2015;60:e20-e26.
57. Bernard S, et al. Symptomatic cytomegalovirus gastrointestinal infection with positive quantitative real-time PCR findings in apparently immunocompetent patients: a case series. Clin Microbiol Infect. 2015;21:1121.e1-7.
58. McCoy MH, et al. qPCR is a sensitive and rapid method for detection of cytomegaloviral DNA in formalin-fixed, paraffin-embedded biopsy tissue. J Vis Exp. 2014;89:51570.
59. Juric-Sekhar G, et al. Cytomegalovirus (CMV) in gastrointestinal mucosal biopsies: should a pathologist perform CMV immunohistochemistry if the clinician requests it? Hum Pathol. 2017;60:11-15.
60. Hirayama Y, et al. Characteristic endoscopic findings and risk factors for cytomegalovirus-associated colitis in patients with active ulcerative colitis. World J Gastrointest Endosc. 2016;8:301-309.
61. Alonso CD, et al. Epidemiology and outcomes of Clostridium difficile infections in hematopoietic stem cell transplant recipients. Clin Infect Dis. 2012;54:1053-1063.
62. Alonso CD, et al. A multicenter, retrospective, case-cohort study of the epidemiology and risk factors for Clostridium difficile infection among cord blood transplant recipients. Transpl Infect Dis. 2017;19.
63. Johnson S, et al. Clinical Practice Guideline by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA): 2021 Focused Update Guidelines on Management of Clostridioides difficile Infection in Adults. Clin Infect Dis. 2021;73:e1029-e1044.
64. Fishman EK, et al. Pseudomembranous colitis: CT evaluation of 26 cases. Radiology. 1991;180:57-60.
65. Sailhamer EA, et al. Fulminant Clostridium difficile colitis: patterns of care and predictors of mortality. Arch Surg. 2009;144:433-439;discussion 439-40.
66. Davila ML. Neutropenic enterocolitis: current issues in diagnosis and management. Curr Infect Dis Rep. 2007;9:116-120.
67. Ferrada P, et al. Timing and type of surgical treatment of Clostridium difficile-associated disease: a practice management guideline from the Eastern Association for the Surgery of Trauma. J Trauma Acute Care Surg. 2014;76:1484-1493.
68. Neal MD, et al. Diverting loop ileostomy and colonic lavage: an alternative to total abdominal colectomy for the treatment of severe, complicated Clostridium difficile associated disease. Ann Surg. 2011;254:423-427;discussion 427-429.
69. Olivas AD, et al. Avoiding colectomy during surgical management of fulminant Clostridium difficile colitis. Surg Infect. 2010;11:299–305.
70. Tartaglia D, et al. Acute diverticulitis in immunocompromised patients: evidence from an international multicenter observational registry (Web-based International Register of Emergency Surgery and Trauma, Wires-T). Tech Coloproctol. 2023;27:747-757.
71. Hwang SS, et al. Diverticulitis in transplant patients and patients on chronic corticosteroid therapy: a systematic review. Dis Colon Rectum. 2010;53:1699-707.

72. Larson ES, et al. Diverticulitis occurs early after lung transplantation. J Surg Res. 2014;190:667-671.
73. Biondo S, et al. Outcomes of colonic diverticulitis according to the reason of immunosuppression. Am J Surg. 2016;212:384-390.
74. Etzioni DA, et al. Diverticulitis in the United States: 1998-2005: changing patterns of disease and treatment. Ann Surg. 2009;249:210-217.
75. Reshef A, et al. Case-matched comparison of perioperative outcomes after surgical treatment of sigmoid diverticulitis in solid organ transplant recipients versus immunocompetent patients. Colorectal Dis. 2012;14:1546-1552.
76. Salem L, et al. Hartmann's colectomy and reversal in diverticulitis: a population-level assessment. Dis Colon Rectum. 2005;48:988-995.
77. Tyau ES, et al. Acute diverticulitis. A complicated problem in the immunocompromised patient. Arch Surg. 1991;126:855-858;discussion 858-859.
78. Chandra V, et al. Impact of primary resection on the outcome of patients with perforated diverticulitis. Arch Surg. 2004;139:1221-1224.
79. Lambrichts DPV, et al. Hartmann's procedure versus sigmoidectomy with primary anastomosis for perforated diverticulitis with purulent or faecal peritonitis (LADIES): a multicentre, parallel-group, randomised, open-label, superiority trial. Lancet Gastroenterol Hepatol. 2019;4:599-610.
80. Sartelli M, et al. 2020 update of the WSES guidelines for the management of acute colonic diverticulitis in the emergency setting. World J Emerg Surg. 2020;15:32.
81. Coccolini F, et al. Colonic perforation after renal transplantation: risk factor analysis. Transplant Proc. 2009;41:1189-1190.
82. Khan S, et al. Acute diverticulitis in heart- and lung transplant patients. Transpl Int. 2001;14:12-15.
83. Oor JE, et al. A systematic review of complicated diverticulitis in post-transplant patients. J Gastrointest Surg. 2014;18:2038-2046.
84. Paiva JA, et al. Intra-abdominal infection and sepsis in immunocompromised intensive care unit patients: Disease expression, microbial aetiology, and clinical outcomes. Eur J Intern Med. 2024:S0953-6205(24)00313-3.

Chapter 130

Timing and type of surgical treatment of *Clostridioides difficile* infections

Asanthi M. Ratnasekera
Department of Surgery, Division of Trauma and Surgical Critical Care, Drexel College of Medicine, Philadelphia PA, Christianacare Health, Newark DE, USA.

Paula Ferrada
Department of Surgery, Division and System Chief of Trauma and Acute Care Surgery Professor, University of Virginia, INOVA Fairfax Health System, Fairfax VA, USA.

Introduction

Fulminant colitis (FC) represents a severe and life-threatening complication of *Clostridioides difficile*-associated disease (CDAD). CDAD is the most common nosocomial diarrhea and affects up to 8% of all hospitalized patients. Progression of CDAD to FC occurs in approximately 1-3% of all cases and carries a high risk of mortality. It is characterized by rapid progression to systemic toxicity, often necessitating urgent medical and surgical intervention. Associated mortality in FC has been cited to range from 34-80%. Further, epidemiologic studies have demonstrated that CDAD is not only nosocomial in nature but may also originate from long-term care facilities and the community. In recent years, there has been a growing recognition of the clinical significance of FC and the need for timely and appropriate management strategies to improve patient outcomes. This essay aims to provide a comprehensive review of the literature on FC in patients with CDAD, focusing on clinical predictors, surgical interventions, and medical treatments. By synthesizing the available evidence, this essay aims to offer recommendations for clinical practice and highlight areas for future research.

Summary of the literature

A critical aspect of managing FC is the early identification of patients at risk of developing this severe form of colitis. Increased incidence, severity and mortality may be associated with new strains, antibiotic resistance, immunosuppression, and a rise in the elderly population with comorbid conditions. FC is defined as the presence of systemic inflammatory response with the presence of two or more of the following: temperature >38°C or <36°C, heart rate >90 beats/min, respiratory rate >20 breaths/min, or $PaCO_2$ lower than 32 mmHg, white blood cells >12,000 µL or lower than 4000/µL, or 10% band cells, hypotension, need for volume resuscitation or requirement of vasopressors in the setting of documented CDAD by stool toxin assay. Girotra *et al.* conducted a retrospective review comparing FC patients who underwent colectomy with non-fulminant CDAD patients. Their findings identified several clinical and laboratory predictors for the development of FC, including advanced age, prior CDAD, leukocytosis, hemodynamic instability, and the use of anti-peristaltic

medications such as anticholinergics and narcotic agents. Additionally, a change in mental status was highlighted as a potential indicator of significant toxemia. The authors also emphasized that a triad of presenting clinical symptoms with diarrhea, abdominal pain and distension were common amongst patients with FC. Further, the authors demonstrated that lack of or the resolution of diarrhea did not rule out FC. In fact, the resolution of diarrhea or the development of ileus may be an ominous sign of impending clinical deterioration.

Halabi *et al.* demonstrated in their 10-year retrospective study of the Nationwide Inpatient Sample that the period between 2006 to 2010 witnessed a 47% increase in the rate of CDAD. The authors further identified risk factors for mortality after colectomy which included coagulopathy (OR 2.38), age greater than 60 years (OR 1.97), acute renal failure (OR 1.67), respiratory failure (OR 1.61), sepsis (OR 1.40), peripheral vascular disease (OR 1.39), and congestive heart failure (OR 1.25). Lee *et al.* identified similar risk factors in a review of the American College of Surgeons Trauma Quality Improvement Program database. Those aged 80 years or older had an associated ninefold increase in the odds of mortality (95% confidence interval [CI]: 3.0-13.0). Other factors associated with increased mortality were preoperative shock (OR 2.8, 95% CI: 1.6-5.4), preoperative dialysis dependence (OR 2.3, 95% CI: 1.1-4.8), chronic obstructive pulmonary disease (OR 3.7, 95% CI: 2.0-7.1), wound class III (OR 2.1, 95% CI: 3.0-13), thrombocytopenia, coagulopathy, and renal insufficiency. Other studies have also identified advanced age, preoperative comorbidities and complications such as COPD, respiratory failure, renal failure, coagulopathy, and other organ dysfunctions to be predictors of mortality.

Early surgical consultation is recommended for patients with severe CDAD who progress to systemic toxicity. Delaying surgery in this patient population can lead to increased mortality rates, emphasizing the importance of timely intervention. Ferrada *et al.* emphasized the role of early surgery before the development of shock, recommending surgical intervention within 3 to 5 days of diagnosis for patients who are not clinically improving with medical therapy. Risk scoring systems have been developed to stratify patients based on their likelihood of developing FC, with age, white blood cell count, cardiorespiratory failure, and abdominal tenderness identified as high-risk factors. Multidisciplinary and collaborative management of FC is imperative to prevent mortality. Surgical intervention after the development of systemic toxicity and end-organ failure significantly increases the risk of mortality. Therefore, early recognition of signs of shock, systemic toxicity, and end-organ failure would decrease the risk of mortality in this critical population.

Medical management

Per the Infectious Disease Society of America (IDSA) guidelines, the medical treatment of choice for FC is oral vancomycin 500 mg four times per day. If an ileus is present, rectal vancomycin 500 mg in 100 cc of saline administered as a retention enema 4 times per day is preferred. The IDSA further recommends intravenous metronidazole be administered along with oral or rectal vancomycin, especially if an ileus is present.

Surgical management

The standard of care for the surgical management of FC remains a total or subtotal colectomy, offering better outcomes compared to partial colectomy. Loop ileostomy with lavage is an alternative approach that preserves the colon and has been associated with reduced mortality rates. The choice of surgical intervention depends on various factors, including the patient's clinical status, comorbidities, and surgical risk.

Ideally, patients who have FC should be identified for surgical management before end-organ failure and the development of signs of shock. Ali *et al.* demonstrated that survivors had earlier surgical interventions as compared to non-survivors (mean 3.2 *vs.* 5.4 days). Similarly, Sailhamer *et al.* demonstrated survivors had earlier surgical intervention as compared to non-survivors (1.9 *vs.* 3.9 days). Halabi *et al.* further demonstrated that delaying surgical intervention more than 3 days after admission was associated with higher mortality (OR 1.09; 95% CI 1.05 to 1.14; $p<0.05$).

In FC, performing a total or subtotal colectomy preserving the rectum is an emergent procedure. Although earlier surgical intervention is supported, most commonly these patients are already compromised due to systemic toxicity. This patient population is critically ill and is expected to have various physiologic derangements such as acidosis, coagulopathy, fluid shifts, and end-organ hypoperfusion requiring vasopressors and fluid resuscitation. These physiologic derangements may require a surgeon to perform the most abbreviated and complete operation, ensuring the entire colon is removed to avoid any further physiologic decompensation. A damage control technique may need to be utilized by performing a total or subtotal colectomy without abdominal closure and a re-exploration when physiologic derangements are reversed. Risks of complications such as abdominal compartment syndrome, acute respiratory distress syndrome and others related to fluid shifts and systemic inflammatory response may occur. While this technique guarantees complete removal of the source, it lends to significant blood loss which may worsen physiologic derangements.

Alternatively, a diverting loop ileostomy has been described. A study performed on 42 patients by Neal *et al.* demonstrated that creating a diverting loop ileostomy with access to the colon for antibiotic lavage may reduce morbidity and preserve the colon. In a multicenter study, Ferrada *et al.* demonstrated a significant decrease in adjusted mortality (controlled for preprocedural confounders) in the group who received a diverting loop ileostomy (17.2% *vs.* 39.7%; $p=0.002$). This procedure also lends to an abbreviated surgical time and decreases blood loss and transfusion requirements. However, it does not guarantee complete elimination of the source. The risk of this operation remains the need for reoperation in the event of decompensation or worsening end organ failure. Ferrada *et al.* demonstrated that there was a higher absolute reoperation rate and unplanned operation rate in the diverting loop ileostomy group with a 23% relative increase in adjusted mortality. However, in their study group, there were no patients in the diverting loop ileostomy group who required an unplanned operation and died. If performing a diverting loop ileostomy, the patient must receive antegrade vancomycin flushes through the ileostomy. A structured protocol must be followed to ensure the appropriate dose and timing of vancomycin is delivered. Patients must be closely monitored for signs of decompensation or worsening end-organ dysfunction, at which point the patient should have a total or subtotal colectomy. An Eastern Association for the Surgery of Trauma practice management guideline strongly recommended early surgical intervention and conditionally recommended a total or subtotal colectomy in patients undergoing surgery.

In evaluating patients with FC, the surgeon must evaluate patient comorbidities, admission risk factors, physiologic derangements and organ dysfunction in the decision for the initial technique. The decision for surgical management must occur prior to the end-organ dysfunction to reduce the risk of mortality. A multidisciplinary approach to the management and identification of risk factors is essential for these patients.

The technical aspects of surgical intervention

Subtotal or total colectomy

Frequent communication with anesthesia ensuring the availability of antibiotics, fluids, vasopressors, blood and blood products is essential. The patient should be placed supine with bilateral arms extended out. A

midline laparotomy incision is carried out. The small bowel should be packed away to the left upper quadrant. It is important to note, that pseudomembranous colitis is a mucosal disease, therefore the colon may appear distended and large but may also appear to have “healthy” outer layers. The right colon is mobilized along the White Line of Toldt up to the hepatic flexure. The posterior attachments are incised and the duodenum is maintained in its retroperitoneal position. The omentum is divided above its attachment to the transverse colon. The small bowel is reduced from the left upper quadrant and the peritoneum along the White Line of Toldt on the left paracolic gutter is incised from the splenic flexure down to the sigmoid colon. It is important to take care not to perforate the colon during mobilization. The posterior attachments of the left colon are incised from the retroperitoneal tissue. The ureters on both sides are identified and maintained in their retroperitoneal location. The terminal ileum close to the ileocecal valve is divided. Using mechanical suture ligature or a vessel sealing device, the entire mesentery of the colon is divided including the ileocolic branch, right colic, middle colic, two branches of the left colic and the sigmoidal vessels. Care must be taken to avoid significant blood loss during this step to avoid further progression of clinical decompensation. The rectosigmoid is transected using a thoracoabdominal stapler. An end ileostomy is matured in the right mid to lower quadrant ensuring appropriate placement. The decision to close the abdomen should be based on the patient’s physiologic derangements.

Loop ileostomy

The patient is placed supine with bilateral arms extended. A midline laparotomy incision is created. The distal ileum is identified. The proximal ileum can be marked with a suture. A trephine in the right mid or lower quadrant is created. A cruciate incision is made in the anterior and posterior rectus sheath. The orifice is stretched to accompany two fingers. A Babcock clamp is placed through the trephine and the distal ileum is brought out through the abdominal wall. The proximal limb is arranged cephalad. The distal portion of the ileum is partially transected and everted so that the proximal stoma is larger than the distal stoma to facilitate complete fecal diversion. The loop ileostomy is matured using 3-0 or 4-0 interrupted sutures from the ileum (full thickness) to the subcuticular skin. A red rubber catheter can be passed through the mesentery to maintain the position of the ileostomy.

Future research

A randomized clinical trial to assess patients who had diverting loop ileostomy and total colectomy was initiated, however, was not completed due to a lack of patient recruitment (ClinicalTrials.gov Identifier: NCT01441271.) Further studies in identifying patient characteristics who would benefit from a total abdominal colectomy and diverting loop ileostomy is required to aid the clinician in making decisions in patient selection. Studies on long-term outcomes of patients who underwent total colectomy or diverting loop ileostomy are lacking. Questions regarding the timing of ileostomy reversal and recurrent risk of CDAD further need investigation.

Conclusion and recommendations

In conclusion, FC represents a significant clinical challenge in patients with CDAD, necessitating prompt recognition and appropriate management strategies. Early surgical consultation is essential for patients who

progress to systemic toxicity, with total or subtotal colectomy or loop ileostomy recommended based on individual patient characteristics. High-dose vancomycin combined with intravenous metronidazole is the preferred medical treatment for FC. However, further research is needed to refine risk stratification models and evaluate the long-term outcomes of surgical and medical interventions. By advancing our understanding of FC and optimizing treatment approaches, we can improve outcomes and reduce the morbidity and mortality associated with this severe complication of CDAD.

Competing interests

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

References

1. Seder CW, et al. Early colectomy may be associated with improved survival in fulminant Clostridium difficile colitis: an 8-year experience. Am J Surg. 2009;197:302-307.
2. Greenstein AJ, et al. Risk factors for the development of fulminant Clostridium difficile colitis. Surgery. 2008;143:623-629.
3. Garg S, et al. Epidemiology of Clostridium difficile-associated disease (CDAD): a shift from hospital-acquired infection to long-term care facility-based infection. Dig Dis Sci. 2013;58:3407-3412.
4. Byrn JC, et al. Predictors of mortality after colectomy for fulminant Clostridium difficile colitis. Arch Surg. 2008;143:150-154. discussion 155.
5. Wysowski DK. Increase in deaths related to enterocolitis due to Clostridium difficile in the United States, 1999-2002. Public Health Rep. 2006;121:361-362.
6. Girotra M, et al. Clinical predictors of fulminant colitis in patients with Clostridium difficile infection. Saudi J Gastroenterol. 2012;18:133-139.
7. Halabi WJ, et al. Clostridium difficile colitis in the United States: a decade of trends, outcomes, risk factors for colectomy, and mortality after colectomy. J Am Coll Surg. 2013;217:802-812.
8. Lee DY, et al. Predictors of mortality after emergency colectomy for Clostridium difficile colitis: an analysis of ACS-NSQIP. Ann Surg. 2014;259:148-156.
9. Sailhamer EA, et al. Fulminant Clostridium difficile colitis: patterns of care and predictors of mortality. Arch Surg. 2009;144:433-439.
10. Lamontagne F, et al. Impact of emergency colectomy on survival of patients with fulminant Clostridium difficile colitis during an epidemic caused by a hypervirulent strain. Ann Surg. 2007;245:267-272.
11. Abou Khalil M, et al. Development and validation of a clinical risk calculator for mortality after colectomy for fulminant Clostridium difficile colitis. J Trauma Acute Care Surg. 2019;87:856-864.
12. Ferrada P, et al. Loop ileostomy versus total colectomy as surgical treatment for Clostridium difficile-associated disease: An Eastern Association for the Surgery of Trauma multicenter trial. J Trauma Acute Care Surg. 2017;83:36-40.
13. McDonald LC, et al. Clinical Practice Guidelines for Clostridium difficile Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). Clin Infect Dis. 2018;66:e1-e48.
14. Lipsett PA, et al. Pseudomembranous colitis: a surgical disease? Surgery. 1994;116:491-496.
15. Ali SO, et al. Early surgical intervention for fulminant pseudomembranous colitis. Am Surg. 2008;74:20-26.
16. Neal MD, et al. Diverting loop ileostomy and colonic lavage: an alternative to total abdominal colectomy for the treatment of severe, complicated Clostridium difficile associated disease. Ann Surg. 2011;254:423-427.

17. Ferrada P, et al. Timing and type of surgical treatment of Clostridium difficile-associated disease: a practice management guideline from the Eastern Association for the Surgery of Trauma. J Trauma Acute Care Surg. 2014;76:1484-1493.

Chapter 131

Abdominal tuberculosis. Diagnosis and management

Sanjay Marwah
Department of Surgery, Post-graduate Institute of Medical Sciences, Rohtak, India.

Ritesh Kumar
Department of Surgery, Post-graduate Institute of Medical Sciences, Rohtak, India.

Mahavir Jangra
Department of Surgery, Post-graduate Institute of Medical Sciences, Rohtak, India.

Introduction

Almost a quarter of the world population is infected with tuberculosis causing annual mortality of about 3 million people. Its incidence is rising in developed countries as well due to the emergence of multidrug resistance, global migration and the AIDS pandemic. Pulmonary tuberculosis is the commonest manifestation whereas abdominal tuberculosis is the sixth most common site of extra-pulmonary involvement. The diagnosis of abdominal tuberculosis remains difficult due to its insidious course, non-specific symptoms and low yield of investigations. It further mimics a variety of abdominal conditions such as Crohn's disease, GI malignancies and infections causing delay in the diagnosis leading to morbidity and mortality. Hence high index of suspicion is required, especially in endemic regions and in immunocompromised patients, for its timely diagnosis and management. Although many investigations are reported as gold standard tests, establishing the diagnosis in clinical practice remains a challenge. Many times, indirect evidence of tubercular infection is considered sufficient to start the medical treatment. The abdominal tuberculosis is primarily treated with anti-tubercular drugs and the majority of the patients respond well to them. The surgical treatment is the last resort and is indicated only in cases with failure of medical treatment leading to the occurrence of complications such as intestinal obstruction, perforation and GI bleeding.

Etiopathogenesis

Tuberculosis is caused by *Mycobacterium tuberculosis* that is acquired through droplet infection primarily involving the lungs causing pulmonary tuberculosis. The spread of infection to the abdominal organs occurs in various ways such as swallowing infected sputum, seeding through the hematogenous route, lymphatic spread from the infected lymph nodes and direct spread from adjacent organs like fallopian tubes. Ingestion of unpasteurized milk contaminated with *Mycobacterium bovis* causing intestinal tuberculosis is rarely seen these days.

The predisposing factors for contracting tubercular infection are diabetes, malnutrition, chronic kidney and liver disease, AIDS, patients on cancer chemotherapy and prolonged use of steroids.
Tubercular infection can involve any part of the GI tract right from the oral cavity to the anal canal including the peritoneum and solid organs in the abdomen. The morphological features of abdominal organs having tubercular infection are as follows:

- Intestines: ulcerative, hypertrophic, ulcerohypertrophic
- Peritoneal: wet, fibrotic, dry, acute primary peritonitis
- Mesenteric: mass, matted lymph nodes, cold abscess

In intestinal tuberculosis, the ulcerative type usually involves the terminal ileum. The ingested bacilli pass through mucosal Peyer's patches and reach submucosa where they cause granulomatous inflammation and ulceration. The tubercular ulcers are superficial, small-sized (3-6 mm), multiple, transversely placed and with normal intervening mucosa. 'Caseating' epithelioid cell granulomas are characteristically seen in the submucosal and serosal layers. Healing of ulcers leads to fibrosis and the formation of circumferential napkin ring strictures. The occlusive arterial changes due to endarteritis of submucosal vessels further contribute to stricture formation but significantly reduce the risk of massive GI bleed. In the hypertrophic type, the cecum is the commonest site of involvement and there is a pseudonodular appearance that mimics malignancy.
In peritoneal tuberculosis, the wet type is commonly manifesting with ascites. In the fibrotic type, there is thickening of mesentery and omentum, and matting of bowel loops with loculated ascites. In advanced cases, small bowel loops get encased in thick fibrous membranes leading to the formation of the abdominal cocoon. The dry type is the least common and is characterized by the formation of dense adhesions and caseating nodules.

Clinical features

Abdominal tuberculosis is a great mimicker having a highly variable and nonspecific presentation. The patient can have acute, chronic or acute on chronic presentation or may even present as an incidental finding. The usual spectrum of presentation includes nonspecific abdominal pain, intestinal obstruction and GI perforation. In children, clinical presentation is different from the adults since lymph nodal involvement and peritoneal adhesions are more common than intestinal involvement. The majority of the patients present with constitutional symptoms such as anorexia, weight loss, low-grade fever with evening rise of temperature, pain abdomen and night sweats. Females of reproductive age usually have oligomenorrhea or amenorrhea. The specific features of the involvement of different abdominal organs are as follows:

Intestinal tuberculosis
The commonest site of involvement is the ileocecal region due to the presence of rich lymphoid tissue (Peyer's patches), high absorption and prolonged physiological stasis of ileal contents. After the ileocecal region, the next common site is the colon followed by the jejunum. The stomach and duodenum are rarely involved due to the presence of less lymphoid tissue and rapid gastric emptying.
The *ulcerative type* of lesion presents with features of malabsorption and chronic diarrhea. Once there is the formation of strictures, the patients usually have features of recurrent subacute intestinal obstruction such as vomiting, abdominal distension with feeling of moving ball of wind, colicky pain, and alternating diarrhea with constipation. Some cases end up with acute intestinal obstruction or perforation peritonitis.
The *hypertrophic type* usually presents with ileocecal mass with or without intestinal obstruction. The abdomen has a typical doughy feel on palpation.

Colonic tuberculosis presents with lower abdominal pain and hematochezia with diarrhea or constipation. *Anorectal tuberculosis* presents with multiple fistulae-in-ano, usually high type that recur after surgery.

Peritoneal tuberculosis

The peritoneal tuberculosis is the most common type of abdominal tuberculosis seen in up to 58% of cases. It is usually seen in young females (20-40 years) having insidious onset with progress spanning over weeks to several months. The patient usually presents with gradually increasing abdominal distension and ascites. In elderly females from endemic areas, such presentation needs to be differentiated from ovarian cancer with malignant ascites especially if an ovarian mass is picked up on imaging that could very well be a tubercular tubo-ovarian lesion. Both these conditions have raised CA-125 levels. However, abdominal tuberculosis rarely has very high CA-125 levels whereas in ovarian carcinoma, the value is usually >1000U/mL.

In some cases, there can be a soft cystic abdominal lump due to loculated fluid collection. The fibrotic type may lead to adhesions and abdominal cocoon formation that usually presents with a lump abdomen with subacute or acute intestinal obstruction.

Mesenteric tuberculosis

It usually presents as a mass of matted mesenteric lymph nodes in the central abdomen (tabes mesenterica) with abdominal pain and fever. The commonly involved lymph nodes are upper paraaortic, mesenteric, omental and peripancreatic groups since these are draining the primary infection from the small gut, caecum and right-sided colon. The involvement of lower paraaortic lymph nodes is uncommon and may occur through direct pelvic organs or hematogenous spread.

Tuberculosis involving solid organs

In cases of disseminated tuberculosis, the common pattern of involvement of solid abdominal organs (liver, spleen and pancreas) is in the form of miliary lesions. In 20% of cases, the liver and spleen may be involved through portal vein dissemination leading to the formation of macronodules and tubercular abscesses. The patients may present with jaundice, abdominal lump or portal hypertension. Patients with pancreatic tuberculosis may present with obstructive jaundice and pancreatic mass on imaging that mimics pancreatic malignancy.

Differential diagnosis

Many abdominal diseases mimic tuberculosis and missed or delayed diagnosis may result in high morbidity as well as mortality. Various conditions having clinical presentation similar to abdominal tuberculosis are:

Infective – Amoebic colitis, typhoid enteritis, *Yersinia enterocolitis*, appendicitis, diverticulitis. Neoplastic – Carcinoma cecum, peritonealcarcinomatosis, lymphoma, ovariancancer. Inflammatory – Crohn'sdisease, ulcerative colitis. Others – Post-laparotomy adhesion, strangulation, malrotation, intussusception, ischemic enteritis.

Out of all, differentiating Crohn's disease from abdominal tuberculosis specifically remains a big challenge since both of these present with chronic diarrhea and pain abdomen. Most of the radiological, endoscopic and histopathological findings of the two entities also resemble very much. There is a rising incidence of Crohn's disease in developing countries and abdominal tuberculosis in developed countries due to lifestyle changes and global migration. Misdiagnosis and giving the wrong treatment in both situations can have serious complications. The salient differentiating features between the two conditions are given in **Table 1**.

Table 1. Differentiating features between abdominal tuberculosis and Crohn's disease.

	Abdominal tuberculosis	Crohn's disease
Duration of illness	Short	Long (exacerbations and remissions)
Clinical symptoms	Night sweats, evening rise of temperature, moving ball of wind, alternating constipation and diarrhea, subacute intestinal obstruction, pulmonary symptoms	Diarrhea, hematochezia, anorectal disease, extra-intestinal manifestations
Radiological findings	Concentric short strictures, Ileo-cecal involvement, necrotic lymph nodes, ascites, omental thickening	Eccentric long strictures, skip lesions, comb sign (engorged mesenteric vessels)
Endoscopic findings	Transversely placed circumferential ulcers, patulous ileo-cecal valve	Longitudinal ulcers, pseudopolyps, cobblestone appearance, fistulae
Histopathology findings	Caseating, confluent, large granulomas with acid-fast bacilli	Deep fissuring ulcers, cryptitis with abscess formation, Noncaseating, discrete, sparse, microgranulomas
Molecular testing	PCR for *M. tuberculosis* +ve	PCR for *M. tuberculosis* -ve
Therapeutic trial of anti-tubercular drugs	Clinical and endoscopic response	No response

Diagnosis

The diagnosis of abdominal tuberculosis is often difficult due to the poor yield of microbiological tests. The gold standard for the diagnosis is the demonstration of caseating granulomas on histopathology or detection of acid-fast tubercular bacilli under a microscope or with Gene Xpert. However, this is not achievable in most cases due to the requirement of surgical specimens. Moreover, the available investigations take a long time (AFB culture), are non-specific (ultrasound, CT scan), costly (Gene Xpert, CT scan, laparoscopy) and invasive (endoscopy, colonoscopy). Various investigations used for the diagnosis of abdominal tuberculosis are:

Ancillary investigations

Tuberculin skin test is of ancillary value and is not diagnostic for tuberculosis since it can give false positive (BCG vaccination, other mycobacterial infection) as well as false negative (immunocompromised patient, widespread tuberculosis) results. *Interferon-gamma release assay (IGRA)* in blood or ascitic fluid has largely replaced the tuberculin skin test since it is not affected by BCG vaccination and has no cross-reaction with other mycobacterial strains. It is also helpful in diagnosing latent tuberculosis and differentiating between abdominal tuberculosis and Crohn's disease. For the diagnosis of peritoneal tuberculosis, blood levels of IGRA have 91% sensitivity and 78% specificity. However, IGRA has low sensitivity in immunocompromised cases and patients with disseminated disease.

Radiological investigations

The radiological findings help in localizing the site of lesion indicative of abdominal tuberculosis but are unable to provide the final diagnosis.

X-ray chest may detect fibro-cavitarylesions; usually seen in the apex of the right lung, pleural effusion or mediastinal lymphadenopathy. Koch's chest is reported to be associated with abdominal tuberculosis in 25% of cases.

Ultrasound abdomen is primarily useful for extra-intestinal tuberculosis (peritoneal and lymph nodes). The ultrasound findings suggestive of abdominal tuberculosis are enlarged mesenteric nodes with marked central hypoechogenicity, loculated ascites with echogenic debris, thickened and rolled up omentum and dilated, matted and thickened small bowel loops. Interloop ascites due to localized collection of fluid between radially arranged bowel loops is classically described as 'Club sandwich sign.' The ultrasound may show concentric bowel thickening of the ileocecal region giving a pseudokidney appearance. However, in a Cochrane review of 11 studies, abdominal ultrasound had a relatively low sensitivity and specificity (63% and 68% respectively) in bacteriologically confirmed cases.

Ultrasound is also helpful in guided diagnostic procedures such as peritoneal fluid aspiration, fine needle aspiration cytology or tru-cut biopsy of the enlarged lymph nodes. Endoscopic ultrasound-guided FNAC (EUS-FNA) is another advanced diagnostic tool for taking samples from deep-seated lymph nodes and pancreatic lesions.

CT enterography has largely replaced barium studies due to the better resolution of cross-section images and the ability to pick up intra as well as extra-luminal findings. The CT findingsindicative of peritoneal tuberculosis arehigh-density ascitic fluid (25-45 HU) due to rich protein content, smudged omentum and smooth peritoneal thickening with nodules (<5 mm). In peritoneal carcinomatosis that mimics tuberculosis, there is thick, irregular peritoneal enhancement with nodularity.

In intestinal tuberculosis, the commonest finding is concentric mural thickening involving the terminal ileum, cecum or both. The ileal thickening leads to short strictures with proximal dilatation. The cecum may be pulled up due to fibrosis. CT enterography is useful in giving better delineation of intestinal strictures.

Tubercular lymphadenitis appears as an increased number of nodes (>3/CT section) that are conglomerate with perinodal fat stranding. In a case with typical clinical features, mesenteric lymphadenopathy showing peripheral rim enhancement with hypodense center (indicative of caseation necrosis) on a CT scan is almost diagnostic of abdominal tuberculosis (**Figure 1**).

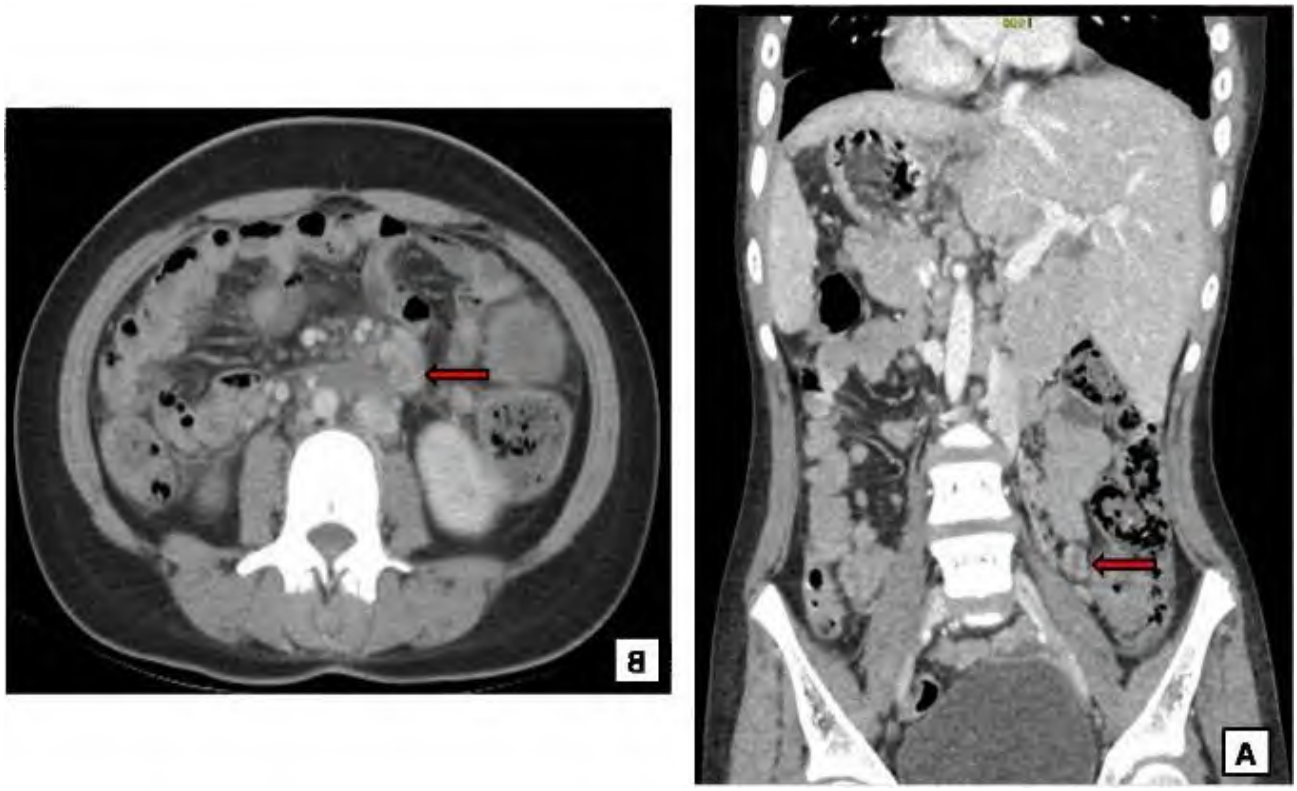

Figure 1. CECT abdomen sagittal (A) and coronal (B) views showing enlarged mesenteric lymph nodes with peripheral rim enhancement and central hypodensity (arrow).

MRI enterography is preferred over CT enterography in patients requiring repeated imaging so as to avoid radiation exposure.
CECT thorax is indicated in a suspected case of abdominal tuberculosis as concomitant active pulmonary tuberculosis has been diagnosed in as high as 38% of cases.

Hematological investigations
Blood examination may show varying degrees of anemia, leucopenia, raised ESR and low serum albumin levels. There may also be raised serum LDH levels (>90 U/I), and raised serum ADA levels (>42 U/I). IgG ELISA for tuberculosis has high specificity (84-88%) and helps in making rapid diagnosis.

Biochemical investigations
Ascitic fluid analysis in peritoneal tuberculosis shows raised lymphocytes and high protein values with low serum ascites albumin gradient. Ascitic adenosine deaminase (ADA) level estimation is an easy, readily available, quick and cost-effective investigation. A meta-analysis of 12 studies has shown that ADA value of 39 has high sensitivity (100%) and specificity (97%. However high ADA levels may also be seen in cases with liver cirrhosis and lymphoma.

Microbiological investigations
The tests include a smear and culture of tubercular bacilli, anda positive report is a gold standard for the diagnosis. However, it takes 6-8 weeks to get the culture result and the sensitivity of ascitic fluid culture is as low as 35%.
The molecular studies such as PCR assay for the detection of *M. tuberculosis*have shown promising results in the diagnosis. Its main advantage over conventional culture is the quick detection of mycobacterial DNA even from a very low burden of tubercular infection (1-2 bacilli/mL specimen). A recent meta-analysis has shown that the pooled sensitivity of PCR in diagnosing abdominal tuberculosis was low (58%, 95% CI 51%-64%) whereas its specificity was quite high (99%, 95% CI 97%-99%) in comparison to clinicopathological and radiological evidence. However, it is an expensive and complicated technique.
GeneXpert MTB/RIF assay is a cartridge-based PCR assay that has the added advantage of simultaneously detecting *M. tuberculosis* (MTB) as well as rifampicin resistance (RIF) within two hours.
The multiplex PCR amplifies multiple DNA targets in a single reaction and has much higher sensitivity than simple PCR and Gene-Xpert in detecting *M. tuberculosis* (82%, *vs.* 56% and 45%, respectively).
PCR assay in stool samples is a non-invasive test that has shown 64% sensitivity in diagnosing GI tuberculosis.
Circulating cell-free DNA (cfDNA) detection in urine, blood or ascitic fluid is another non-invasive investigation for the diagnosis of abdominal tuberculosis. A recent meta-analysis has shown its sensitivity of 40% and specificity of 90% in ascitic fluid against reference standards.
The lipoarabinomannan (LAM) is a glycolipid in the mycobacterial cell wall and lateral-flow LAM assay is an inexpensive test for the detection of LAM antigen in the urine. Its detection in the urine helps in diagnosing disseminated tuberculosis with or without HIV co-infection. The sensitivity of the urine LAM test has been reported to be 40% in HIV-positive patients and 20% in HIV-negative patients. A positive urine LAM test is also associated with significantly higher mortality, especially in cases with HIV infection (p=0.02).

Colonoscopy
It is helpful in the visualization of characteristic lesions and in taking biopsies for microbiological and histopathological examination. Colonoscopic findings of transverse intestinal ulcers, nodularity, pseudopolyps, inflammatory masses, short strictures and involvement of the ileocaecal valve are indicative of intestinal

tuberculosis. At least 6-8 biopsies should be taken from the representative areas. It has been shown that increasing the number, volume and depth of biopsy specimens improves the diagnostic accuracy. Colonoscopy is also useful in monitoring the response of antitubercular treatment in cases of ileocecal tuberculosis.

Diagnostic laparoscopy

It is indicated when clinical findings and investigation reports are equivocal. The typical findings of thickened and nodular peritoneum, intergut adhesions, dilated and thickened small bowel loops with ileocaecal mass and enlarged matted mesenteric lymph nodes are indicative of tuberculosis. The biopsies for histopathological and microbiological examination are taken from the representative areas. In a study of 87 patients, visual appearance on laparoscopy was found to be more useful than histopathology, AFB culture as well as guinea pig inoculation.

Treatment

The treatment of abdominal tuberculosis is primarily antitubercular chemotherapy. Since the tubercular bacilli grow and replicate slowly and have the capacity to remain dormant, so prolonged treatment is indicated for a minimum of six months. Moreover, multiple drugs are used to prevent the emergence of resistance since mutation for resistance occurs independently for any specific drug. The modern chemotherapy drugs are highly effective against the mycobacteria and are able to reach various tissue compartments harboring the organisms. Thus, drug treatment ensures making patients non-contagious, eradication of infection and prevention of the emergence of drug resistance. After the start of medical treatment, the infectivity decreases very rapidly to the extent of >90% on day two and >99% in 2-3 weeks.

As per current WHO recommendations, first-line regimens consist of four drugs: isoniazid (INH), rifampicin, pyrazinamide and ethambutol (H, R, Z, E) given for 2 months (intensive phase) followed by three drugs: INH, rifampicin and ethambutol (H, R, E) for next 4 months (continuation phase). These drugs are given in daily regimens as fixed-dose combinations and the regimen is the same for the new cases as well as previously treated cases.

The drug dosage is as follows:

INH 5 mg/kg, Rifampicin 10 mg/kg, Pyrazinamide 25 mg/kg and Ethambutol 15 mg/kg.

Tablet pyridoxine 10 mg/day should be given along with INH since it causes peripheral neuritis. Rifampicin and pyrazinamide are hepatotoxic whereas ethambutol causes visual impairment due to retrobulbar neuritis.

The main cause of failure of drug treatment in the endemic areas is poor compliance by the patient. A patient resistant to both INH and rifampicin with or without resistance to other first-line drugs is categorized as *Multiple drug-resistant tuberculosis (MDR-TB*). In such cases, the culture of tubercular material is required for the identification of drug sensitivity and the duration of treatment is 12-18 months. The second-line chemotherapy for such cases includes levofloxacin, linazolid, quinolones, clofazimine, cycloserine, ethionamide, imipenem, meropenem, kanamycin, capreomycin and amikacin (or streptomycin).

A patient with MDR-TB and also resistant to any fluoroquinolone is categorized as *pre-XDR-TB*.

A patient resistant to isoniazid and rifampicin, plus any fluoroquinolone and at least one of three injectable second-line drugs (i.e., amikacin, kanamycin, or capreomycin) is categorized as *Extensively drug-resistant TB (XDR-TB).* This rare type of tuberculosis has arisen after the mismanagement of individuals with MDR-TB and is a real challenge to treat.

In 2022 update, WHO has recommended a four-drug regimen consisting of bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM) for a period of six months instead of 9–18-month regimens in patients with

resistance to rifampicin (MDR/RR-TB). Moxifloxacin is omitted and only BPaL is given in patients with pre-XDR-TB.

Anti-tubercular treatment in HIV-infected patients may lead to immune reconstitution inflammatory syndrome (IRIS). It usually occurs after initiation of antiretroviral therapy in patients taking anti-tubercular drugs due to abnormal, excessive immune response against mycobacteria. The patient presents with flaring up of clinical features of tuberculosis and it is managed with corticosteroids.

A therapeutic trial of anti-tubercular treatment is indicated in patients when clinical findings and investigation reports are highly suggestive but not diagnostic of tubercular infection. It is more likely to happen in abdominal tuberculosis due to the poor yield of investigations. The trial should be started after taking written informed consent from the patient. The response to treatment is assessed by improvement in constitutional symptoms, weight gain, decreasing ESR and healing lesions on colonoscopy done at three and six months. If C-reactive protein is persistently high, it is indicative of some alternate diagnosis such as Crohn's disease.

The antitubercular treatment has been shown to improve the symptoms in >90% of patients having intestinal strictures indicating that most of the strictures are due to inflammation rather than fibrosis. However, at the same time, if there is a delay in the start of treatment, the disease may heal but the abdominal symptoms may persist due to fibrotic intestinal strictures and interloop adhesions.

Surgical treatment is required in cases with complications such as recurrent intestinal obstruction, gut perforation and massive GI bleeding. The cases of abdominal tuberculosis presenting with an acute abdomen and requiring surgical intervention are associated with high mortality rates.

Intestinal obstruction not responding to drug treatment is the most common complication that requires surgical intervention. It is seen in 12-60% of cases and the cause of obstruction is gut thickening, non-passable strictures and intergut adhesions. Such cases are managed surgically in the following ways:

1. The site of intestinal obstruction is bypassed by entero-enterostomy or ileo-transverse anastomosis. However, these procedures are not preferred these days due to the high chances of blind loop syndrome and fistula formation.
2. Segmental small bowel resection for ileal stricture or ileocaecal resection for obstructing ileocaecal mass is done under the cover of anti-tubercular chemotherapy. The limited ileocecal-resection instead of right hemicolectomy helps in preserving the healthy bowel in chronically emaciated patients. Multiple closely placed tight strictures or long strictures with active inflammation are best managed with resection and end-to-end anastomosis. However, extensive bowel resection in the case of widely placed, multiple strictures may lead to short bowel syndrome. Additionally, the patients with recurrent sub-acute intestinal obstruction are chronically debilitated and malnourished. Hence before venturing for major intestinal resection, preoperative build-up of the patient is necessary to avoid serious post-operative complications like anastomotic leak, fecal fistula, interloop abscess and wound dehiscence.
3. Strictureplasty is considered a best option since it is not associated with complications like blind loop syndrome and short bowel syndrome. The strictured segment is incised longitudinally along the anti-mesenteric border and closed transversely in two layers leading to widening of the gut lumen without any loss of the intestinal segment.

Tubercular perforation is seen in 1-10% of cases of intestinal tuberculosis, the commonest site being ileum. The low incidence of perforation is due to peritoneal thickening and adhesion formation. The perforation is single in 90% of the cases and mostly occurs just proximal to an ileal stricture. Resection of the diseased segment with end-to-end anastomosis is the treatment of choice since primary closure in an area of active disease and inflammation has a high chance of leaking. Resection with end ileostomy can be considered a lifesaving option in a malnourished and immunocompromised patient having generalised peritonitis with septicaemia.

If a patient undergoes laparotomy for acute abdomen and is found to have tubercular peritonitis with mesenteric lymphadenopathy, it should be managed with lymph node biopsy and peritoneal lavage and the abdomen is closed without a drain.
A concise outline of the diagnosis and management of abdominal tuberculosis is given in the flowchart (**Figure 2**).

Conclusion

Diagnosis of abdominal tuberculosis largely remains a challenge for the treating physician since it has a myriad of clinical and radiological manifestations whereas the laboratory tests lack specificity. The clinical features resemble a wide spectrum of abdominal diseases leading to the high probability of misdiagnosis and its associated complications. Many times, it is not possible to get the sample for microbiological or histopathological confirmation of diagnosis. Although newer molecular tests have shown some promising results, but still a high index of clinical suspicion and correlation of investigation reports help in making the diagnosis in the large majority of the cases. Anti-tubercular chemotherapy is the mainstay of treatment and surgical intervention is required only in cases with complications. Drug treatment for a minimum of six months is required to treat the disease and poor compliance is the main cause of treatment failure. In view of emerging resistance in the form of MDR and XDR TB, a consensus of international experts from multiple related disciplines is highly desirable to outline the algorithm for the diagnosis and management of abdominal tuberculosis.

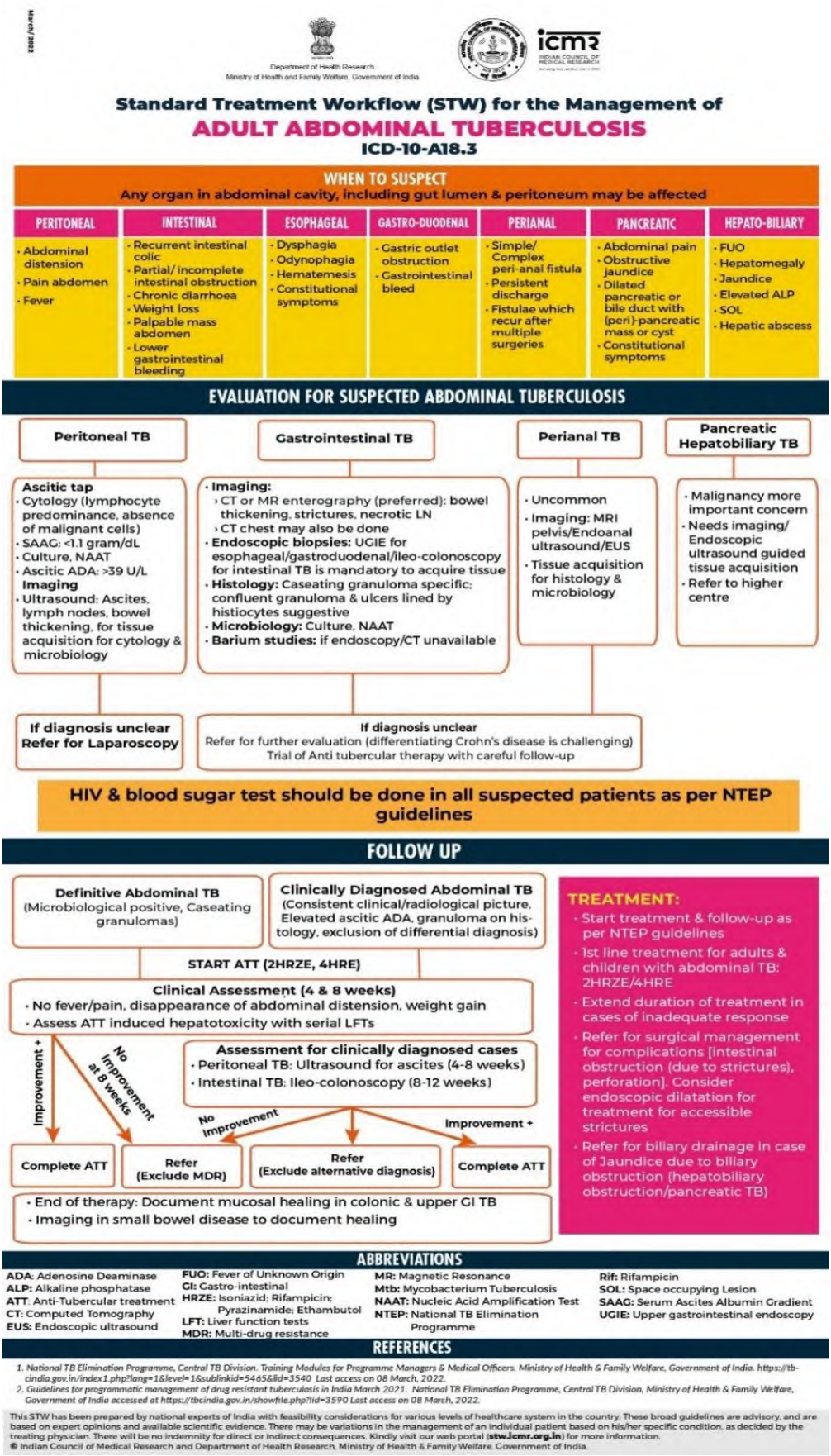

Figure 2. Flowchart for the management of abdominal tuberculosis (Reproduced with permission from Indian Council of Medical Research).

Competing interests

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

References

1. Uzunkoy A, et al. Diagnosis of abdominal tuberculosis: Experience from 11 cases and review of the literature. World J Gastroenterol. 2004;10:3647-3649.
2. Singh A, et al. Abdominal tuberculosis in Indians: Still very pertinent. J ClinTuberc Other Mycobact Dis. 2019;15:100097.
3. Choi EH, et al. Gastrointestinal tuberculosis. MicrobiolSpectr. 2016;4.
4. Sharma MP, et al. Abdominal tuberculosis. Indian J Med Res. 2004;120:305–315.
5. Sanai FM, et al. Systematic review: Tuberculous peritonitis--Presenting features, diagnostic strategies and treatment. Aliment Pharmacol Ther. 2005;22:685-700.
6. Huong DLT, et al. Specificity of CA 125 tumor marker. A study of 328 cases of internal medicine. Presse Med.1988;17:2287-2291.
7. Sharma V, et al. Role of conservative management in tubercular abdominal cocoon: A case series. Infection. 2017;45:601-616.
8. Ladumor H, et al. TB or not TB: a comprehensive review of imaging manifestations of abdominal tuberculosis and its mimics. Clin Imaging. 2021;76:130–143.
9. Luo Y, et al. Diagnostic Value of T-SPOT.TB Assay for Tuberculous Peritonitis: A Meta-Analysis. Front Med (Lausanne). 2020;7:585180.
10. Maulahela H, et al. Recent advances in the diagnosis of intestinal tuberculosis. BMC Gastroenterol.2022;22:89.
11. Van Hoving DJ, et al. Abdominal ultrasound for diagnosing abdominal tuberculosis or disseminated tuberculosis with abdominal involvement in HIV-positive individuals. Cochrane Database SystRev. 2019;9:CD012777.
12. De Backer AI, et al. Abdominal tuberculous lymphadenopathy: MRIfeatures. EurRadiol. 2005;15:2104–2109.
13. Dahiya D, et al. Duodenaltuberculosis–a rare case report and review of literature. Pol PrzeglChir. 2013;85:464–466.
14. Harboe M, et al. The 38 kDa protein of Mycobacterium tuberculosis: a review. J Infect Dis.1992;166(4):874-884.
15. Riquelme AM, et al. Value of adenosine Deaminase in Ascitic fluid for the diagnosis of Tuberculous peritonitis: a meta-analysis. J Clin Gastroenterol. 2006;40:705-710.
16. Shen Y, et al. Meta-analysis of diagnostic accuracy of nucleic acid amplification tests for abdominal tuberculosis. PLoS One. 2023;18:e0289336.
17. Brown L, et al. Gastrointestinal tuberculosis: Diagnostic approachesfor this uncommon pathology. World J Clin Cases. 2024;12:5283-5287.
18. Yu G, et al. Diagnostic accuracy of Mycobacterium tuberculosis cell-free DNA for tuberculosis: A systematic review and meta-analysis. PLoS One. 2021;16:e0253658.
19. Suwanpimolkul G, et al. Utility of urine lipoarabinomannan (LAM) in diagnosing tuberculosis and predicting mortality with and without HIV: prospective TB cohort from the Thailand Big City TB Research Network. Int J Infect Dis. 2017;59:96-102.
20. Bhargava DK, et al. Peritoneal tuberculosis: laparoscopic patterns and its diagnostic accuracy. Am J Gastroenterol. 1992;87:109-112.
21. Jindani A, et al. Bactericidal and sterilizingactivities of antituberculosis drugs during the first 14 days. Am J RespirCrit Care Med. 2003;167:1348-1354.
22. World Health Organization. WHO consolidated guidelines on tuberculosis. Module 4: treatment — drug-resistant tuberculosis treatment. 2022. Available at: https://iris.who.int/bitstream/handle/10665/365333/9789240065116-eng.pdf?sequence=1. Last accessed: 8 August 2024.

23. Anand BS, et al. Response of tuberculous stricture to antituberculous treatment. Gut. 1988;29:62-69.
24. Makanjuola D, et al. Radiological evaluation of complications of intestinal tuberculosis. Eur J Radiol. 1998;26:261–268.
25. Sharma A. Imaging in abdominal tuberculosis. Indographics. 2024;03:045-063.
26. Indian Council of Medical Research. Standard treatment workflows of India. Special edition on pediatric and extrapulmonary tuberculosis 2022. Available at: https://main.icmr.nic.in/sites/default/files/upload_documents/ICMR_STW_PTB_EPTB.pdf. Last accessed: 8 August 2024.

Chapter 132

Typhoid intestinal perforation

Harissou Adamou
Department of Surgery and gastrointestinal diseases, Zinder National Hospital, Faculty of Health Sciences, André Salifou University, Zinder, Niger.

Mahamadou Doutchi
Department of infectious and tropical diseases, Zinder National Hospital, Faculty of Health Sciences, André Salifou University, Zinder, Niger.

Ibrahim Amadou Magagi
Department of Surgery and gastrointestinal diseases, Zinder National Hospital, Faculty of Health Sciences, André Salifou University, Zinder, Niger.

Illa Hamidine
Department of Surgery and gastrointestinal diseases, Zinder National Hospital, Faculty of Health Sciences, André Salifou University, Zinder, Niger.

Introduction

Intestinal perforation is a common complication of typhoid fever (TF). It is a severe intra-abdominal infection due to the opening of the intestinal lumen into the peritoneum, resulting in acute infectious peritonitis. TF is a lymphatic-initiated infection caused by a Gram-negative bacterium *Salmonella enterica, serovar Typhi*, transmitted by contaminated water and food. TF is an endemic-epidemic worldwide infectious disease with varying degrees of prevalence between 11 and 20 million cases each year, including more than 160,000 deaths. Estimates of the incidence of TF report between 110 cases to more than 2,000 cases per 100,000 inhabitants, with a greater concentration in Low-Income countries. There are many serious complications, and typhoid intestinal perforation is one of the most frequent. Despite scientific advances in prevention, typhoid intestinal perforation (TIP) remains a real socio-economic burden in these poor countries where access to healthcare, water, hygiene and sanitation remains precarious. It constitutes one of the main causes of abdominal emergency surgery in high-prevalence countries of TF. The diagnosis of TIP is based on a bundle of epidemiological, clinical and especially biological factors such as blood culture and stool culture. However, these exams are not always conclusive or available. Typically, the patient presents with fever lasting more than 2 to 3 weeks, living in a typhoid-endemic area, with clinical signs of peritonitis due to perforation of a hollow organ. The management of TIP entails enormous expenses for the predominantly poor population, living far from health facilities, on the one hand, and an enormous burden in surgical activities on the other hand. The high morbidity and mortality of TIP are associated with several factors, including the severity of the clinical aspects, the inadequacy of the technical platform, diagnostic and therapeutic delays, etc. Added to this is an increase in the resistance of *Salmonella Typhi* strains to the usual antibacterials leading to the

use of more expensive antibiotics; which represents an additional challenge in the management of TIP. Understanding the epidemiology, diagnostic, therapeutic and prognostic aspects of TIP is an important element of its management. However, prevention of TF through promoting conjugate vaccines, provision of drinking water, a healthy diet and the control of faecal peril.

Epidemiological aspects

Typhoid fever is caused by *Salmonella enterica serovar Typhi (S. typhi)* which is transmitted mainly through human-contaminated water or food. This may explain its high frequency in areas where water supply and sanitation remain a challenge. It contributes significantly to mortality and morbidity from infectious diseases in resource-limited settings. The incidence of typhoid fever, expressed as the number of cases per 100,000 persons per year, varies from one region of the world to another. It is classified as low, medium, high and very high according to the following respective values: <10; 10-100; >100-<500 and ≥500 per 100,000 per year, respectively. Of the 20 million cases of typhoid fever recorded each year worldwide, the vast majority are in sub-Saharan Africa and Asia. These are often populations from impoverished social strata. Socio-economic precariousness, difficult geographical accessibility, insufficient healthcare resources, delays and misdiagnoses and the emergence of *S. Typhi* resistance to antibiotics are all factors that favour the occurrence of complications. The most common of which is typhoid intestinal perforation (TIP). It represents one of the main causes of acute peritonitis in sub-Saharan African and endemic Asian countries. In some African countries, typhoid intestinal perforation constitutes a heavy burden on the health system accounting for over 50% of emergency abdominal surgery. In these countries, the age group of 0 to 15 years constituted the largest part of the general population and indigent patients can reach more than 71% of cases. TIP also concerned children with a median age between 5 and 15 years. The overall postoperative morbidity of TIP is very high ranging from 15% to over 90%, dominated by surgical site infections. The case fatality rate varies from 4 to more than 30% depending on the series. The overall average cost of managing a patient operated for TIP can vary from 300 to 600 dollars. Which leads to catastrophic expenses and financial hardship for families.

Pathophysiology of typhoid perforation

Humans are the only natural host and reservoir of *Salmonella Typhi*. Infection is transmitted by ingestion of food or water contaminated with faeces. Inadequate post-defecation hygiene can lead to the spread of *S. Typhi* to the food or water supplies in endemic areas. After ingestion, *Salmonella Typhi* crosses the intestinal barrier, reaches the mesentery lymph nodes and multiplies their (inoculation period) before disseminating via the blood and lymphatics to systemic sites, including the liver, spleen, bone marrow and gallbladder. Colonization of the gallbladder by *S. Typhi* and excretion of the bacteria into the gastrointestinal tract via infected bile is a feature found in chronic and asymptomatic carriers, but who can transmit the disease to others. The story of "*Typhoid Mary*" was a good illustration of this mechanism. Typhoid manifestations are due to the endotoxin secreted by the bacilli which acts on the intestine and the nerve centers. *Salmonella Typhi* lives preferentially in the terminal ileum, multiplies and infects the PEYER's patches which hypertrophy. In the intestine, it leads to ulceration, haemorrhage, necrosis and perforation of the intestinal wall. The passage of ileal faeces into the aseptic peritoneal cavity will cause a cascade of phenomena:

- The peritoneal inflammatory reaction which causes pain. The presence of typhoid endotoxins leads to the formation of a fibrinogen-rich plasma exudate. This protein is transformed into fibrin, forming the adhesions and false membranes that help to compartmentalize the infection with the omentum. If this barrier is effective, localized peritonitis is formed; but if the defences are overwhelmed, the infection spreads to the entire peritoneal cavity, resulting in generalized peritonitis. Inflammation of the parietal peritoneum leads to the contraction of the parietal muscles (explaining the abdominal contracture or defence). Intestinal perforation can also cause a tertiary blood infection due to the multitude of enterobacteria and other enteric microorganisms.
- Increased vascular permeability is responsible for a significant plasma leakage into the peritoneal cavity and digestive lumen, leading to the "3rd sector". This results in dehydration with hydroelectrolytic disorders, hypovolemia and hypotension.
- Paralytic ileus: vomiting, cessation of matter and gas.
- Increased serous absorption and diffusion of toxins and bacteria in the general circulation leads to multi-organ failure (kidney, cardio-circulatory, pulmonary, haematological, hepatic, metabolic, and nutritional).

Together, these phenomena result in clinical and paraclinical signs that allow us to describe the diagnostic aspects of TIP.

Diagnosis

Inadequate and/or delayed diagnostic capacity and/or delayed diagnosis of FT is still a concern in resource-limited settings. Indeed, in regions where malaria and typhoid fever are co-endemic, treatment of febrile conditions is often irrational, leading to delayed diagnosis, emergence of antibacterial resistance and additional costs for patients. All of which runs counter to recommendations on the judicious and proper use of antibiotics. Treatment of fever should be based on laboratory results and/or a judicious approach so as not to expose patients to side effects and the spread of antibiotic resistance. In the tropics, one of the common conditions that delay diagnosis and treatment of FT is malaria. Efforts should be made to equip the most remote settings with diagnostic capacity for *Salmonella Typhi* infections. This will enable appropriate treatment of febrile patients in endemic regions of sub-Saharan Africa and Asia and avoid complications.

Clinically, typhoid intestinal perforation results in a peritoneal syndrome due to perforation of a hollow organ. The functional signs are dominated by constant abdominal pain, nausea/vomiting and cessation of faeces and gas. In some cases, deceptive diarrhoea is present, with a bland, foul-smelling odour. Fever is constant, and hypothermia is a sign of severity in all cases of intra-abdominal sepsis.

Physical examination reveals a disappearance of pre-hepatic dullness on percussion. On palpation, there may be abdominal tenderness or rigid contracture, a pathognomonic sign of sthenic peritonitis. In many cases of TIP, there is no abdominal tenderness or contracture; this is often asthenic peritonitis, where palpation reveals only an “umbilical cry” and pelvic touch (vaginal and/or rectal) reveals a bulging, painful cul-de-sac of Douglas. This is a clinical condition often found in children who have more than 14 days of severe typhoid fever that has progressed to perforation. They often consult late after several attempts and a long and complex therapeutic pathway. The patient's general condition is profoundly altered, realizing the classic peritoneal facies. This is “drawn facies” with dry lips, sunken eyes, pinching of the wings of the nose, an earthy complexion in leucoderma, a dry tongue, and skin folds of dehydration. In the African context, it is often said that “*typhoid perforation is a disease that worsens the condition of a patient who is already ill*”.

A standard abdominal X-ray or, better still a CT scan can confirm the presence of a pneumoperitoneum. Its presence confirms the perforation of the digestive tract. It should be noted that these morphological

examinations are not essential to undertake therapeutic measures for TIP, as the diagnosis of peritonitis is essentially clinical. Biologically, typhoid fever is defined by all cases where *Salmonella Typhi* is isolated in blood cultures, stool cultures or bone marrow samples, as well as by the polymerase chain reaction (PCR). These tests are not always available in endemic areas. For practical reasons, suggestions have been made to establish the diagnosis of TIP based on a bundle of epidemiological, clinical, and paraclinical arguments. Taking these proposals into account, the diagnosis of TIP can be categorized into 2 levels of evidence:

- *Level 1:* formally confirmed cases of TIP. Intestinal perforation is visualized intraoperatively, and bacteriological confirmation of *Salmonella Typhi* is obtained from blood cultures, stool cultures and/or intraperitoneal fluid or other samples.
- *Level 2*: probable cases of TIP. At this level, the diagnosis is based on epidemiological criteria (TF endemic area), low levels of environmental hygiene, history of illness that finds fever lasting more than 2 weeks with other signs of TF and intestinal perforation confirmed intraoperatively. However, there is no confirmation of a stool culture, a blood culture or a culture of the surgical sample for *S. Typhi*. The intraoperative macroscopic examination notes one or more perforations, oval and regular on the anti-mesenteric edge of the intestine (**Figure 1A**); most often at the distal end of the ileum.

These probable cases appear to be more commonly reported in the literature, due to the difficulty of biological diagnosis in resource-limited settings. Without treatment, it progresses in a few hours to a few days towards worsening of the signs, with profound deterioration in general condition, multi-visceral failure and death of the patient. Death rates are high even after well-managed treatment.

Therapeutic strategies

Before instituting treatment, a pre-therapeutic assessment is necessary. This includes the Rhesus blood group, the prothrombin levels, a blood count which often shows hyperleukocytosis, sometimes leukopenia, and haemoconcentration (indicating dehydration). A renal assessment (creatinine and uremia to look for functional renal failure), a liver assessment and a blood ionogram.

The goal of curative treatment of TIP

It consists of:

- Correcting the induced disorders: hydroelectrolytic troubles, visceral failures, anaemia, malnutrition.
- Controlling and/or eliminating the source of contamination and eradicating the infectious focus.
- Cleaning the peritoneal cavity.
- Preventing and treating complications.

To achieve this goal, there are several therapeutic procedures and methods. Medical resuscitation must be energetic and short-term, usually 3 or 4 hours, to transfer a balanced patient to the operating room. It consists of placing the 4 access ports (nasogastric tube for digestive aspiration, vesical tube for hourly diuresis collection, well-calibrated venous ports for filling with crystalloid solutions, macromolecules and/or transfusion, oxygen therapy).

Antibiotic therapy: initially empirical, based on epidemiology, ecology and the notion of resistance to antimicrobials in the environment; it will be adapted later to the results of the antibiogram. It must be a broad-spectrum, massive, administered intravenously and presumed to be active on *S. Typhi* and other Gram-negative germs. Indeed, after perforation, other enterobacteria become involved in the infectious phenomenon. A combination of a beta-lactam agent such as ceftriaxone, an aminoglycoside and metronidazole is classically used. In some cases, beta-lactam can be replaced by a fluoroquinolone agent. The duration of this antibiotic

therapy should not exceed 15 days except in special cases. These antibiotics must be used efficiently, effectively and appropriately. Antibacterial treatment is a real challenge at the moment since some strains of *S. Typhi* are highly resistant to the usual antibiotics (**Figure 1B**). Treatment also combines analgesics, vasopressive drugs, prevention of thromboembolic disease, corticosteroid therapy, and a residue-free diet.

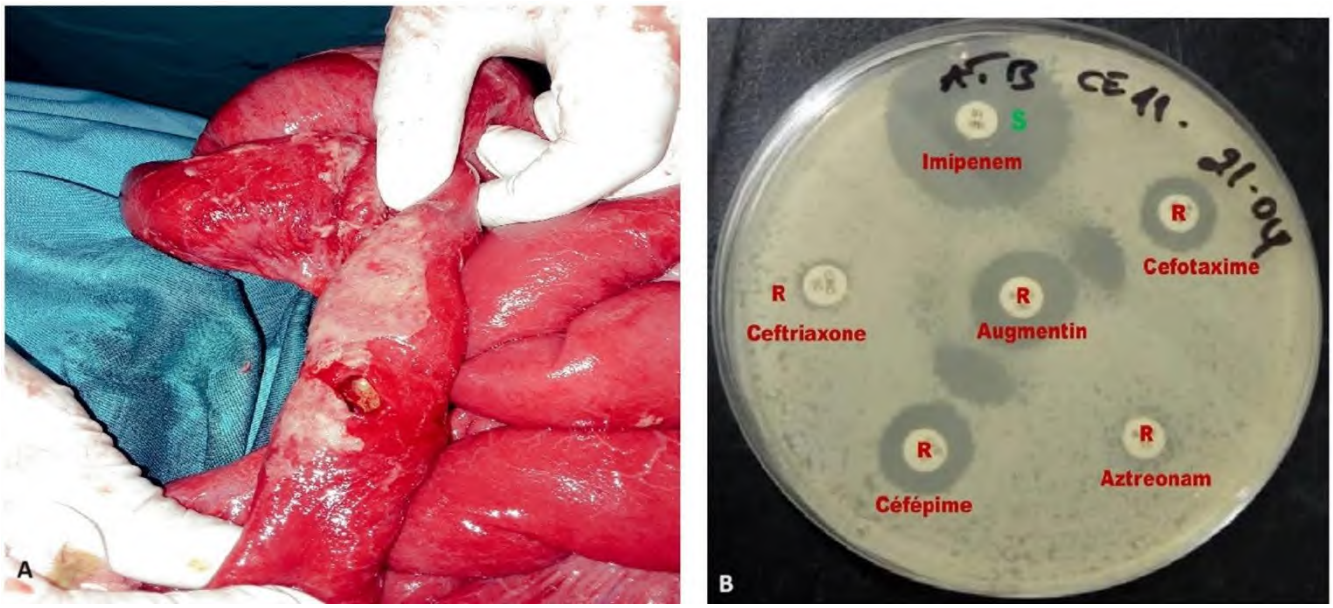

Figure 1A. Intraoperative aspects of a typhoid intestinal perforation.
Figure 1B. *Salmonella Typhi* strain BLSE isolated on coproculture, recognizable by the synergistic image between cefepime, cefotaxime and Amoxicillin+clavulanic acid.

Surgical procedures and indications

Median supra- and sub-umbilical or wide transverse laparotomy is the approach for all patients. The main surgical procedures performed are excision and closure of the perforation, intestinal resection with immediate anastomosis, or ileostomy with or without intestinal resection. Whichever procedure is chosen, thorough cleansing with saline and drainage of the abdominal cavity is essential. The choice of surgical procedures depends on the surgeon, the patient clinical and nutritional status, the degree of peritoneal contamination and the lesions found. Several surgical procedures and scores have been proposed to categorize the severity of the TIP and choose the appropriate technique:

- Simple closure is performed in patients with a single or double perforation, abdominal contamination considered less soiled (non-faecal, non-purulent) and a patient with a good general status.
- Resection and anastomosis are performed in case of several perforations close together and in patients with a good general status.
- Ileostomy should be performed routinely in case of a dirty abdominal cavity, a patient in poor general condition or undernutrition, regardless of the number of perforations. It is performed in front of the most proximal perforation to protect possible distal closures, or a perforation not suitable for closure is brought to the skin as an ileostomy. The ileostomy is also performed to protect a closure located within 2-5 cm from the ileocecal junction (zone of anatomical turbulence). It can also be the first-line procedure, regardless of the patient's condition, to avoid the risk of suturing in septic zones. Today, several authors agree on the principle that ileostomy is a recommended procedure in TIP, since it is often involving a patient

with a very dirty peritoneal cavity, with a poor general and nutritional status. In some cases, ileostomy has been performed as part of damage control surgery, indicated for patients in poor general condition (severe sepsis, malnutrition, respiratory distress, etc.). It is a procedure borrowed from the management of abdominal trauma, which consists of rapidly opening the abdominal cavity, to wash, and exteriorize the perforation(s) in the form of an ileostomy. It is possible to see the patient again for a "second look" within 48-72 hours if necessary. The restoration of digestive continuity is offered within 30 to 90 days depending on the case.

Treatment outcomes

Monitoring of surgical treatment is based on the assessment of general signs such as blood pressure, pulse, respiratory rate, diuresis, fever and examination of the calves. It is also necessary to look for the resumption of transit, the disappearance of peritoneal signs and the normalization of biological signs (hemogram, renal function). This clinical and paraclinical monitoring enables complications to be identified. The postoperative morbidity of TIP is high, varying from 15 to more than 80% depending on the series. They are dominated by:

- Surgical site infections, toxin-induced consequences of sepsis, anastomotic leakage which can induce generalized or localized postoperative peritonitis (residual abscess, particularly subphrenic or Douglas pouch abscess), dehiscence of the abdominal wall, resulting in free or fixed evisceration.
- Complications such as haemorrhages, thromboembolisms and bedsores.
- Complications specific to ileostomies such as infections, stoma necrosis and often peristomal skin burns are the consequence of corrosive digestive fluid leaks and are sometimes associated with defective stomal appliance.

In the long term, as in other causes of intra-abdominal infections, occlusions on flanges and adhesions and incisional hernia have often been reported after surgery for typhoid perforation.

Prognosis of TIP

Typhoid intestinal perforation is a serious condition whose prognosis depends on several factors. Several severity assessment systems and prognostic scoring have been described in predicting the prognosis of peritonitis. However, the use of these scoring systems is not always easy and adaptable to typhoid intestinal perforations in sub-Saharan Africa and other resource-limited countries. The “Typhoid Intestinal Perforation Prognostic Score (TIPPS)” proposed by Adamou *et al.*, constructed taking into account previous scores, has broken down the severity and mortality risk TIP. The total "TIPPS" score ranges from 8 to 20 = “*Respiratory rate + mean systolic blood pressure + serum creatinine level + haemoglobin + comorbidity + ASA score + time to admission and management + number of perforations”*. Patients were divided into four grades of increasing severity, with a progressively higher risk of mortality (%):

- grade I: low risk (score: 8-10), mortality: 3.5%;
- grade II: moderate risk (score: 11-13), mortality: 7.4%;
- grade III: high risk (score: 14-16), mortality: 28.6%;
- and grade IV: very high risk (score: 17-20), mortality: 80%.

Prevention

Preventive treatment of TIP is based primarily on the control of faecal peril. Typhoid fever must also be diagnosed and treated early and effectively before complications occur. The implementation of typhoid fever vaccination on a large scale may be a much more effective way to combat this disease. Indeed, the World Health Organization (WHO) recommends typhoid conjugate vaccines which are available, affordable and suitable for vaccination campaigns and routine vaccination programs, as they are recommended from the age of 6 months.

Conclusion

Typhoid fever, a disease of dirty hands and faecal peril is endemic in many countries in sub-Saharan Africa and Asia. One of the most frequent complications is typhoid intestinal perforation (TIP), which results in acute peritonitis in a condition already weakened by the causative disease. This is a huge surgical burden and a socio-economic tragedy affecting a young population from low-income countries. Diagnosis is based on a bundle of epidemiological, clinical, intraoperative and especially biological exams by the isolation of *Salmonella Typhi*. The treatment of TIP should combine surgery, appropriate perioperative resuscitation with hydroelectrolytic correction and judicious antibiotic therapy, as broad as possible, oriented against *Salmonella Typhi* and other digestive enterobacteria. Cleaning of the peritoneal cavity is essential and ileostomy is a surgical procedure highly recommended in critically ill patients. The morbidity and mortality of TIP are high. However, a better policy of early management and prevention, through access to safe drinking water, promotion of personal hygiene, use of sanitary facilities and vaccination against TF, can reduce this burden. Consideration of TF, a preventable disease, as a public health problem is essential on the part of experts, and political and technical decision-makers, with a view to including typhoid fever vaccination in the Expanded Program on Immunization (EPI) for endemic countries.

Competing interests

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

References

1. Birkhold M, et al. Characterization of Typhoid Intestinal Perforation in Africa: Results From the Severe Typhoid Fever Surveillance in Africa Program. Open Forum Infect Dis. 2023;10:S67-S73.
2. Meiring JE, et al. Typhoid fever. Nat Rev Dis Primer. 2023;9:71.
3. Marchello CS, et al. Complications and mortality of typhoid fever: A global systematic review and meta-analysis. J Infect. 2020;81:902-910.
4. Sukri L, et al. Typhoid intestinal perforation in Francophone Africa, a scoping review. PLOS Glob Public Health. 2024;4:e0003056.
5. Kim JH, et al. Mapping the incidence rate of typhoid fever in sub-Saharan Africa. PLoS Negl Trop Dis. 2024;18:e0011902.

6. Kim C, et al. Associations of water, sanitation, and hygiene with typhoid fever in case-control studies: a systematic review and meta-analysis. BMC Infect Dis. 2023;23:562.
7. John J, et al. Burden of Typhoid and Paratyphoid Fever in India. N Engl J Med. 2023;388:1491-500.
8. Antillón M, et al. The burden of typhoid fever in low- and middle-income countries: A meta-regression approach. PLoS Negl Trop Dis. 2017;11:e0005376.
9. Adamou H, et al. Le fardeau de la perforation typhique de l'intestin grêle au Niger. J Sah sci santé. 2021;1:131-139.
10. Crump JA. Progress in Typhoid Fever Epidemiology. Clin Infect Dis Off Publ Infect Dis Soc Am. 15 févr 2019;68:S4-S9.
11. Seyi-Olajide JO, et al. Burden of Complicated Intra-Abdominal Infections in Children in Nigeria: Recent Experience and Systematic Review. Surg Infect. 2020;21:501-508.
12. Adamou H, et al. Typhoid Intestinal Perforation Prognostic Score in Poor-Resource Settings. J West Afr Coll Surg. 2023;13:9-17.
13. Birkhold M et al. Morbidity and Mortality of Typhoid Intestinal Perforation Among Children in Sub-Saharan Africa 1995-2019: A Scoping Review. World J Surg. 2020;44:2892-2902.
14. Teferi MY et al. Prevalence and antimicrobial susceptibility level of typhoid fever in Ethiopia: A systematic review and meta-analysis. Prev Med Rep. 2022;25:101670.
15. World Health Organization. Typhoid vaccines: WHO position paper, March 2018 - Recommendations. Vaccine. 2019;37:214-216.
16. Mogasale V, et al. Case fatality rate and length of hospital stay among patients with typhoid intestinal perforation in developing countries: a systematic literature review. PloS One. 2014 ;9(4): e93784.
17. Sartelli M, et al. WSES/GAIS/SIS-E/WSIS/AAST global clinical pathways for patients with intra-abdominal infections. World J Emerg Surg WJES. 2021;16:49.
18. Rufai T, et al. Malaria and typhoid fever among patients presenting with febrile illnesses in Ga West Municipality, Ghana. PloS One. 2023;18:e0267528.
19. Worldwide Antimicrobial Resistance National/International Network Group (WARNING) Collaborators. Ten golden rules for optimal antibiotic use in hospital settings: the WARNING call to action. World J Emerg Surg WJES. 2023;18:50.
20. Verma A, et al. Defunctioning ileostomy for typhoid ileal perforations: Out of the frying pan into the fire? Trop Doct. 2024;54:245-247.

Chapter 133

Postoperative peritonitis: from early recognition to optimal management in a challenging landscape

Yong Yi Tan
Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore.

Wee Teck Ong
Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore.

Matthias Yi Quan Liau
Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore.

Vishalkumar Girishchandra Shelat
Department of General Surgery, Tan Tock Seng Hospital, Jalan Tan Tock Seng, Singapore;
Surgical Science Training Centre, Tan Tock Seng Hospital, Jalan Tan Tock Seng, Singapore.

Introduction

An abdomen is a common place for interventions by diverse groups of surgical professionals, including gastrointestinal surgeons, urologists, gynecologists, vascular surgeons, and alike for a variety of organ system pathological conditions. A patient may experience bleeding or sepsis-related morbidity following surgical interventions. Postoperative peritonitis (PP) is not an uncommon complication of intra-abdominal procedures and intra-abdominal infection (IAI) is associated with high morbidity and mortality due to associated systemic inflammation and organ dysfunction. The complicated course of PP applies not just to urgent surgical procedures, but elective ones as well. In a retrospective study of intensive care unit (ICU) admissions following elective surgery, Vesteinsdottir *et al.* reported that most patients developed sepsis following gastrointestinal procedures, while the most common infection source was the abdomen. One of the common causes of PP was anastomotic leakage (AL) due to a host of patient-related, procedure-related, and provider-related factors. Recent recommendations by the Italian Council for the Optimization of Antimicrobial Use described key aspects of PP management, including prompt diagnosis and risk stratification, sufficient source control, appropriate antimicrobial therapy and early patient stabilization. The importance of postoperative IAI is illustrated by it being considered a key outcome metric to define textbook outcomes following trauma and non-trauma emergency procedures. In our opinion, this remains true and valid for elective procedures too. Despite recent advancements in surgical procedures to minimize AL and protocols to diagnose and treat PP early, rising antimicrobial resistance (AMR) is an emerging challenge for surgeons and intensivists. Thus, this chapter

aims to describe some recent developments and trends in PP vis-a-vis AMR, while further contextualizing the elective setting.

Definitions

Inflammation of the peritoneal lining due to infection results in peritonitis. Peritonitis is classically categorized into primary, secondary and tertiary peritonitis. In general, peritonitis is secondary to abdominal visceral pathology. PP is classified as a form of secondary peritonitis owing to disruption of the intestinal wall following surgical intervention and it can only be hospital-acquired or healthcare-associated in nature. Furthermore, PP is also a form of IAI. PP can also sometimes be described as perforation peritonitis or intra-abdominal sepsis in the literature.

Etiology and microbiology

A breach in bilio-digestive lumen or an AL is the most common cause of PP. This is typically observed as a postoperative complication of hepatobiliary interventions or gastrointestinal procedures such as colorectal resections. In general, the blood supply of the stomach and small bowel is better compared to the colon and thus hindgut procedures have a higher AL risk compared to foregut or midgut procedures. The watershed area at the splenic flexure where the superior mesenteric artery supply territory ends, and the inferior mesenteric artery supply territory begins is usually dependent on blood supply from the marginal artery of Drummond. In some patients, this is absent, and the part of the splenic flexure is relatively less perfused, Griffith's point, making it vulnerable to AL, especially on a background of diabetes mellitus and atherosclerosis. However, leakages can also occur in other areas such as the appendix, small intestine and even more proximally in the stomach and pancreas. A nationwide retrospective study found that risk factors for leakage include a higher body mass index, emergency surgery, poor preoperative clinical status, extensive tumor resection and preoperative irradiation. As such, patients in the elective setting may be at lower risk of leakage as their preoperative nutritional and physiologic status can be optimized.

The gastrointestinal microbiome is often the pathogenic source for PP, especially following perforation or AL. PPs often involve a polymicrobial infection that is influenced by the localization of infectious foci. For example, more proximal sources along the upper gastrointestinal tract are associated with infections by Gram-negative and Gram-positive facultative aerobic bacteria, while sources in the lower gastrointestinal tract are associated with infections by predominantly Gram-negative bacteria that are either facultative or obligate anaerobes. In addition, proximal perforations can also lead to fungal spread in the peritoneal cavity due to oral commensals. Roehrborn *et al.* demonstrated that Enterococci and *Escherichia coli* are among the most common causative pathogens. Interestingly, they also found that there were significantly more *E. coli* and less *Enterobacter* spp. at relaparotomy in survivors of PP than non-survivors, indicating an association between the microbial spectra of PP and its prognosis. In contrast to primary or community-acquired peritonitis, an additional consideration of PP is that of AMR. This is due to the hospital-acquired nature of the infection which can be further exacerbated by antimicrobial therapies administered to the patient preoperatively. Clinically significant resistance phenotypes observed include inducible cephalosporinases, extended-spectrum beta-lactamases, carbapenemases and vancomycin resistance. AMR complicates management not due to the increased virulence of the pathogens but due to the lack of efficacy of initial empiric antibiotics. As such, early detection of not

just PP but also the causative pathogen and AMR patterns can optimize early empirical antimicrobial therapy and guide necessary infection control measures. It is expected that surgical professionals familiarize themselves with local antibiograms and champion antimicrobial stewardship initiatives to provide safe, timely, and effective care to patients who already have morbidity from index intervention.

Risk factors and prognostication

Given the potential for high morbidity and mortality from gastrointestinal surgeries, it is crucial to accurately predict surgical outcomes. This is especially so for elective surgeries given that the patient's clinical status can be optimized preoperatively. Initiatives such as enhanced recovery after surgery and prehabilitation programs serve to improve clinical outcomes as well as save costs and deliver value for all stakeholders. Risk stratification is important to guide the assessment and management of PP when a clinical suspicion is developed postoperatively. Such factors as advanced age, comorbidities and presence of malignancy are utilized in peritonitis or sepsis risk-scoring systems such as the Manheim Peritonitis Index (MPI), APACHE-II and Boey scores. However, the current suite of risk scores is either nonspecific for peritonitis or incorporates intra- and postoperative measurements, which decreases its utility of guiding preoperative optimization. Anabalakan *et al.* have emphasized the importance of preoperative variables in patient and family counselling, consenting, and timely management of their expectations in addition to determining the right siting and timing of care. Currently, the APACHE II score has the best accuracy in stratifying patients by mortality and morbidity, while MPI is a peritonitis-specific alternative that is easier to derive and apply. Furthermore, in a single institution retrospective study including 332 perforated peptic ulcer patients, Anabalakan *et al.* reported that MPI was the only scoring system which predicted intra-abdominal collection, leak, re-operation and mortality.

Evaluation

History and physical examination

In general, any deviation from the expected norm of recovery should be considered as a surgical morbidity until proven otherwise. A detailed clinical history of physical symptoms, chart reviews, and operative records are necessary to inform clinical judgments and guide care decisions. Key symptoms to note include nausea, vomiting, fever, chills, bloating, dysuria, urinary retention, and changes in bowel function. Persistent abdominal pain, focal tenderness, spiking fevers, tachycardia, prolonged ileus, and unexplained pleural effusion can indicate an IAI. In critical care settings, where patients may be sedated or intubated, close monitoring of hemodynamic status and tolerance to enteral feeds is crucial. Speaking with the in-charge nurse or a family member can provide additional clues. On physical examination, new unexplained tachycardia, high-spiking fevers, and hypotension are concerning signs that could indicate infection, while peritonism (i.e. guarding and rebound tenderness) can suggest PP. Vital chart trends review provides vital data! It is essential to note that pain score is a component of vital chart trends. Often tachypnoea and desaturation are the presenting features and should not be neglected as treatment delay is associated with mortality. In patients with drainage tubes, the quality of effluent can aid detection of complications. For example, a bilious drainage following a cholecystectomy can suggest a bile leak (**Figure 1**).

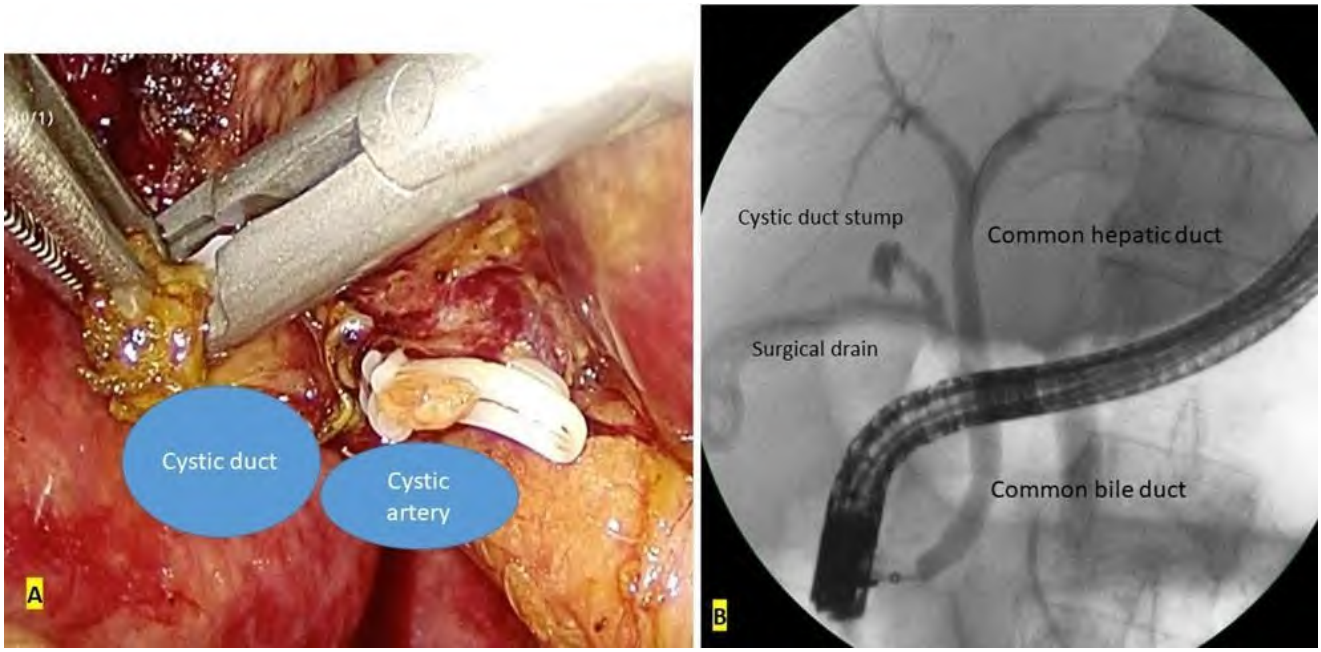

Figure 1. Characteristics of drainage effluent can aid in identifying complications.

A 69-year-old male with a history of hyperlipidaemia, diabetes mellitus, and non-ST elevation myocardial infarction underwent elective laparoscopic cholecystectomy (Image A) after a prior Endoscopic Retrograde Cholangiopancreatography (ERCP) and subsequent pancreatitis. The postoperative course was complicated by a bile leak in the drain. The intra-abdominal sepsis with cystic duct stump bile leak (Image B) was diagnosed and managed by ERCP and stenting.

Quick sequential organ failure assessment (qSOFA) score can be computed from systolic blood pressure, respiratory rate, and Glasgow coma scale and can be a highly specific tool for the diagnosis of sepsis, but it lacks sensitivity. Intra-abdominal hypertension in postoperative patients is also a significant indicator of PP. Though intra-abdominal pressures (IAP) are not routinely measured in all postoperative patients, IAP measurements are warranted in specific situations to diagnose and timely manage abdominal compartment syndrome (ACS). Postoperative inspection of the surgical incision for infective signs is also crucial to assess the risk of PP development. For example, serosanguinous discharge from a laparotomy wound beyond the fifth day heralds a burst abdomen which suggests IAI. In situations that are not clear cut, re-assessments and repeated examination with vital chart trend reviews are crucial to ensure that the golden hour of early intervention is not missed due to diagnostic delays.

Laboratory investigations

The diagnostic work-up of a patient with suspected PP requires a complete blood count comprising hematocrit, hemoglobin, platelets, and a white blood cell count with the differential count. The total white cell count is important to compute systemic inflammatory response syndrome criteria which are used to predict clinical outcomes in patients with sepsis. A septic workup should include cultures from all potential fluid sources, such as blood, urine, and abdominal drains. In septic patients, laboratory data are crucial for guiding fluid management, electrolyte balance, and acid-base correction. Serum lactate, blood gas analysis, and inflammatory markers such as C-reactive protein and procalcitonin can be performed as judged necessary. The blood group and cross-matching and coagulation profile should be performed in anticipation of invasive tests

or procedures. Therapeutic delays are unacceptable to correct coagulopathy that is driven due to sepsis and source control should go hand-in-hand along with correction of coagulopathy.

Diagnostic imaging

Modern diagnostic imaging is crucial in the workup and management of patients with PP. It should be noted that a postoperative chest X-ray showing free air could be a normal finding due to previous laparoscopic procedures. Abdominal X-rays are useful for postoperative ileus and bowel obstruction. They are portable and helpful for bedside evaluations, particularly to confirm the position of intra-abdominal tubes and evaluate abnormal gas patterns. Point-of-care ultrasound is an emerging tool for prompt identification of intraabdominal fluid and detection of source of infection, however, needs training and experience. Computed tomography (CT) scans remain the gold standard for visualizing the intra-abdominal space in the assessment of PP due to high sensitivity and specificity for the detection of pathology as well as free air (**Figure 2**).

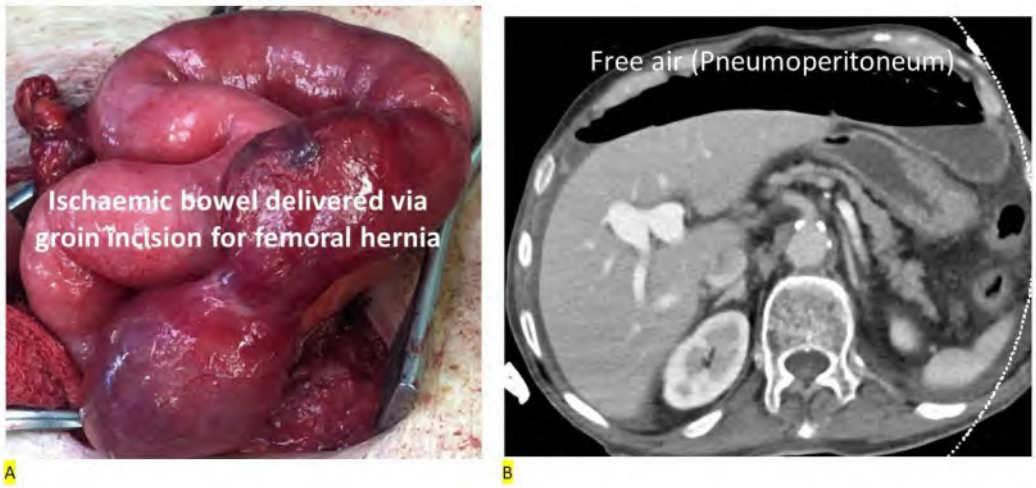

Figure 2. Visualizing the intrabdominal space for free air through computed tomography.

An 88-year-old male with a history of chronic obstructive pulmonary disease, cor pulmonale, pulmonary hypertension, heart failure requiring intermittent oxygen therapy at home, diabetes mellitus, type 2 myocardial infarction, and a right temporal subarachnoid hemorrhage presented with abdominal pain for one week, an irreducible right groin swelling for two weeks, and obstipation for four weeks. A clinical diagnosis of femoral hernia was made and ischemic bowel (Image A) was judged as viable due to pink colour and visible peristalsis after 5 minutes of 100% oxygen and warm saline packs. However, postoperative day two he became unwell with features suggestive of intraabdominal infection and a computed tomography scan showed extensive pneumoperitoneum (Image B). He declined surgical intervention and died a few days later.

Oral and rectal contrasts are particularly helpful in differentiating AL but should be used cautiously in patients who are prone to developing ileus. Caution needs to be exercised in administering oral contrast in patients with nasogastric tubes as the tube should be temporarily spigotted or else contrast will drain out without necessary imaging delineation. Radiographic signs of abscesses on CT may be detected 4-5 days after surgery and include the enhancement of the wall by contrast, debris, loculation and extraluminal gas. CT or ultrasound-guided percutaneous drainage is usually done to treat the identified abscesses that are ≥4 cm. It is essential to communicate with interventional radiologists to have a shared mental model of what will be done

to the patient, and the patient should have the opportunity to speak and engage with the procedurist for informed decision-making. Non-operative management though attractive and less invasive, is not a panacea to all situations of PP, and clinical decisions must be made with caution as delays in definitive surgical intervention may not only put patients at risk of mortality but also expose clinicians at risk of professional negligence. In special situations such as ischaemic stoma, endoscopic assessment may aid in diagnosis and decision-making for revision surgery (**Figure 3**).

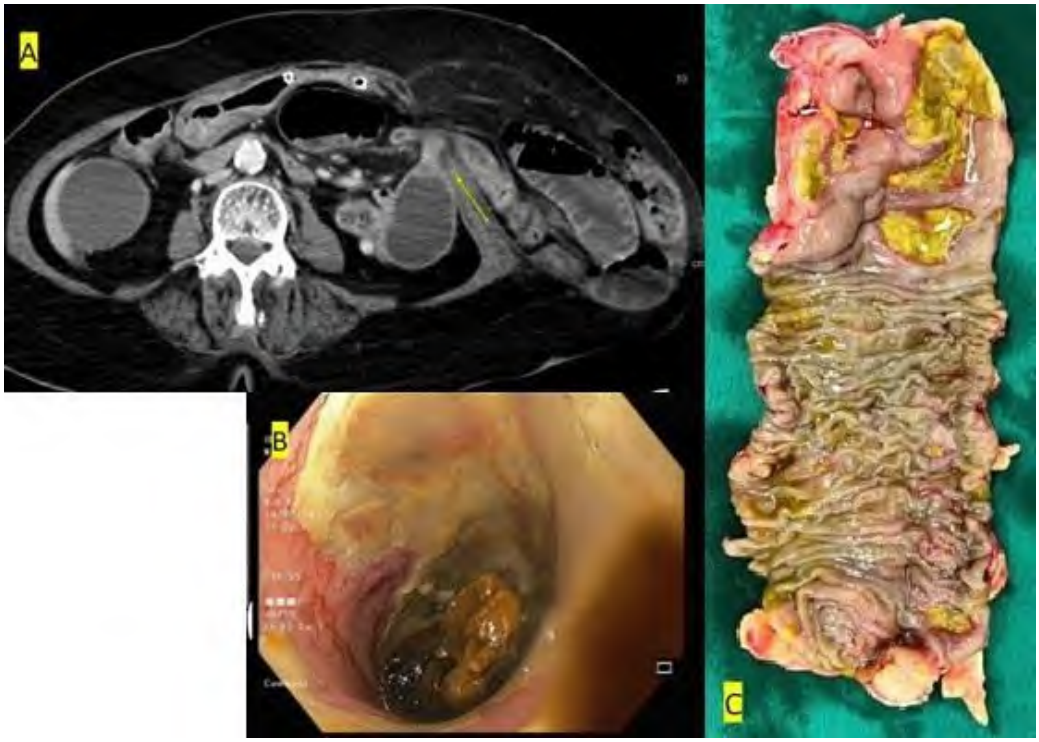

Figure 3. Value of endoscopic assessment in diagnosis and decision-making for ischemic stomas.

An 89-year-old male with a previous history of abdominoperineal resection and permanent end colostomy was admitted with a large parastomal hernia (Image A, yellow arrow) with clinical features of intestinal obstruction and hence a mesh repair was performed with re-siting of stoma. On postoperative day 5, the stoma was dusky and ischaemic as confirmed by stoma-scopy (Image B) and revision surgery was performed during which approximately 18 cm of ischaemic descending colon was excised (Image C).

Management

The management of PP necessitates a multi-faceted approach involving resuscitation for hemodynamic compromise, early administration of broad-spectrum antibiotics, and source control. Improved outcomes in patients with IAIs are attributed to advancements in critical care, availability of broad-spectrum antibiotics, improved nutrition, and earlier recognition and diagnosis. While this chapter focuses on clinical care, a brief mention is necessary that surgeons must also manage themselves during the process. Surgical complications not only affect patients but also have a profound negative impact on surgeons, often referred to as the

'second victims,' with the potential for long-lasting negative emotions and behaviors that can permeate their careers, adversely influencing their social and professional relationships. This chapter shall focus on clinical patient management only.

Resuscitation

Early goal-directed therapies are critical for patients with suspected PP or sepsis. However, it is critical to avoid over-resuscitation, especially with crystalloid fluids, due to the patients' tendency for global endothelial dysfunction and propensity for third spacing and tissue edema. Over-resuscitation can lead to ACS with a secondary impact on diaphragm splinting and pulmonary dysfunction and reduced renal perfusion and kidney injury. Similarly, incorrect resuscitation strategies can worsen the health state of already sick victims. For example, prescribing diuretics for oliguria can worsen dehydration and precipitate acute renal injury. Further, resuscitation should also include collateral considerations. For example, if a contrast-enhanced CT scan is scheduled, then renal protection tools should be used to reduce the risk of renal medullary hypoxia from reactive oxygen species that drive contrast-induced nephropathy (CIN). Fluid volume expansion and avoidance of dehydration increase intravascular volume, renal blood flow and diuresis, reduce the contact time of contrast media with renal tubular cells, and prevent CIN. The patient journey should be streamlined with forward planning to prevent back and forth shifting of patients from one facility to another facility. For example, before sending the patient to the CT scan room, decisions should be made about where the patient will next be shifted by anticipating possible scenarios based on clinical judgment and scan findings. A patient must be accompanied by a qualified healthcare professional, ideally a trained doctor, as well as having necessary resuscitation equipment with him/her. The senior and in-charge doctor should be physically present and engage the family and provide updates on the plans and explain the necessary details for them to understand and provide them opportunity to ask questions or clarify doubts. If a patient is in extremis, time should not be wasted in soliciting imaging tests, but rather clinical decisions must be made for expeditious source control and the ideal place for resuscitating a severely ill person is an operation theatre.

Source control

Source control is a critical aspect of managing PP. Timely and adequate source control significantly affects patient outcomes, with delays or insufficient interventions potentially leading to adverse effects. Traditionally, it is recommended to achieve source control within 6-12 hours in unstable patients, highlighting the need for continuous availability of surgical and radiology services. The three principles of source control are drainage, debridement, and restoration of anatomy and function.

The primary goal of drainage is to remove all infected material from the peritoneal cavity. This can be done surgically or percutaneously, depending on the severity of the septic state, distribution of infected fluid, and presence of AL. In stable patients, percutaneous abscess drainage is preferred if feasible. Surgical drainage is necessary when percutaneous methods fail or are not possible. Emergent surgical exploration is required in patients with generalized peritonitis or hemodynamic instability. In the surgical management of PP, factors such as the infection source, extent of peritoneal infection, physiological reserve of the patient and comorbidities significantly influence decision-making on procedures such as bowel anastomosis, exteriorization, or temporary closure of the abdomen. In cases of severe contamination, the abdominal cavity may be temporarily left open for a relook second procedure for maneuvers such as additional washout or restoring the bowel continuity. In cases of ongoing infection, aggressive physiological restoration after an initial damage control surgery may be beneficial to manage multiple organ dysfunction caused by IAI. A patient and family have to be consented about additional surgical procedures if these are reasonably foreseeable by the primary surgical team (**Figure 4**). Surgical debridement involves removing dead tissue and foreign material from the

abdominal cavity. The extent of debridement is controversial, with some procedures, like "defibrination" at laparotomy, potentially causing more harm than good. It is essential that body fluids are collected for microbial sampling as well as photo documentation of the pathology done so that it enables explanation to the patient and family as well as serve as a medico-legal defense for future disputes. The primary motive of record keeping is to administer good care and shielding from legal matters should be a byproduct and it is professional to refrain from defensive practices.

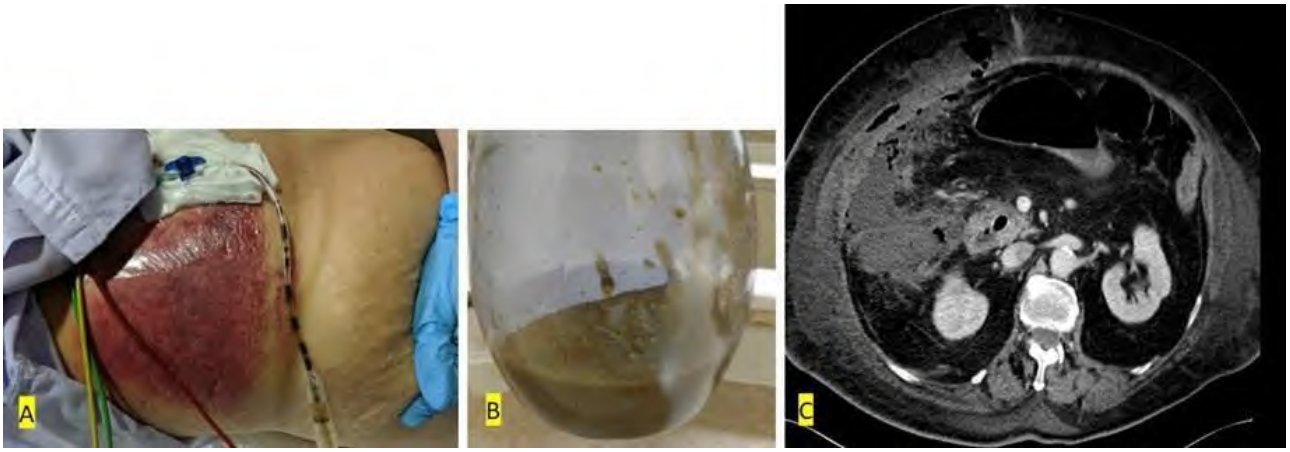

Figure 4. Postoperative complications may necessitate revision surgeries.

A 78-year-old female with a previous open right hemicolectomy for obstructed colon cancer three years ago was managed by endoscopic retrograde cholangiopancreatography (ERCP) for choledocholithiasis. A few weeks after ERCP, an elective laparoscopic cholecystectomy was converted to open due to dense abdominal adhesions. The postoperative recovery was slow and on 7th day the abdomen showed bruising (Image A) and drainage effluent was noted to be feculent (Image B). An urgent CT scan showed a large pocket of fluid collection (Image C) and a reoperative surgery was performed according to damage control principles. The patient underwent a few reoperative procedures and eventually survived.

Care bundles

Beyond resuscitation and appropriate antimicrobial therapy, perioperative care bundles are necessary for enhanced recovery after surgery, which either minimizes the development of PP or optimizes recovery amongst PP patients. The first group of care bundles are goal-directed to reduce the risk of postoperative pneumonia, surgical site infections and central line-associated bloodstream infections. This is important as prevention of hospital-acquired infections can improve survival and recovery amongst PP patients. Also, addressing the risk of developing deep vein thrombosis and stress ulcers perioperatively is crucial for good outcomes. Lastly, considerations for early mobilization and nutritional management should be made towards optimizing the patient towards premorbid functional status. This should be coupled with plans for community discharge the soonest time possible to minimize further exposure to nosocomial infections within institutionalized settings.

Antimicrobial treatment

Early and appropriate antimicrobial treatment is vital for managing PP, which is often associated with multi-drug-resistant organisms. Initial management of PP involves empirical broad-spectrum antimicrobials covering both aerobic and anaerobic organisms as directed by institution guidelines and antibiograms, with ESBL-producing *Enterobacterales* being a common concern. Empiric antibiotic use for PP must consider the likelihood of resistant pathogens, colonization, prolonged hospitalization, and previous antibiotic use, with due consideration for pseudomonal coverage where appropriate. Routine enterococcal coverage is generally not required except in septic shock with previous cephalosporin treatment, immunosuppression, presence of prosthetic heart valves or recurrent IAI with severe sepsis. Hemodynamically stable patients with intra-abdominal abscesses can be treated with tigecycline, although not as monotherapy in the setting of septic shock.

In regions with high susceptibility rates for ESBL-producing *Enterobacterales*, multidrug therapy may be warranted such as piperacillin/tazobactam with daptomycin, linezolid, or vancomycin. Recently, novel beta-lactam beta-lactamase inhibitor (BL-BLI) combinations have shown strong activity against some multidrug-resistant Gram-negative pathogens, such as ceftolozane/tazobactam or ceftazidime/avibactam. These agents should be combined with metronidazole due to limited activity against some *Bacteroides* species.

The duration of antimicrobial therapy depends on the clinical course. For patients managed with early source control, therapy can typically be stopped after the resolution of clinical signs of infection. This is corroborated by the 2018 DURAPOP clinical trials which showed no significant difference in mortality and morbidity between critically ill patients with PP on eight-day antibiotic therapy and similar patients on a more prolonged course of 15 days.

Persistent sepsis after seven days of antibiotic therapy suggests a failure of source control or another focus of infection. Recurrent infections are less likely once symptoms such as fever and leukocytosis resolve and bowel function returns. Patients with *Candida* spp. and *Staphylococcus aureus* infections require close monitoring and treatment continuation for 2-3 weeks.

Antifungal therapy

Abdominal candidiasis, though rare, is more common in patients following major abdominal surgery or trauma, especially those who are immunocompromised or had prolonged antibiotic exposure. Isolation of *Candida* species in post-operative IAI is significant and usually associated with poor prognosis. Empirical antifungal therapy with echinocandins is recommended for hemodynamically unstable patients. Fluconazole may be used if *Candida* cultures are susceptible. Treatment duration is generally 10-14 days, although this is not evidence-based but rather a common practice. Routine treatment for *Candida* spp. in otherwise uncomplicated cases is not recommended in healthy patients.

Nutrition and feeding

Nutritional status is an important determinant of tissue healing, with malnutrition, cachexia, and sarcopenia are associated with poor tissue healing, increased risk of AL as well as postoperative IAI. Such parameters can be optimized in the elective setting postoperatively. Although oral feeding remains the ideal modality of nutrition, this is not possible due to postoperative nausea/vomiting or ileus. Between enteral and parenteral nutrition, a recent meta-analysis concluded that the former was associated with shorter lengths of stay and better postoperative outcomes. The American Society for Parenteral and Enteral Nutrition (ASPEN) guidelines also recommend enteral nutrition within 48 hours of sepsis, including PP, and further support nutritional screening amongst postoperative patients with tools such as the NUTRIC score. ASPEN guidelines also recommend a high-protein diet in such situations, which is echoed by a recent meta-analysis of randomized

controlled trials that found significantly lower rates of PP amongst adults who underwent elective lower gastrointestinal surgery that consumed oral protein-containing diets.

Challenges and future perspectives

Temporal trends of antibiotic resistance

The prevalence of multidrug-resistant organisms in healthcare-associated infections has been observed to be rising in the past few decades. Montravers *et al.* observed that the number of multidrug-resistant *Enterobacterales*, primarily *Klebsiella* spp., was increasing over time in patients receiving treatment for PP. These strains also included extended-spectrum beta-lactamase-producing bacteria, resulting in lower adequacy rates for empirical antibiotic therapy in patients receiving piperacillin/tazobactam monotherapy. Only combinations of carbapenems and vancomycin showed high adequacy rates for empirical antibiotic therapy in PP. In addition, the findings of the prospective, multicenter DURAPOP trial support that piperacillin/tazobactam therapy is associated with therapeutic failure due to increasing antibiotic resistance. Given that the current guidelines for PP and IAIs are based on microbial data published many years ago, further and periodic research is required to identify temporal trends of antibiotic resistance, in order to facilitate updates to existing guidelines on PP. Antimicrobial stewardship is important to prevent the development of multidrug-resistant organisms in surgical patients. A prospective study on 100 patients admitted to the ICU for PP by Augustin *et al.* revealed that the use of broad-spectrum antibiotics between initial intervention and reoperation was a major risk factor for the formation of multidrug-resistant bacteria. Hence, once a patient has improved or results of reliable cultures are available, narrowing the antibiotic regimen is advised to maintain antibiotic efficacy over time. Even if unknown or untreated pathogens are later detected in lower-risk patients, therapy modification is not required if clinical response to source control and early therapy is observed. Recently, the Surgical Infection Society has also published the 2024 update of guidelines on the management of intra-abdominal infections. The updated guidelines also recommend limiting the use of antibiotics to 4 days for patients with source control achieved, and 8 days for critically ill patients, as well as de-escalation of antibiotic use, which is in line with the principles of antimicrobial stewardship.

PP and artificial intelligence

Recently, artificial imaging (AI) technology has been used in diagnosis where pattern recognition from serology or imaging information makes it possible for machine learning algorithms to make accurate predictions. Such algorithms have been applied to predict sepsis risk and prognosticate outcomes, with a systematic review demonstrating area under receiver operating characteristic curve values of up to 0.985, demonstrating high accuracy. Furthermore, AI technology enjoys positive public perception, with approximately 80% of the public having expressed willingness and trust for AI systems to make healthcare diagnosis. Despite its strong performance in the early detection of sepsis and potential application in risk stratification, such models were not necessarily generalizable to other patient cohorts, lacked explainability of results and may have algorithmic data input bias. Furthermore, many ethico-legal issues in incorporating AI decision-making in standard care remain unresolved, such as data privacy and patient confidentiality, equity issues in the underrepresentation of minority groups as well as liability and attribution for patient safety and outcomes. We foresee that AI will have an increasing role in medical decision-making in future.

Implementation issues with PP management

Despite the comprehensive evidence base and guidelines on perioperative prevention and management of PP, implementation of these best practices remains elusive. Factors for lack of adherence include low familiarity with management guidelines, inability to quickly recognize and work up a patient suspicious of PP and misalignment of guidelines with an institution's own practices and processes. As such, lack of compliance can lead to delayed treatment of patients which translates to excess mortality and morbidity, as well as ineffective deployment of care bundles. Solutions to maintain adherence include rigorous and transparent discussions with stakeholders to tailor guidelines to a health system's needs, regular audits and periodical refresher training amongst relevant staff.

Reasons for non-compliance differ significantly in the setting of resource-strapped regions. Many of such places in low-income nations have limited access to medical care because they are too small and far away to support specialized services which are often needed to provide lifesaving and disability-preventing interventions. Despite recommendations to administer empirical antibiotics early in PP, antibiotic administration in isolated regions, like Sub-Saharan Africa, use a "step-up" approach to reduce cost and this causes delay in treatment which increases the risk of mortality. Furthermore, rural areas lack sufficient resources and face severe shortages of medical personnel and supplies. As a result, the World Society of Emergency Surgery recommends the use of a robust triage system in these areas. In addition, patients in need of urgent acute care surgery may be screened using a mix of early warning indications and abdominal signs. Moreover, it is advised to use a tailored diagnostic step-up strategy depending on the hospital's resources. In isolated locations, simple X-rays and ultrasounds could be helpful diagnostic instruments, and the source of infection should be controlled as soon as possible.

Conclusion

The management of PP is a complex and dynamic challenge, especially given the rising threat of AMR. While recent advancements in surgical techniques and early diagnosis protocols have improved outcomes, the need for a multidisciplinary approach remains paramount. Prompt source control tailored antimicrobial therapy, and careful attention to patient resuscitation are essential for achieving success. Recognizing the unique considerations of the elective setting, including optimizing patient status preoperatively, is crucial for preventing and managing PP. Implementation of care bundles, including enhanced recovery after surgery principles, can further enhance outcomes. However, the ongoing challenges of AMR and resource constraints highlight the need for ongoing research, education, and refinement of clinical guidelines. By fostering greater awareness, promoting antimicrobial stewardship, and embracing innovative technologies, we can work towards optimizing patient care and minimizing the impact of PP in a world increasingly impacted by AMR.

Competing interests

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

References

1. Vesteinsdottir E, et al. Sepsis after elective surgery – Incidence, aetiology and outcome. Acta Anaesthesiol Scand. 2021;65:457–465.
2. Sartelli M, et al. Management of intra-abdominal infections: recommendations by the Italian council for the optimization of antimicrobial use. World J Emerg Surg. 2024;19:23.
3. Naumann DN, et al. Novel Textbook Outcomes following emergency laparotomy: Delphi exercise. BJS Open. 2024;8:zrad145.
4. Mann MR, et al. The marginal artery of Drummond revisited: A systematic review. Transl Res Anat. 2021;24:100118.
5. Sparreboom CL, et al. Different Risk Factors for Early and Late Colorectal Anastomotic Leakage in a Nationwide Audit. Dis Colon Rectum. 2018;61:1258–1266.
6. Chan KS, et al. Should Empiric Anti-Fungals Be Administered Routinely for All Patients with Perforated Peptic Ulcers? A Critical Review of the Existing Literature. Pathogens. 2024;13:547.
7. Roehrborn A, et al. The microbiology of postoperative peritonitis. Clin Infect Dis Off Publ Infect Dis Soc Am. 2001;33(9):1513–1519.
8. Chan KS, et al. Outcomes of an outpatient home-based prehabilitation program before pancreaticoduodenectomy: A retrospective cohort study. Ann Hepato-Biliary-Pancreat Surg. 2022;26:375–385.
9. Chan KS, et al. Sustaining a Multidisciplinary, Single-Institution, Postoperative Mobilization Clinical Practice Improvement Program Following Hepatopancreatobiliary Surgery During the COVID-19 Pandemic: Prospective Cohort Study. JMIR Perioper Med. 2021;4:e30473.
10. Anbalakan K, et al. Five year experience in management of perforated peptic ulcer and validation of common mortality risk prediction models - are existing models sufficient? A retrospective cohort study. Int J Surg Lond Engl. 2015;14:38–44.
11. Mak MHW, et al. A prospective validation of Sepsis-3 guidelines in acute hepatobiliary sepsis: qSOFA lacks sensitivity and SIRS criteria lacks specificity (Cohort Study). Int J Surg Lond Engl. 2019;72:71–77.
12. Yaow CYL, et al. Should Procalcitonin Be Included in Acute Cholecystitis Guidelines? A Systematic Review. Med Kaunas Lith. 2023;59:805.
13. Wang Z, et al. Acute Cholangitis. In: Sartelli M, Bassetti M, Martin-Loeches I, editors. Abdominal Sepsis: A Multidisciplinary Approach. Cham: Springer International Publishing; 2018, p. 65–81. Available at: https://doi.org/10.1007/978-3-319-59704-1_7. Last accessed: 10 September 2024.
14. Shelat VG. Appendicectomy, intra-abdominal abscess, percutaneous drainage and non-operative management. ANZ J Surg. 2020;90:2145–2146.
15. Ahmed S, et al. Percutaneous drainage for giant pyogenic liver abscess—is it safe and sufficient? Am J Surg. 2016;211:95–101.
16. Siddaiah-Subramanya M, et al. The psychosocial impact of surgical complications on the operating surgeon: A scoping review. Ann Med Surg 2012. 2021;67:102530.
17. Leow KS, et al. Renal-related adverse effects of intravenous contrast media in computed tomography. Singapore Med J. 2015;56:186–193.
18. Coccolini F, et al. Source control in emergency general surgery: WSES, GAIS, SIS-E, SIS-A guidelines. World J Emerg Surg. 2023;18:41.
19. Marshall JC. Principles of Source Control in the Early Management of Sepsis. Curr Infect Dis Rep. 2010;12:345–353.
20. Sartelli M, et al. The role of the open abdomen procedure in managing severe abdominal sepsis: WSES position paper. World J Emerg Surg. 2015;10:35.
21. Holubar SD, et al. American Society for Enhanced Recovery (ASER) and Perioperative Quality Initiative (POQI) joint consensus statement on prevention of postoperative infection within an enhanced recovery pathway for elective colorectal surgery. Perioper Med. 2017;6:4.
22. Ljungqvist O, et al. Enhanced Recovery After Surgery: A Review. JAMA Surg. 2017;152:292–298.
23. Montravers P, et al. Short-course antibiotic therapy for critically ill patients treated for postoperative intra-abdominal infection: the DURAPOP randomised clinical trial. Intensive Care Med. 2018;44:300–310.

24. Shelat VG, et al. Nutritional Support in Dysphagia. In: Seminars in Dysphagia. IntechOpen; 2015. Available at: https://www.intechopen.com/chapters/48986. Last accessed: 10 September 2024.
25. McClave SA, et al. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient. J Parenter Enter Nutr. 2016;40:159–211.
26. Pu H, et al. Early oral protein-containing diets following elective lower gastrointestinal tract surgery in adults: a meta-analysis of randomized clinical trials. Perioper Med Lond Engl. 2021;10:10.
27. Augustin P, et al. Risk factors for multidrug resistant bacteria and optimization of empirical antibiotic therapy in postoperative peritonitis. Crit Care. 2010;14:R20.
28. Huston JM, et al. The Surgical Infection Society Guidelines on the Management of Intra-Abdominal Infection: 2024 Update. Surg Infect. 2024;25:419–435.
29. Schinkel M, et al. Clinical applications of artificial intelligence in sepsis: A narrative review. Comput Biol Med. 2019;115:103488.
30. Drezga-Kleiminger M, et al. Should AI allocate livers for transplant? Public attitudes and ethical considerations. BMC Med Ethics. 2023;24:102.
31. Gerke S, et al. Chapter 12 - Ethical and legal challenges of artificial intelligence-driven healthcare. In: Bohr A, Memarzadeh K, editors. Artificial Intelligence in Healthcare. Academic Press; 2020; p. 295–336. Available at: https://www.sciencedirect.com/science/article/pii/B9780128184387000125. Last accessed: 10 September 2024.
32. Kissoon N. Sepsis guideline implementation: benefits, pitfalls and possible solutions. Crit Care. 2014;18:207.
33. Perrone G, et al. Management of intra-abdominal-infections: 2017 World Society of Emergency Surgery guidelines summary focused on remote areas and low-income nations. Int J Infect Dis IJID Off Publ Int Soc Infect Dis. 2020;99:140–148.

Chapter 134

Biomarkers use in surgical patients

Enrico Cicuttin
Unit of General Surgery I, IRCCS Fondazione Policlinico San Matteo di Pavia, Pavia, University of Pavia, Italy.

Andrea Dagnoni
Unit of General Surgery I, IRCCS Fondazione Policlinico San Matteo di Pavia, Pavia, University of Pavia, Italy.

Paola Fugazzola
Unit of General Surgery I, IRCCS Fondazione Policlinico San Matteo di Pavia, Pavia, University of Pavia, Italy.

Luca Ansaloni
Unit of General Surgery I, IRCCS Fondazione Policlinico San Matteo di Pavia, Pavia, University of Pavia, Italy.

Introduction

Contemporary surgical medicine is currently on the edge of a historic turning point, as it grapples with the complex challenges and promising opportunities presented by infectious diseases. The field has recognized that these diseases are not only the most arduous to overcome, but also hold the potential for significant enhancement in surgical outcomes. With the advent of durable and highly relevant molecular techniques for the precise detection of specific pathogens, surgeons are now prepared to dominate infections with newfound precision and efficacy. This breakthrough could revolutionize the treatment of infections, which persistently afflict nearly all surgical specialties. Moreover, by immersing itself further within the patient paradigm, the field of surgery has the remarkable potential to transcend its conventional role as a technical specialty and assume a pivotal position within the core model of care. This comprehensive integration will seamlessly integrate surgical interventions into the holistic approach to patient well-being and healthcare delivery. The urgency for such evolution is particularly evident in the context of surgically caused infections, which inflict massive suffering upon patients and demand a staggering toll on healthcare systems worldwide. The ramifications of this transformation extend far beyond the realm of medical practice. By harnessing the power of advanced molecular techniques, surgeons can envision a future where infections are conquered in an unparalleled manner. This newfound ability will not only alleviate the burden of affliction and restore countless lives, but it will also mitigate the inefficiencies and wastage embedded within healthcare systems across the globe. As we stand at the precipice of this groundbreaking shift in surgical medicine, it becomes increasingly evident that the progress and success of the field rely heavily on embracing infectious diseases as both a challenge and an opportunity. By doing so, surgeons are poised to revolutionize the landscape of healthcare, eradicating the adversities imposed by infections and spearheading a new era of uncompromising excellence in surgical outcomes.

Infective biomarkers, assessed with the help of laboratory medicine, hold great potential in addressing the challenges of surgery. In particular, C reactive protein (CRP) and procalcitonin (PCT) have the strongest

literature support for biomarker use in antibacterial stewardship. This narrative review seeks to assist improving the surgical implementation of these biomarkers, focusing on their pathophysiology, normal ranges in surgery, sampling and interpretation, as well as current strengths and limitations.

Background on C reactive protein and procalcitonin

CRP was serendipitously found in the 1930s, during the investigation of a patient who had viral pneumonia. This significant finding marked the identification of the very first biological substance categorized as an "acute phase reactant". In terms of functionality, CRP serves as an opsonin within the innate immune response. It specifically binds to phosphocholine found in injured cells, bacteria, and apoptotic cells, thereby initiating the process of cell clearance. Originating from liver hepatocytes, CRP production occurs in response to pro-inflammatory cytokines, particularly interleukin 6, when infections or injuries are present. Remarkably, CRP acts as a sensitive and prototypic marker for inflammation, exhibiting rapid and robust responses as early as six hours following an injury. Numerous studies have indicated that CRP serves as a predictive indicator for post-operative infections (POI) and post-operative acute kidney injury (AKI). These particular findings contribute to the understanding of the vital role played by CRP in various pathological conditions. By expanding our knowledge on the involvement of CRP, we gain valuable insights into its potential as a diagnostic and prognostic tool for these specific medical scenarios.

PCT is the prohormone of the peptide calcitonin (CT) normally produced by C cells of the thyroid gland and by certain neuroendocrine cells in the lung. In healthy individuals, ProCT is produced in a tissue-distributing manner, and its plasma levels are typically low, ranging from 0.05 to 0.1 ng/mL. However, in response to bacterial and/or severe systemic inflammatory exposure, cells throughout the body secrete PCT and its associated peptides, which may also enter the blood circulation. Furthermore, recent studies have highlighted the multifaceted role of PCT in various physiological processes. In addition to its well-established biomarker function in septic-like conditions, PCT also appears to act as a biomediator, exerting direct and independent toxic effects on cells. This suggests that PCT plays a broader role in immune response regulation and tissue homeostasis. Moreover, investigations using monoclonal antibodies have revealed that certain PCT fragments circulating in the blood are not PCT itself, but rather processed peptides of PCT and mid-PCT. These findings shed light on the complexity of PCT processing and highlight the need for further research to unravel the specific functions and clinical implications of these fragments. While there has been ample documentation supporting the significant increase in serum PCT levels in various septic-like conditions, where it correlates with disease severity and mortality, little attention has been given to the potential influence of baseline PCT and its associated peptides that circulate at low concentrations in healthy individuals. This knowledge gap warrants further exploration to determine whether these baseline levels have any predictive value or serve as early indicators of underlying inflammation or tissue stress. Furthermore, it is becoming increasingly evident that inflammatory and tissue stress stimuli can downregulate a family of plasma membrane transporters responsible for the regulation of toxic ions such as sodium and calcium. This downregulation occurs through the modulation of gene expression and protein phosphorylation mediated by activated intracellular signaling pathways. As PCT has been implicated in tissue stress response, it is plausible to hypothesize that PCT and its associated peptides may contribute to the modulation of ion transporters, thereby influencing cellular ion homeostasis and potentially exacerbating the detrimental effects of inflammatory insults. In conclusion, PCT and its associated peptides, particularly in their processed forms, have emerged as crucial players in immune response regulation, tissue homeostasis, and disease pathogenesis. While their biomarker role in septic-like conditions is well-established, further research is needed to unravel the specific functions and clinical

implications of these molecules in both healthy and diseased states. Additionally, understanding their potential involvement in modulating ion transporters and cellular ion homeostasis could provide valuable insights into the mechanisms underlying the toxic effects of inflammation and tissue stress.

Role of biomarkers in the diagnosis of surgical infections

Surgery may sometimes lead to infections, with an occurrence of 0.5% to% of surgical procedures. Diagnosis is often difficult, with a delay in the identification of causative organisms. Diagnosis is typically made by using the clinical picture (fever, tachycardia, and local signs), imaging techniques (CT, MRI), and samples from drained pus or tissue. There are several difficulties with this method. First, not all abscesses can be imaged. Secondly, in certain events (e.g., surgical procedures involving the bowel), there may be a Gram-negative, culture-negative polymicrobial flora (*Bacteroides* species or other anaerobes). Thirdly, initial tests are often false negative. Finally, time from sending a sample to reporting results may take days. Therefore, one of the solutions would be the use of infective biomarkers 10. The utilization of infective biomarkers in surgical procedures is considered a potential solution for the various challenges encountered in diagnosing infections post-surgery. These biomarkers serve as essential indicators with the capability to aid in early detection and accurate identification of causative organisms. By incorporating infective biomarkers in the diagnostic process, medical professionals can address the limitations encountered with the traditional methods of diagnosis. One of the primary advantages of utilizing infective biomarkers is their ability to overcome the hurdle of abscesses that cannot be imaged. Through their unique properties and characteristics, these biomarkers offer a non-invasive alternative for identifying infections in challenging cases where imaging techniques prove ineffective. By tapping into the potential of these biomarkers, healthcare providers can ensure a more comprehensive and accurate diagnosis, leading to improved patient outcomes. Moreover, when dealing with surgical procedures involving the bowel, it is not uncommon to encounter a Gram-negative, culture-negative polymicrobial flora that includes *Bacteroides* species or other anaerobes. The conventional diagnostic methods often struggle to detect these specific pathogens accurately, resulting in delayed or missed diagnoses. However, the inclusion of infective biomarkers in the diagnostic process can help overcome this challenge by providing a more targeted approach for identifying and distinguishing between various strains of microorganisms. This targeted approach significantly improves the accuracy and efficiency of the diagnostic process, enabling timely interventions and appropriate treatment plans. In addition to addressing the challenges associated with abscess imaging and culture-negative polymicrobial floras, infective biomarkers also prove beneficial in overcoming the issue of false-negative initial tests. Traditional diagnostic methods may fail to detect the presence of infections during the early stages, leading to false-negative results and potential delays in initiating proper treatment. However, by incorporating infective biomarkers, healthcare professionals can enhance the sensitivity and reliability of the diagnostic process, reducing the risk of false negatives and ensuring that infections are detected and treated promptly. Furthermore, the time it takes from sending a sample to receiving the results can be a significant concern in the diagnosis of surgical infections. Delays in obtaining accurate results can lead to prolonged patient suffering, increased healthcare costs, and potential complications. However, the use of infective biomarkers offers a promising solution to this problem. These biomarkers are designed to provide rapid and reliable results, reducing the time required for diagnosis and enabling healthcare providers to make timely and informed decisions regarding patient care. By streamlining the diagnostic process, infective biomarkers contribute to improved efficiency and effectiveness in managing post-surgical infections. In conclusion, the incorporation of infective biomarkers in the diagnosis of surgical infections presents a valuable solution to the challenges encountered with traditional diagnostic methods. By leveraging

the unique properties of these biomarkers, healthcare professionals can overcome limitations related to abscess imaging, culture-negative polymicrobial floras, false-negative initial tests, and lengthy result reporting times. Embracing the use of infective biomarkers not only enhances the accuracy and efficiency of the diagnostic process but also contributes to improved patient outcomes and overall healthcare quality.

As already pointed out, there are two well-known infective biomarkers, CRP and PCT. They are acute-phase reactants that have been used for several years in clinical practice to detect and manage inflammation/infection. The aim of this narrative review was to elaborate on a methodology that could help surgeons in achieving an optimal use of these infective biomarkers by presenting their basic principles and characteristics, the evidence supporting their use in the diagnosis of surgical infections, current clinical practice, and exploring potential future applications. Additionally, the review discusses the different interpretive thresholds and cutoff values used in clinical settings, the limitations and challenges associated with these biomarkers, and potential strategies to overcome these limitations. Furthermore, the review highlights the importance of interdisciplinary collaboration between surgeons, infectious disease specialists, and laboratory experts to enhance the interpretation and utilization of CRP and PCT in surgical care. The review also addresses the emerging role of other biomarkers in the field of surgical infections, potential synergistic use of multiple biomarkers, and the need for further research to validate and refine the clinical utility of infective biomarkers in surgical practice. Overall, this narrative review provides a comprehensive overview of the current understanding and practical implications of CRP and PCT as infective biomarkers in surgical infections, offering valuable insights for surgeons and healthcare professionals involved in the management of surgical patients.

Clinical value and constraints of C reactive protein and procalcitonin in the field of surgery

As reported by several studies, CRP and PCT are predominantly utilized in surgical practice for a multitude of applications. These applications can be categorized into two main domains: clinical practice and scientific research. In clinical practice, CRP and PCT have proven to be invaluable tools for diagnosing postoperative infective complications subsequent to both elective and emergency surgeries. Furthermore, they are utilized for the diagnosis and prognostic assessment of infective complications associated with implantable materials, as well as for evaluating the efficacy of therapeutic interventions in managing infectious postoperative diseases. In the realm of scientific research, these biomarkers are employed for the evaluation of investigational drugs with antimicrobial activity. Additionally, they play a pivotal role in assessing surgical techniques that may potentially induce postoperative infectious complications. Moreover, CRP and PCT are utilized for monitoring the progression of various diseases with secondary inflammatory statuses. Notably, they are also employed in case-control studies for comprehensive evaluations of the pathogenesis of the respective diseases. Although CRP has traditionally been the most utilized biomarker in surgical practice, the preference for PCT has steadily increased since 2015 due to its heightened sensitivity, increased effectiveness, and swift response. By taking advantage of these remarkable qualities, healthcare professionals can make more accurate and timely diagnoses, resulting in improved patient outcomes and optimal treatment plans.

Expanding on the limitations of C-reactive protein (CRP) and procalcitonin (PCT) in surgical practice, it is worth noting that their usage in the clinical setting differs from their application in scientific research. Clinical practice often requires higher cut-off values for PCT when diagnosing postoperative infective complications, which may come as a surprise. This discrepancy can create challenges, particularly in outpatient services where quicker results are needed within a 24–48-hour timeframe. On the other hand, the costs associated with

conducting a single surgery case present a considerable barrier in both clinical and research practice. These tests are relatively costly, especially PCT, in comparison to the expenses associated with other conventional parameters involved in the diagnosis of postoperative infections. Nonetheless, there is a glimmer of hope as the utilization of CRP tests increases, potentially leading to a decrease in their overall costs. Conversely, it is expected that the costs of PCT will rise as its sensitivity levels increase. Such dynamics paint a complex picture of the limitations of CRP and PCT, highlighting the need for further research and exploration in this domain. It is essential to understand these limitations and continue to investigate ways to overcome them, ensuring optimal patient care and improved outcomes in surgical practice. To achieve this, interdisciplinary collaboration between clinicians, researchers, and industry experts is crucial. By pooling resources and knowledge, we can develop innovative solutions to address the limitations of CRP and PCT, ultimately enhancing the diagnostic capabilities and cost-efficiency of these tests. Additionally, ongoing research and technological advancements will undoubtedly contribute to refining these biomarkers' sensitivity and specificity, further optimizing their utility in surgical practice. Through a comprehensive understanding of the limitations and continuous improvement efforts, we can unlock the full potential of CRP and PCT in postoperative care, facilitating timely and accurate diagnosis of infective complications, and subsequently guiding appropriate treatment decisions. As we navigate the evolving landscape of surgical practice, a relentless pursuit of excellence and innovation will drive us towards overcoming these limitations, transforming the field and improving patient outcomes.

Future directions and emerging technologies in infective biomarkers and the development of novel diagnostic tools

CRP and PCT research in the field of surgery will encompass well-defined protocols focused on the usefulness and applicability of CRP and PCT. The implementation of CRP and PCT will significantly enhance the accuracy and reliability in predicting surgical site infections (SSIs). To achieve this, it is imperative to conduct prospective multicenter studies incorporating agreed-upon upper and/or lower measurement cutoff levels for CRP and PCT before the surgical intervention and at designated intervals thereafter. Additionally, it is crucial to consider and account for various confounding factors such as age, nutritional status, malignancy, preoperative infection, and diabetes, which contribute to the development of SSIs. In recent advancements, novel molecules have been developed as an innovative approach to graphically represent the PCT concentrations over time. By analyzing the slopes of the resulting curves, healthcare professionals can determine the "kinetics" of the PCT concentration changes, enabling a more accurate differentiation between patients with bacterial infections and those who have undergone cardiac surgery. Moreover, ongoing research is currently underway to develop new procalcitonin formulations that can be evaluated among patients undergoing surgery. These formulations serve two primary purposes: first, as an *in vitro* diagnostic tool for needle biopsies, and second, as a point-of-care device for rapid measurement of PCT levels in serum or plasma. Furthermore, they are also being explored as an *in vivo* diagnostic option by labeling procalcitonin molecules with radioactive isotopes for detection using positron emission tomography. The development of such innovative approaches demonstrates promising potential in improving the efficacy and precision of diagnosing and managing patients undergoing surgical procedures. As the future unfolds, the integration of artificial intelligence (AI) and machine learning algorithms will further enhance the understanding and utilization of CRP and PCT in surgical settings. AI-powered systems can analyze vast amounts of patient data, including clinical history, laboratory results, and imaging findings, to provide real-time predictions and decision support for healthcare professionals. By

leveraging these advanced technologies, surgical teams can make more informed decisions regarding the timing of interventions, post-operative monitoring, and personalized patient care. This level of precision and predictive power has the potential to revolutionize the field of surgery and significantly improve patient outcomes. Furthermore, the future of CRP and PCT research will also explore the potential of targeted therapies and interventions based on individual patient profiles. By identifying specific molecular markers associated with CRP and PCT dysregulation, researchers can develop targeted interventions that address the underlying causes of surgical complications. These personalized approaches hold great promise in reducing the incidence of SSIs and improving overall surgical outcomes. In conclusion, the future of CRP and PCT research in surgery is characterized by well-defined protocols, advanced diagnostic tools, integration of AI and machine learning, and personalized interventions. Through these developments, the accuracy, reliability, and predictive power of CRP and PCT in predicting and managing surgical site infections are expected to be significantly enhanced. This progress will ultimately lead to improved patient outcomes, reduced healthcare costs, and a revolution in the field of surgery.

Competing interests

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

References

1. Baker RE, et al. Infectious disease in an era of global change. Nature Rev Microbiol. 2022;20:193-205.
2. Godman B, et al. Strategies to improve antimicrobial utilization with a special focus on developing countries. Life. 2021;11:528.
3. Póvoa P, et al. How to use biomarkers of infection or sepsis at the bedside: guide to clinicians. Intens Care Med. 2023;49:142-153.
4. Li P, et al. From Diagnosis to Treatment: Recent Advances in Patient-Friendly Biosensors and Implantable Devices. ACS Nano. 2021;15:1960-2004.
5. Kramvis A, et al. A roadmap for serum biomarkers for hepatitis B virus: current status and future outlook. Nature Rev Gastroenterol Hepatol. 2022;19:727-745.
6. Kyriazopoulou E, et al. Antimicrobial Stewardship Using Biomarkers: Accumulating Evidence for the Critically Ill. Antibiotics (Basel). 2022;11:367.
7. Dias RF, et al. Use of C-reactive protein to guide the antibiotic therapy in hospitalized patients: a systematic review and meta-analysis. BMC Infect Dis. 2023;23:276.
8. August BA, et al. Biomarkers in the intensive care setting: A focus on using procalcitonin and C-reactive protein to optimize antimicrobial duration of therapy. Pharmacotherapy. 2023;43:935-949.
9. Kim CJ. Current Status of Antibiotic Stewardship and the Role of Biomarkers in Antibiotic Stewardship Programs. Infect Chemother. 2022;54:674-698.
10. Seok H, et al. Role of biomarkers in antimicrobial stewardship: physicians' perspectives. Korean J Intern Med. 2024;39:413-429.
11. Panico C, et al. Procalcitonin beyond the acute phase: novel biomediator properties? BMC Med. 2013;11:189.
12. Rizo-Téllez SA, et al. C-reactive protein: a target for therapy to reduce inflammation. Front Immunol. 2023;14:1237729.
13. Rajab IM, et al. How C-Reactive Protein Structural Isoforms With Distinctive Bioactivities Affect Disease Progression. Front Immunol. 2020;11:2126.

14. Chambliss AB, et al. AACC Guidance Document on the Clinical Use of Procalcitonin. J Appl Lab Med. 2023;8:598-634.
15. Vishalashi SG, et al. Serum Procalcitonin as a Biomarker to Determine the Duration of Antibiotic Therapy in Adult Patients with Sepsis and Septic Shock in Intensive Care Units: A Prospective Study. Indian J Crit Care Med. 2021;25:507-511.
16. Bassetti M, et al. Role of procalcitonin in predicting etiology in bacteremic patients: Report from a large single-center experience. Journal of Infection and Public Health. 2020;13:40-45.
17. Dupuy AM, et al. Role of biomarkers in the management of antibiotic therapy: an expert panel review: I - currently available biomarkers for clinical use in acute infections. Ann Intensive Care. 2013;3:22.
18. Tocu G, et al. The Contribution of Procalcitonin, C-Reactive Protein and Interleukin-6 in the Diagnosis and Prognosis of Surgical Sepsis: An Observational and Statistical Study. J Multidiscip Healthc. 2023;16:2351-2359.
19. Chen Y, et al. Predictive value of perioperative procalcitonin, C reactive protein and high-sensitivity C reactive protein for the risk of postoperative complications after non-cardiac surgery in elderly patients: a nested case-control study. BMJ Open. 2023;13:e071464.
20. Tatsuoka T, et al. Early detection of infectious complications using C-reactive protein and the procalcitonin levels after laparoscopic colorectal resection: a prospective cohort study. Surgery Today. 2021;51:397-403.
21. Zhou Q, et al. The predictive value of procalcitonin for postoperative early pancreatic fistula. BMC Surg. 2020;20:90.
22. You P, et al. Postoperative plasma presepsin as a biomarker of postoperative infectious complications in different surgical departments: A meta-analysis and systematic review. Am J Surg. 2024;229:65-75.
23. Yang W, et al. Diagnostic accuracy of C-reactive protein and procalcitonin in the early diagnosis of infections after laparoscopic rectal cancer surgery. ANZ J Surg. 2022;92:2600-2606.
24. Kong X, et al. The Predictive Value of PCT and Other Infection Indicators in Postoperative Infection of Epithelial Ovarian Cancer. Infect Drug Resist. 2023;16:1521-1536.
25. Li H, et al. Simultaneous detection of fungal (1,3)-β-d-glucan and procalcitonin using a dual-label time-resolved fluorescence immunoassay. Biotechnol Appl Biochem. 2021;68:157-164.
26. Schuetz P, et al. Procalcitonin for diagnosis of infection and guide to antibiotic decisions: past, present and future. BMC Med. 2011;9:107.
27. Li D, et al. Diagnostic value of inflammatory indicators for surgical site infection in patients with breast cancer. Front Cell Infect Microbiol. 2023;13:1286313.

Chapter 135

Risk factors, diagnosis and management of infected pancreatitis

Valentina Murzi
Emergency Surgery Unit, Department of Surgical Science, University of Cagliari, Italy.

Eleonora Locci
Emergency Surgery Unit, Department of Surgical Science, University of Cagliari, Italy.

Adolfo Pisanu
Emergency Surgery Unit, Department of Surgical Science, University of Cagliari, Italy.

Mauro Podda
Emergency Surgery Unit, Department of Surgical Science, University of Cagliari, Italy.

Introduction

Acute pancreatitis (AP) is a disease characterized by acute inflammation of the pancreas and histologically acinar cell destruction. It occurs when digestive enzymes produced by the pancreas become prematurely activated within the pancreas itself, leading to inflammation and damage. The global incidence of AP ranges from 13 to 45 cases per 100,000 individuals annually. In most patients, the disease takes a mild course, but the severe form comprises about 20–30% of the patients, with hospital mortality rates of about 15%. According to the revised Atlanta classification (RAC), the patients are classified as having severe AP based on persistent organ failure for more than 48 hours. Approximately 20% of AP cases progress to necrotizing pancreatitis, a severe form characterized by the death of pancreatic and peripancreatic tissue. A heterogeneous collection of fluid and necrosis in the early phase of necrotizing pancreatitis is described as an acute necrotic collection. Once this collection matures into an encapsulated collection, usually after four weeks, it is described as walled-off necrosis (WON). Among those with severe necrotizing pancreatitis, approximately one-third develop infected pancreatitis, named IPN (infected pancreatic necrosis).
Because mortality in severe AP disease is bimodal, with 30 to 50% of patients dying within the first weeks, a survivor bias may be present given that these patients may not live long enough to develop infection. Therefore, if patients survive the initial phase, infection is a likely complication. The probability of infection is also related to the extent of pancreatic necrosis: up to 50% of patients with more than half of the pancreas affected by necrotizing processes develop infection.
The reported incidence of IPN has seemed to decrease in recent years. This may be due to improvements in the general ICU care for these patients, the use of preventive strategies such as enteral nutrition, or the early recognition of problems such as intraabdominal hypertension that may facilitate translocation.

The epidemiology of IPN is influenced by the availability and quality of healthcare resources. Developed regions with advanced diagnostic and therapeutic capabilities may have better outcomes, while resource-limited settings may face higher mortality and morbidity rates.

Risk factors

Understanding the risk factors is crucial for the early identification and management of patients at risk for IPN. Prompt and appropriate medical interventions can help mitigate these risks and improve patient outcomes.

Several risk factors can increase the likelihood of developing IPN:

- The severity of AP and consequent extent of the necrosis (the more extensive the necrosis, the higher the risk of infection).
- The underlying health conditions like gallstones, chronic alcohol abuse, hypertriglyceridemia.
- The risk of delayed medical interventions that can lead to the progression of necrosis and increase the likelihood of infection.
- Invasive procedures, such as endoscopic retrograde cholangiopancreatography (ERCP), can introduce pathogens into the pancreatic area, raising the risk of infection. Surgery or other invasive procedures involving the pancreas or abdominal area can also be risk factors.

There are also patient characteristics that may increase the risk of IPN:

- Immunocompromised state: patients with weakened immune systems, such as those with HIV/AIDS, cancer, or those on immunosuppressive medications.
- Older age is associated with a higher risk of complications including IPN, due to a generally weaker immune response and the presence of comorbidities.
- Obesity is linked to more severe forms of AP and an increased risk of complications, including IPN.

Other factors:

- Presence of comorbidities such as diabetes, cardiovascular disease, and chronic liver disease.
- Persistent Systemic Inflammatory Response Syndrome (SIRS).
- Poor nutritional status: malnutrition or poor nutritional status can weaken the immune system and increase susceptibility to infections.
- Smoking is a risk factor for AP and can exacerbate its severity.

Prognostic factors

Considering the high mortality rates associated with IPN, the identification of high-risk patients in the early stage of the disease (within 48–72 hours from hospital admission) is critical as it can help clinicians guide aggressive interventions and implement more effective management strategies.

Prognostic factors associated with the development of IPN in patients with acute necrotizing or severe AP include older age (>76 years), gallstone etiology, greater than 50% necrosis of the pancreas, delayed oral or enteral nutrition, multiple or persistent organ failure, and invasive mechanical ventilation. Established scores such as the APACHE II and Ranson's have been proposed to grade disease severity and predict mortality.

Similarly, several laboratory parameters, such as inflammatory markers, kidney and liver function tests, have been trialed to accurately predict severe AP, development of necrosis and mortality. Patients with IPN have been found to have higher APACHE II scores and higher values of lipase, C-reactive protein, and procalcitonin compared to patients with sterile necrosis.

Mortality predictors

Predictive factors of mortality have been studied: cholangitis, abdominal compartment syndrome, number of organ failures and duration of organ failure, age, time from onset to first intervention, gastrointestinal/intra-abdominal bleeding, bloodstream infection, and severity classification were the most crucial predictors of mortality of IPN patients. Moreover, the most relevant and potentially modifiable factors to reduce mortality are early hemodynamic and renal support, managing cholangitis with ERCP/ES ≤ 48 h from hospital admission, providing oral or enteral nutrition, and reserving open necrosectomy to patients for whom the minimally invasive and endoscopic step-up approaches have failed to improve clinical conditions.

Pathophysiological mechanisms

The first event in the pathogenesis of AP is the premature activation of pancreatic enzymes within the pancreas, resulting in cell damage, and leading to autodigestion of pancreatic tissue. This autodigestion process triggers an inflammatory response, resulting in the release of inflammatory cytokines and mediators, which cause further tissue damage and inflammation.

Persistent inflammation and enzyme activity lead to local ischemia, cellular injury, and necrosis of pancreatic and peripancreatic tissues. The release of inflammatory mediators and elements of dead tissue on the blood system can extend the damage beyond the pancreas, causing SIRS, characterized by tachycardia, fever, tachypnea and leukocytosis.

Necrotic tissue serves as an ideal medium for bacterial growth. Bacteria can translocate from the gastrointestinal tract to the necrotic pancreatic tissue. This translocation is facilitated by mucosal ischemia, which causes an increase in intestinal cell permeability approximately 72 hours after the acute episode, peaking after seven days, with loss of gut barrier function and immune suppression. The necrotic tissue can become secondarily infected by Gram-negative pathogens such as *Escherichia coli, Klebsiella, Pseudomonas,* and *Enterococcus* species. Infections can occur either spontaneously or be introduced during medical procedures. Less frequently, distant sources of infection such as pneumonia, vascular or urinary tract infections associated with central venous catheters, or bladder catheters are associated with bacteremia and pancreatic necrosis. Finally, local contamination, following surgery or interventional procedures such as ERCP, may be responsible for the infection of pancreatic necrosis.

Infection exacerbates the inflammatory response, leading to increased production of cytokines like TNF-α, IL-1, and IL-6, which amplify local and systemic inflammation. The infected necrotic tissue may form abscesses, and purulent collections can develop, leading to further complications. The systemic spread of infection can result in sepsis, characterized by widespread inflammation, tissue damage, and organ dysfunction. This can lead to multi-organ failure involving the lungs, kidneys, liver, and cardiovascular system.

IPN can cause metabolic disturbances, including hyperglycemia and electrolyte imbalances like hypocalcemia, hypokalemia, hyponatremia, hypomagnesemia and metabolic acidosis. The inflammatory and septic process

can lead to coagulopathies, increasing the risk of bleeding and thrombotic events. Persistent systemic inflammation can progress to multiple organ dysfunction syndrome (MODS), significantly increasing morbidity and mortality.

Clinical presentation

The symptoms of IPN often overlap with those of severe AP but also include signs of systemic infection. Abdominal symptoms include severe abdominal pain: persistent and intense pain in the upper abdomen that may radiate to the back. The pain is usually constant and severe, often worsening after meals. The abdomen may be tender at the palpation and appear swollen or distended. Systemic symptoms include fever and chills (high fever - >38°C - is common, often accompanied by chills, indicating an infection); tachycardia and hypotension, especially if the infection leads to sepsis. Gastrointestinal symptoms include nausea and vomiting: they are common and can lead to dehydration and electrolyte imbalances; jaundice if the bile ducts are obstructed or if there is significant liver involvement.
In patients with IPN is possible to see also signs of SIRS: respiratory distress with rapid breathing or difficulty breathing can occur due to systemic inflammation affecting the lungs or fluid overload; altered mental status with confusion, agitation, or decreased level of consciousness, that indicates severe systemic infection or sepsis.
Complications:

- Sepsis, characterized by widespread inflammation, tissue damage, organ dysfunction, and septic shock, is a critical condition involving severe hypotension and multi-organ failure.
- Organ failure: acute kidney injury, respiratory failure, and cardiovascular insufficiency are potential complications due to systemic infection and inflammation.

Diagnosis
Regarding the diagnosis of IPN, despite numerous studies exploring the role of clinical presentation, laboratory tests, and imaging in diagnosing or predicting the development of IPN, there are still no established diagnostic criteria. The clinical signs of IPN include fever (>38.5°C), abdominal pain, deterioration of clinical parameters, and the persistence of organ failure after the initiation of supportive therapy for AP. In terms of laboratory tests, monitoring white blood cell count, procalcitonin (PCT), and C-reactive protein (CRP) levels are useful, with PCT being more accurate than CRP in predicting the onset of IPN and/or multiple organ dysfunction, as it increases over time compared to patients with sterile pancreatic necrosis. IL-6 and phospholipase A2 are two markers under investigation as potential predictors of IPN. Regarding radiological investigations, contrast-enhanced computed tomography (CE-CT) is the imaging modality of choice (**Figure 1**). The presence of gas bubbles in the pancreatic or peripancreatic collections is a useful sign for detecting or predicting IPN, indicating infection with high certainty (**Figure 2**); however, gas formation occurs in only about half of the patients with infected necrosis (sensitivity 56%, specificity 97%). False positives can result from spontaneous fistulization into the gastrointestinal tract or prior interventions, which can be associated with the presence of gas. In cases where CE-CT is inconclusive, a diagnosis can be made through the analysis of a sample obtained by fine needle aspiration (FNA) under CT or ultrasound guidance for Gram stain and culture. FNA can identify microorganisms and has a higher sensitivity, around 79%, while the risk of introducing microorganisms through FNA into sterile collections is suspected to be very low (<1%). Additionally, culture tests on the collected sample can allow for the de-escalation of broad-spectrum empirical antibiotic therapy and the implementation of targeted therapy. Nevertheless, the use of FNA is limited and not routinely

recommended due to its invasive nature and the high risk of false negatives (20-50%), especially if a CT scan is already suggestive of IPN with the presence of gas in peripancreatic collections. In cases where IPN is not confirmed by (multiple) CT and FNA, but clinical signs of infection persist, "suspected" infected necrosis should be treated as "proven" infected necrosis. Recently, positron emission tomography (PET)/CT with autologous leukocytes labeled with 18F-FDG has been explored for diagnosing IPN with promising results. Finally, diffusion-weighted magnetic resonance imaging (MRI) may have added value in detecting infected pancreatic fluid collections, but results confirming its use in diagnosing IPN are still pending. Since there are no defined criteria or cut-off values, the diagnosis of IPN is based on the evaluation of all these factors. Most patients are diagnosed with suspected IPN based on clinical and biochemical criteria. The persistence of organ failure or the persistence of two inflammatory markers (temperature >38.5°C, leukocytosis, elevated CRP, or PCT) for three consecutive days after the initiation of conservative therapy raises suspicion of IPN. However, these criteria are useful only after the second week of the onset of AP, as IPN typically develops after two to three weeks. Abnormal laboratory values, as well as fever and systemic symptoms during the first weeks, are more likely due to the systemic inflammatory response to AP rather than an infection, while persistent abnormal values beyond two weeks should raise suspicion of an infection.

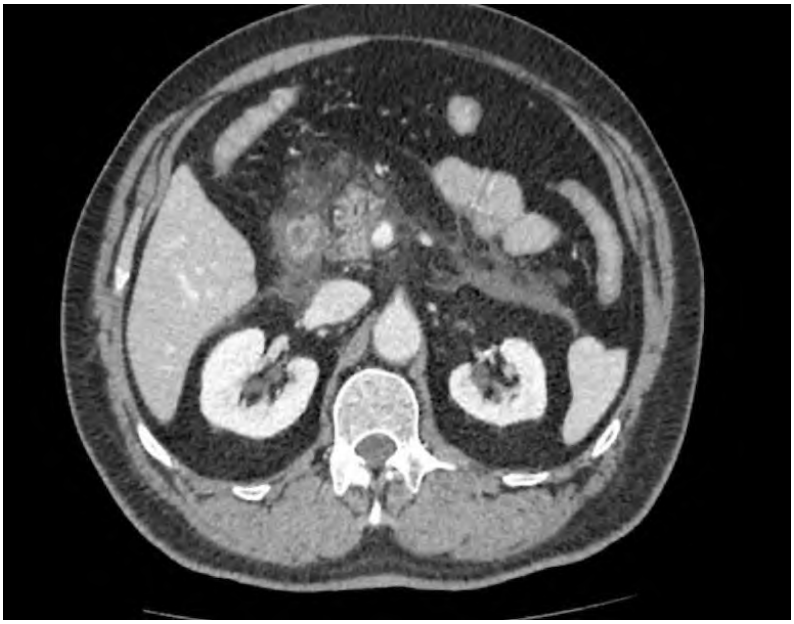

Figure 1. Contrast-enhanced CT scan (CE-CT) performed on hospital admission, demonstrating a stage D Balthazar acute pancreatitis with acute intrapancreatic and peripancreatic necrosis and peripancreatic fluid collections.

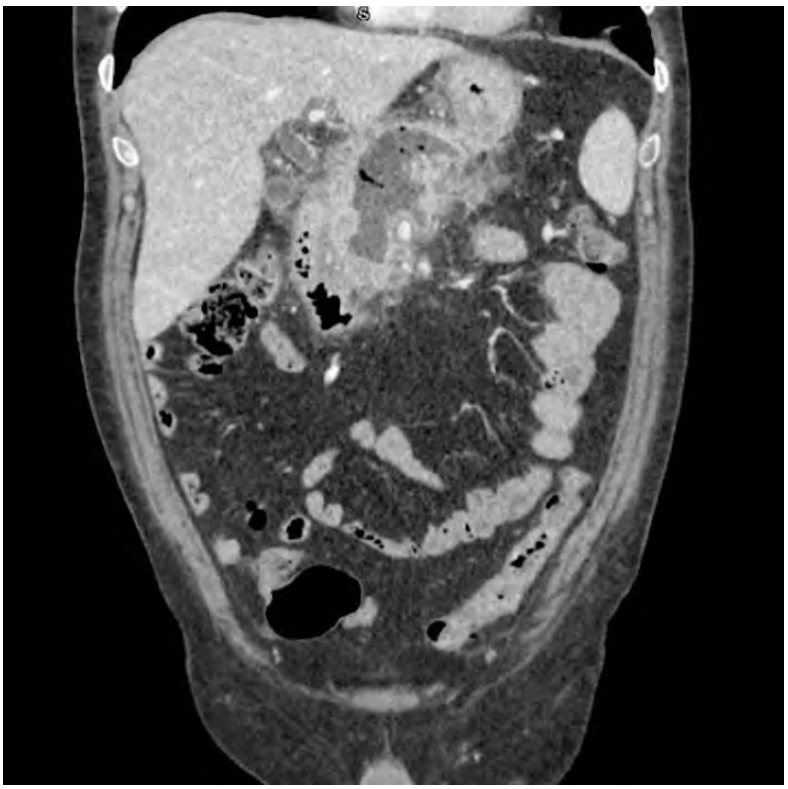

Figure 2. CE-CT scan performed four weeks after the onset of symptoms, demonstrating intrapancreatic walled-off necrosis with signs of infection (intra-necrotic air bubbles).

Management

The treatment of IPN is a challenging process that requires a multidisciplinary approach involving the surgeon, intensivist, radiologist, and endoscopist to determine the appropriate timing for interventions and to identify the most suitable treatment based on the patient's clinical and pathophysiological condition. Over the past decade, the treatment of IPN has evolved from an initially surgical approach with open necrosectomy to what is now called the "step-up approach," which considers a series of interventions—endoscopic, percutaneous, and eventually surgical—applied in steps from the least invasive to the most invasive.

According to the 2019 WSES guidelines on the management of severe AP, the treatment of IPN is based on monitoring, adequate fluid resuscitation, antibiotic therapy, pain management, oral (or enteral) nutrition, ventilation if necessary, and ICU admission if required. Operational management follows the step-up approach, which includes a radiological approach involving percutaneous drainage (PCD), either retroperitoneal or transperitoneal (but preferably retroperitoneal), and an endoscopic approach. In some cases, a combined endoscopic and radiological approach or "dual-modality drainage" may be necessary. If these are insufficient, surgical necrosectomy may be required, using a minimally invasive approach, or ultimately, an open surgical approach.

The first step in managing a patient with IPN is conservative treatment, which includes supporting vital functions, managing organ dysfunction, providing nutritional support, pain management, and administering antibiotic therapy. Monitoring vital signs, organ function, and intra-abdominal pressure is crucial. Early fluid resuscitation is indicated, preferably with isotonic crystalloids at 5–10 ml/kg/h until resuscitation goals are reached, along with frequent monitoring of hemodynamic status and markers of adequate tissue perfusion (hematocrit, blood urea nitrogen, creatinine, lactate). Persistent organ dysfunction despite fluid resuscitation,

requiring specific organ support, is an indication for ICU admission. Mechanical ventilation, invasive or non-invasive, is indicated when high-flow oxygen or continuous positive airway pressure is insufficient to correct dyspnea. In cases of abdominal hypertension, interventions to reduce it include the placement of a nasogastric tube, prokinetics, rectal tube, and if necessary, endoscopic decompression, electrolyte balance management, abdominal cavity expansion with adequate analgesia and sedation, and, if required, invasive procedures such as drainage placement or surgery and a decompressive laparotomy if less invasive measures are not effective. Pain management is a priority in the treatment of AP, with a recommendation to adhere to the latest guidelines on perioperative acute pain management, considering epidural analgesia in selected cases. When oral nutrition is not feasible, enteral nutrition (gastric or jejunal) is recommended, as it maintains the intestinal mucosal barrier, preventing bacterial translocation, infectious complications, and mortality. Total parenteral nutrition should be avoided or considered only as a supplement or when enteral nutrition is not tolerated. Antibiotics are always recommended in the treatment of IPN. The most commonly identified pathogens are Gram-negative bacilli, including *E. coli, Klebsiella* species*, Pseudomonas* species*,* or *Proteus*, followed by Gram-positive cocci, including *Staphylococcus aureus, Streptococcus,* or *Enterococcus* species. Therefore, empirical antibiotic therapy should include agents effective against both aerobic and anaerobic Gram-negative and Gram-positive bacteria. As for the type of antibiotic to use, it should be one with good penetration into pancreatic tissue, such as broad-spectrum penicillins (piperacillin-tazobactam), third-generation cephalosporins, carbapenems (which should be reserved for critically ill patients due to resistance in *Klebsiella pneumoniae*), cefepime, or fluoroquinolones (which, due to high resistance rates, should only be used in patients allergic to beta-lactams) with anaerobic coverage provided by metronidazole. Prophylactic antibiotics have not been shown to prevent the occurrence of extra-pancreatic or pancreatic infections and are therefore not recommended. The routine use of antifungals is also not recommended, although *Candida* infections are common in patients with IPN and in those at high risk of mortality. If a culture sample is obtained through FNA or endoscopic/surgical necrosectomy, antibiotic therapy can be adjusted based on the antibiogram, especially given the incidence of multi-drug-resistant organisms, which can range from 38% to 57% and represent a risk factor for increased morbidity and mortality. Duration of antibiotic therapy is largely determined by the efficacy of source control, as adequate source control is sometimes difficult to assess in IPN, prolonged courses may be required for patients with continued signs of sepsis with organ failure. Despite optimal supportive and conservative therapy, more than half of the patients require operative treatment due to the persistence or worsening of SIRS or organ failure. Operative treatment follows a step-up approach, beginning with image-guided percutaneous (retroperitoneal) catheter drainage (**Figure 3**) or endoscopic transluminal drainage, followed, if necessary, by endoscopic or surgical necrosectomy (VARD, Video-Assisted Retroperitoneal Debridement).

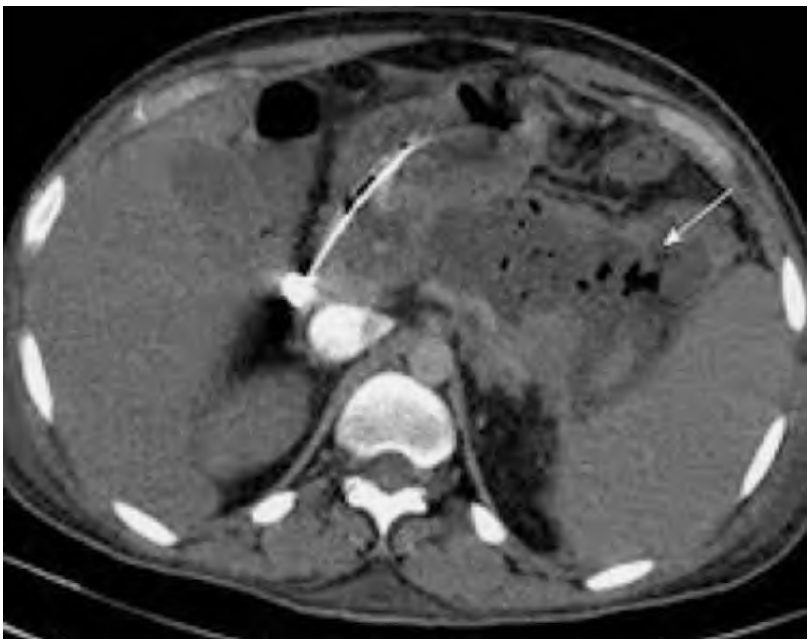

Figure 3. CE-CT scan showing the positioning of a percutaneous retroperitoneal drain inside a large infected necrotic collection, as the first step of a step-up surgical approach.

An operative management should be considered when:

- Organ dysfunction persists for more than four weeks.
- In cases of suspected or documented IPN with clinical deterioration.
- In the absence of documented IPN, when organ dysfunction persists for more than four weeks from the onset of AP, in the case of necrotic collections.
- In cases of symptomatic walled-off necrosis (WON) or pseudocysts causing mechanical obstruction—gastric, intestinal, or biliary—due to mass effect.
- When a symptomatic disconnected pancreatic duct results in a persistent symptomatic peripancreatic collection.

In patients with confirmed or suspected IPN, invasive intervention should be delayed, when possible, until at least four weeks after the initial presentation to allow the collection to become "walled off."

The endoscopic approach includes endoscopic ultrasound (EUS)–guided transmural drainage (ETD) with plastic or metallic stents through single or multiple with or without direct endoscopic necrosectomy (DEN). It can be via either a transgastric or transduodenal approach, depending on the relationship of the collection to the gastric and duodenal walls (**Figure 4**). Collections located in the head of the pancreas are typically drained transduodenally, while others are drained transgastrically. Both plastic and metal stents are used for transmural drainage. Debridement of necrotic tissue can be achieved either through irrigation via a nasocystic tube or a percutaneous catheter, or by DEN, which involves mechanically removing the tissue using an endoscope. While this method has been associated with better outcomes in endoscopic therapy, it also carries significant risks, such as embolism, bleeding, and perforation. Additional treatments include antibiotic irrigation and hydrogen peroxide irrigation.

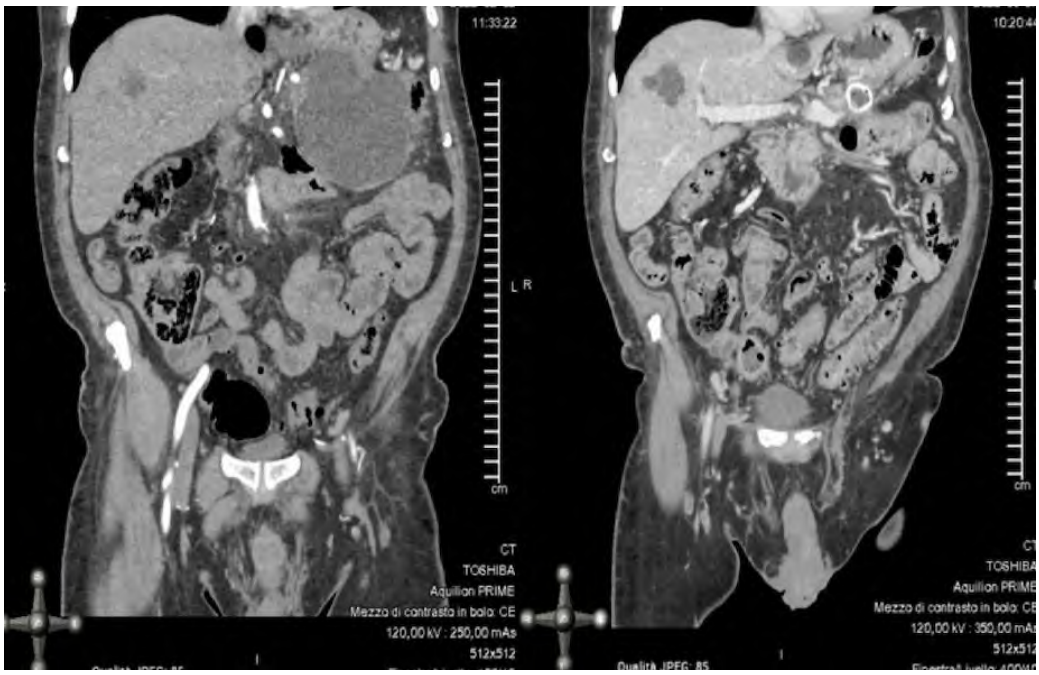

Figure 4. CE-CT scan showing the endoscopic positioning of a trans-gastric AXIOS drain within a large infected necrotic collection, as the second step of a step-up endoscopic approach.

Despite advancements in endoscopic techniques, PCD of pancreatic necrosis still plays an indispensable part in the management of patients with IPN. PCD should be used when endoscopic drainage has failed, is unavailable, or is technically not feasible (para-colic gutter, para-renal, mesenteric, or pelvic location). PCD can be performed under ultrasound or CT guidance. The retroperitoneal approach via the left or right posterolateral site is preferred, as it avoids the risk of peritoneal contamination, but also transperitoneal or transluminal approach can also be used when the retroperitoneal route is not accessible. PCD placed in the retroperitoneum or pelvis not only allows for effective drainage of the collection but also has the advantage of providing an entry point for other minimally invasive debridement methods, such as percutaneous endoscopic necrosectomy (PEN) endoscopic sinus tract debridement (STE) or video-assisted retroperitoneal debridement (VARD). Finally, the use of PCD can be a safe and effective source control in patients in the early stages of IPN (<2–4 weeks) where conservative treatment is failing.

Surgical intervention is indicated when percutaneous and endoscopic procedures have not been successful, in cases of abdominal compartment syndrome, uncontrollable hemorrhage not managed by endovascular procedures, intestinal ischemia, acute gangrenous cholecystitis, or an enteric fistula in continuity with a peripancreatic collection. Surgery should be postponed until at least the fourth week after the onset of symptoms; if urgent surgery is required earlier, routine necrosectomy during the same procedure is not recommended.

- In the VARD (Video-Assisted Retroperitoneal Debridement) approach, the access point created by a previously placed PCD is used to reach the retroperitoneal space for an intracavitary videoscopic necrosectomy. After the procedure, additional drains may be placed for postoperative lavage.
- Surgical transgastric debridement can be performed either laparoscopically or openly and involves creating an anterior gastrotomy to access the posterior wall of the stomach, allowing for transmural access to the necrosis. A nasogastric tube is then placed into the necrotic area for postoperative lavage. Finally,

open debridement may be necessary for critically ill patients who have not benefited from prior minimally invasive treatments or for those with extensive necrosis spread throughout the abdomen.

- Disconnected Pancreatic Duct Syndrome (DPDS) is a complication that occurs in some patients with severe AP, where the main pancreatic duct is disrupted, leading to a lack of continuity between the duct and the gastrointestinal tract. This condition often results in a persistent pancreatic fistula, usually presenting as a peripancreatic fluid collection. Treatment typically involves operative resection, such as a distal pancreatectomy, which can be performed in the subacute phase (30–60 days after onset) or later after initial management with less invasive techniques. The procedure carries risks like morbidity and splenectomy, and in some cases, islet autotransplantation may be considered to preserve endocrine function. Minimally invasive and endoscopic approaches, including EUS-guided transmural stenting, are emerging as alternatives, particularly for patients unsuitable for surgery. These techniques may reduce operative morbidity and provide long-term management options.
- In patients who survive, it is important to identify the cause of AP episodes and eliminate it. This may involve treating gallstones or encouraging the cessation of alcohol consumption, but other potential etiologies should also be considered. Regarding cholecystectomy in cases of acute biliary pancreatitis, it should be performed after the resolution of pancreatic collections or at least 6 weeks after the episode.

Outcomes

The outcomes of IPN can vary significantly depending on several factors, including the timing and effectiveness of treatment, the patient's overall health, and the extent of the necrosis. IPN is associated with a high mortality rate, that ranges from 15% to 30%, but it can be higher in critically ill patients or those with significant comorbidities. IPN often leads to a range of complications, including sepsis, bleeding, abdominal compartment syndrome, and long-term complications such as persistent organ dysfunction with pancreatic insufficiency, both endocrine (diabetes) and exocrine, chronic pancreaticocutaneous fistula, reduced quality of life due to chronic pain, nutritional deficiencies, and need of ongoing medical care. These complications contribute to the high morbidity and can prolong hospital stays and recovery time. The step-up approach has improved outcomes compared to traditional open surgery, but it can be associated with significant morbidity, including post-operative pancreatic fistulas, infections, and the need for repeated procedures. Conservative management can stabilize up to 30-50% of patients without requiring further intervention. However, more than half of the patients with IPN will eventually need an invasive procedure due to persistent or worsening systemic inflammatory response syndrome or organ failure. Endoscopic transmural drainage of pancreatic collections has a success rate of over 95%, with adverse events up to 12%, primarily including bleeding, stent displacement, and perforation. The clinical success rate for PCD is 30-60%; with an adverse event rate of 25%, of which pancreatocutaneous fistula is the most common. The presence of organized collections, failure to reduce in size of the collection, absence of improvement in organ failure a week after drainage and multiple necrotic collections have been identified as predictors for failure in different studies. VARD has a high success rate, especially when combined with prior PCD, with positive outcomes in up to 70-90% of cases. The risks include bleeding, infection, and the need for additional surgeries. However, the morbidity is generally lower than with open surgery, resulting in better long-term outcomes and reduced postoperative complications. Open necrosectomy, while effective in removing extensive necrosis, is associated with higher complication rates and should be used when absolutely necessary. Significant risks include bleeding, organ failure, infection, and prolonged recovery times. Patients may require multiple surgeries and extended ICU stays. Long-

term complications can involve chronic pancreaticocutaneous and enterocutaneous fistulae, pancreatic insufficiency, and abdominal wall hernias.

Conclusion

IPN is a severe clinical condition with no standardized diagnostic criteria, and it carries a high rate of mortality and complications. Management of this condition requires a multidisciplinary approach, involving various specialists such as surgeons, endoscopists, radiologists, intensivists, and infectious disease experts. Key aspects of managing this pathology include monitoring vital signs, inflammation markers, and organ failure indices. Treatment focuses on supporting vital functions, pain control, enteral nutrition, antibiotic therapy, and, if necessary, an operative intervention following a "step-up approach," progressing from the least to the most invasive options to identify the best treatment for each individual patient.

Competing interests

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

References

1. Leppäniemi A, et al. 2019 WSES guidelines for the management of severe acute pancreatitis. World J Emerg Surg. 2019;14:27.
2. Banks PA, et al. Classification of acute pancreatitis--2012: revision of the Atlanta classification and definitions by international consensus. Gut. 2013;62:102-111.
3. Roy M, et al. Pancreatitis sepsis: Evolution and principles in the management of necrotizing pancreatitis. Surgery. 2023;174:406-409.
4. Podda M, et al. Compliance with evidence-based clinical guidelines in the management of acute biliary pancreatitis: the MANCTRA-1 study protocol. Updates Surg. 2021;73:1757-1765.
5. Podda M, et al. Infected pancreatic necrosis: outcomes and clinical predictors of mortality. A post hoc analysis of the MANCTRA-1 international study. Updates Surg. 2023;75:493-522.
6. Podda M, et al. coMpliAnce with evideNce-based cliniCal guidelines in the managemenT of acute biliaRy pancreAtitis): The MANCTRA-1 international audit. Pancreatology. 2022;22:902-916.
7. Tran A, et al. Prognostic factors associated with development of infected necrosis in patients with acute necrotizing or severe pancreatitis-A systematic review and meta-analysis. J Trauma Acute Care Surg. 2022;92:940-948.
8. Ning C, et al. Prediction of survival in patients with infected pancreatic necrosis: a prospective cohort study. Int J Surg. 2024;110:777-787.
9. Ji L, et al. Risk factors of infected pancreatic necrosis secondary to severe acute pancreatitis. Hepatobiliary Pancreat Dis Int. 2016;15:428-433.
10. Roberts SE, et al. The incidence and aetiology of acute pancreatitis across Europe. Pancreatology. 2017;17:155-165.
11. Townsend JCM, et al. (2016). Sabiston textbook of surgery (20th ed.) Elsevier - Health Sciences Division.
12. De Waele JJ. Rational use of antimicrobials in patients with severe acute pancreatitis. Semin Respir Crit Care Med. 2011;32:174-180.
13. Shah J, et al. Infected pancreatic necrosis-Current trends in management. Indian J Gastroenterol. 2024 ;43:578-591.

14. Baron TH, et al. American Gastroenterological Association Clinical Practice Update: Management of Pancreatic Necrosis. Gastroenterology. 2020;158:67-75.e1..
15. Wolbrink DRJ, et al. Management of infected pancreatic necrosis in the intensive care unit: a narrative review. Clin Microbiol Infect. 2020;26:18-25.
16. Working Group IAP/APA Acute Pancreatitis Guidelines. IAP/APA evidence-based guidelines for the management of acute pancreatitis. Pancreatology. 2013;13:e1-15.
17. van Santvoort HC, et al. A step-up approach or open necrosectomy for necrotizing pancreatitis. N Engl J Med. 2010;362:1491-502.
18. Podda M, et al. The 2023 MANCTRA Acute Biliary Pancreatitis Care Bundle: A Joint Effort Between Human Knowledge and Artificial Intelligence (ChatGPT) to Optimize the Care of Patients With Acute Biliary Pancreatitis in Western Countries. Ann Surg. 2024;279:203-212.
19. Carter CR, et al. Percutaneous necrosectomy and sinus tract endoscopy in the management of infected pancreatic necrosis: an initial experience. Ann Surg. 2000;232:175-80.
20. Tan V, Charachon A, et al. Endoscopic transgastric versus surgical necrosectomy in infected pancreatic necrosis. Clin Res Hepatol Gastroenterol. 2014;38:770-776.
21. Bugiantella W, et al. Necrotizing pancreatitis: A review of the interventions. Int J Surg. 2016;28 Suppl 1:S163-71.
22. Di Martino M, et al. Timing of Cholecystectomy After Moderate and Severe Acute Biliary Pancreatitis. JAMA Surg. 2023;158:e233660. Erratum in: JAMA Surg. 2024;159:353.

Chapter 136

Intra-abdominal candidiasis

Gabriele Sganga
Emergency Surgery and Trauma, Fondazione Policlinico Universitario A. Gemelli IRCC 1, Roma, Italy; Università Cattolica del Sacro Cuore, Roma, Italy.

Antonio La Greca
Emergency Surgery and Trauma, Fondazione Policlinico Universitario A. Gemelli IRCC 1, Roma, Italy; Università Cattolica del Sacro Cuore, Roma, Italy.

Pietro Fransvea
Emergency Surgery and Trauma, Fondazione Policlinico Universitario A. Gemelli IRCC 1, Roma, Italy.

Introduction

Intra-abdominal candidiasis (IAC), which includes forms such as pancreatic candidiasis, *Candida* peritonitis, and biliary candidiasis, continues to be a significant challenge due to its high mortality rates and the complexity of its management.
The incidence of systemic fungal infections in surgical patients, particularly in modern surgical intensive care units, has increased over the last decade. This increase is notable among patients who are not as critically ill as previously thought due to multiple risk factors.

Global incidence of fungal infections

Fungal diseases affect over a billion people and kill more than 1.5 million annually. Key statistics include:

- 3,000,000 cases of chronic pulmonary aspergillosis.
- 223,100 cases of cryptococcal meningitis complicating HIV/AIDS.
- 700,000 cases of invasive candidiasis.
- 500,000 cases of *Pneumocystis jirovecii* pneumonia.
- 250,000 cases of invasive aspergillosis.
- 100,000 cases of disseminated histoplasmosis.
- 10,000,000 cases of fungal asthma.
- 1,000,000 cases of fungal keratitis.

The Leading International Fungal Education (LIFE) portal has estimated the burden of serious fungal infections country by country for over 5.7 billion people since 2013.

Nosocomial fungal infections

The incidence of nosocomial fungal infections has increased, especially in departments where complex and invasive procedures are performed. The SOAP Study in 2002 observed that 37% of ICU patients had an infection, with 24% acquiring it in the ICU. Nosocomial *Candida* infections have become more prevalent, now the fourth most common cause of nosocomial bloodstream infections.

Surgical patients

A study in Spanish hospitals found that candidemia occurs in one critical patient for every 500 ICU admissions, with an incidence of systemic candidiasis around 2.2%. The incidence of *Candida* infections in surgical patients has increased from 2.5% to 5.6% per 1000 discharges. *Candida* peritonitis is associated with a mortality rate of 60-70%.

Risk factors

The following factors contribute to the increased risk of systemic fungal infections:

1. Surgery: advances in surgery have extended operations to patients with multiple risk factors and to new areas like organ transplantation and trauma surgery.
2. Immunocompromised patients: more patients with conditions like asthma, AIDS, cancer, and organ transplants are being admitted to surgical wards.
3. Technological and pharmacological improvements: these have prolonged survival but increased the risk of multi-organ dysfunctions and invasive replacement therapies like mechanical ventilation and dialysis.
4. Antibiotic use: prolonged use of antibiotics and endovascular catheters contributes to the risk.

Pathogenesis

Gut origin of sepsis

The "gut origin of sepsis" hypothesis suggests that bacteria from the intestinal tract translocate across the epithelial barrier, causing sepsis at distant sites. *Candida albicans*, normally a harmless commensal, can translocate due to immune system alterations and gastrointestinal mucosa damage, leading to systemic candidiasis.

Factors contributing to fungal spread

1. Central venous catheters: provide direct access to the bloodstream.
2. Broad-spectrum antibacterials: enable fungal overgrowth.
3. Trauma or gastrointestinal surgery: disrupt mucosal barriers.
4. Critical illness: often associated with proximal gut overgrowth of enteric organisms due to anti-acid use, non-use of the digestive tract, and shock states.

Bacterial translocation

Although bacterial translocation's clinical significance remains unclear, measures like reducing gastric cytoprotective therapy, using selective digestive decontamination, early enteral diets, and optimizing circulation can decrease bacterial translocation and infection rates.

Risk factors for invasive candidiasis

Intra-abdominal candidiasis occurs frequently in patients with gastrointestinal perforations, with incidences varying from 30% to 48% depending on the type of perforation. Gastro-duodenal perforations are particularly associated with higher rates of *Candida* peritonitis compared to appendicular perforations. The disease is also seeing a shift from *Candida albicans* to non-*albicans* species, such as *Candida glabrata* and *Candida krusei*, which are often less susceptible or resistant to common antifungals like fluconazole. In **Table 1**, risk factors for invasive candidiasis are illustrated. In **Table 2** specific risk factors for IAC are illustrated.

Table 1. Risk factors for invasive candidiasis.

Risk factor	Description
Surgery	Increased complexity and invasiveness
Immunocompromised status	Underlying diseases and treatments (asthma, AIDS, cancer, transplants)
Technological advances	Prolonged survival with multi-organ dysfunctions
Antibiotic use	Prolonged and broad-spectrum usage
Central venous catheters	Direct bloodstream access
Gastrointestinal surgery	Disruption of mucosal barriers
Trauma	Increased susceptibility
Nutritional status	Malnutrition and total parenteral nutrition use
Hyperglycemia	Increased risk in diabetic patients

Table 2. Specific risk factors for intra-abdominal candidiasis.

Risk factor	Description
Increased surgical procedures	Premature, newborn, elderly, fragile patients
Critical underlying diseases	Tumors, leukemia, organ transplants, AIDS
Complex abdominal surgery	Higher risk of intra-abdominal candidiasis
Re-laparotomies	Increased risk of intra-abdominal sepsis
Severe burns	Higher risk due to immune suppression
Immunocompromised status	Due to chemotherapy, immunotherapy, corticosteroids

Diagnosis

Diagnosing intra-abdominal *Candida* infections is challenging due to the nonspecific nature of clinical signs and laboratory findings. Positive blood cultures confirm the diagnosis but have a sensitivity of just 70%.

Samples from non-sterile sites often lack specificity. Histologically proven invasive fungal growth in a biopsy of sterile tissues confirms the diagnosis.

Diagnostic tools

1. Blood test for *Candida* infections. Measures (1-3)-β-D-glucan (BDG) with a sensitivity of 76% and specificity of 85%.
2. PCR and molecular methods. Polymerase chain reaction (PCR) assays and other molecular methods can detect *Candida* DNA in blood or tissue samples, providing rapid and sensitive diagnosis. These methods are still being evaluated for routine clinical use but show promise in improving diagnostic accuracy.
3. Culture and microscopy. The definitive diagnosis of IAC involves isolating *Candida* species from normally sterile sites such as peritoneal fluid, abscess material, or tissue biopsy. Cultures can be obtained via percutaneous or surgical sampling. Direct microscopic examination using Gram stain or Calcofluor white staining can rapidly identify *Candida*.
4. Tissue biopsy. Histopathological examination of tissue biopsies can reveal the presence of fungal elements. Special stains like periodic acid-Schiff (PAS) or Gomori methenamine silver (GMS) are used to visualize *Candida*. This method can confirm invasive infection and differentiate between colonization and true infection.
5. CT scans. Contrast-enhanced computed tomography (CT) is the imaging modality of choice for identifying abscesses, fluid collections, and other intra-abdominal pathology. CT can help guide percutaneous drainage or surgical intervention.
6. T2 Magnetic Resonance (T2MR) panels. Detects *Candida* species quickly, useful for diagnosing candidemia.

Combining clinical, radiological, microbiological, and histopathological data is crucial for accurate diagnosis. An integrated diagnostic approach helps to distinguish IAC from other intra-abdominal infections and guides appropriate antifungal therapy.

Treatment and outcomes

Early and aggressive management, including source control and antifungal treatment within five days, improves survival rates. The management often requires a combination of surgical intervention and antifungal therapy. Mortality rates for *Candida* peritonitis range from 25% to 60%, with higher rates in ICU patients. Lack of adequate therapy or source control significantly increases mortality.

Antifungal treatment

Empirical antifungal treatment with echinocandins or lipid formulations of amphotericin B is recommended for critically ill patients or those with previous azole exposure. Fluconazole can be used for non-severe cases, but resistance is a concern.

One promising new treatment is rezafungin, a novel echinocandin. Rezafungin has shown potential due to its excellent pharmacokinetics and pharmacodynamics, including a long half-life that reduces dosing frequency. This agent has demonstrated effectiveness against echinocandin-resistant strains of *Candida glabrata* in recent studies, suggesting it may be a valuable addition to the therapeutic arsenal against IAC

Importance of surgical intervention

Surgical intervention is often a crucial component in the management of intra-abdominal candidiasis (IAC). The primary goal of surgery is to control the source of infection, which often involves drainage of abscesses, debridement of necrotic tissue, and repair of any perforations in the gastrointestinal tract. Effective surgical management can significantly reduce fungal load and improve patient outcomes.

1. Source control: this is paramount in managing IAC. Surgical procedures aim to eliminate the source of infection, such as repairing perforated ulcers or removing infected tissues. This helps in reducing the fungal burden and facilitates the effectiveness of antifungal therapy.
2. Drainage of abscesses: in cases where intra-abdominal abscesses are present, percutaneous drainage or surgical drainage may be necessary. This intervention helps in directly removing the localized collection of infection, thus aiding in quicker recovery
3. Debridement: surgical debridement involves the removal of necrotic or infected tissue, which can serve as a reservoir for fungal infection. This procedure is essential in cases where the infection is not controlled by antifungal therapy alone.

Conclusion

Systemic fungal infections in surgical patients are increasing due to various risk factors. Early diagnosis and aggressive treatment are crucial for improving outcomes. The diagnosis of intra-abdominal candidiasis involves a high index of clinical suspicion, appropriate imaging studies, and microbiological confirmation through culture and non-culture methods. Coordinated, multidisciplinary patient care is essential for managing these infections effectively.

Competing interests

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

References

1. Bassetti M, et al Incidence and outcome of invasive candidiasis in intensive care units (ICUs) in Europe: results of the EUCANDICU project. Crit Care. 2019;23:219.
2. Bassetti M, et al. A multicenter multinational study of abdominal candidiasis: epidemiology, outcomes and predictors of mortality. Intensive Care Med. 2015;41:1601-1610.
3. Vincent JL, et al. Epidemiology, diagnosis and treatment of systemic Candida infection in surgical patients under intensive care. Intensive Care Med. 1998;24:206-216.
4. Bongomin F, et al. Global and Multi-National Prevalence of Fungal Diseases-Estimate Precision. J Fungi (Basel). 2017;3:57.
5. Denning, D.W. Global fungal Burden. Mycoses 2013;56:13.
6. Limper AH, et al. Fungal infections in HIV/AIDS. Lancet Infect Dis. 2017;17:e334-e343.
7. Vincent JL, et al. Sepsis in European intensive care units: results of the SOAP study. Crit Care Med. 2006;34:344-353.

8. Vincent JL, et al. The prevalence of nosocomial infection in intensive care units in Europe. Results of the European Prevalence of Infection in Intensive Care (EPIC) Study. EPIC International Advisory Committee. JAMA. 1995;274:639-644.
9. Miguel N, et al. Sepsis-related organ failure assessment and withholding or withdrawing life support from critically ill patients. Crit Care. 1998;2:61-66.
10. Aguilar G, et al. Epidemiology of invasive candidiasis in a surgical intensive care unit: an observational study. BMC Res Notes. 2015;8:491.
11. Sganga G. Clinical aspects of invasive candidiasis in the surgical patient. Drugs. 2009;69 Suppl 1:29-32.
12. Haltmeier T, et al. Candida Score as a Predictor of Worse Outcomes and Mortality in Severely Injured Trauma Patients with Positive Candida Cultures. Am Surg. 2015;81:1067-1073.
13. Enoch DA, et al. The Changing Epidemiology of Invasive Fungal Infections. Methods Mol Biol. 2017;1508:17-65.
14. Blyth DM, et al. Resistance patterns and clinical significance of Candida colonization and infection in combat-related injured patients from Iraq and Afghanistan. Open Forum Infect Dis. 2014;1:ofu109.
15. Manolakaki D, et al. Candida infection and colonization among trauma patients. Virulence. 2010;1:367-375.
16. Mathur P, et al. Five-year profile of candidaemia at an Indian trauma centre: High rates of Candida auris blood stream infections. Mycoses. 2018;61:674-680.
17. Cruciani M, et al. Prophylaxis of Candida infections in adult trauma and surgical intensive care patients: a systematic review and meta-analysis. Intensive Care Med. 2005;31:1479-1487.
18. Guery BP, et al. Management of invasive candidiasis and candidemia in adult non-neutropenic intensive care unit patients: Part I. Epidemiology and diagnosis. Intensive Care Med. 2009;35:55-62.
19. Deitch EA. Gut-origin sepsis: evolution of a concept. Surgeon. 2012;10:350-356.
20. MacFie J, et al. Gut origin of sepsis: A prospective study investigating associations between bacterial translocation, gastric microflora, and septic morbidity. Gut. 1999; 45:223-228.
21. Schweinburg FB, et al. Transmural migration of intestinal bacteria during peritoneal irrigation in uremic dogs. Proc Soc Exp Biol Med. 1949;71:150-153.
22. Assimakopoulos SF, et al. Gut-origin sepsis in the critically ill patient: pathophysiology and treatment. Infection. 2018;46:751-760
23. Lu F, et al. Functions and regulation of lipocalin-2 in gut-origin sepsis: a narrative review. Crit Care. 2019;23:269.
24. Jiang LY, et al. Changes of the immunological barrier of intestinal mucosa in rats with sepsis. World J Emerg Med. 2010;1:138-143.
25. Orasch C, et al. Candida species distribution and antifungal susceptibility testing according to European Committee on Antimicrobial Susceptibility Testing and new vs. old Clinical and Laboratory Standards Institute clinical breakpoints: a 6-year prospective candidaemia survey from the fungal infection network of Switzerland. Clin Microbiol Infect. 2014;20:698-705.
26. Lilly EA, et al. Immune Protection against Lethal Fungal-Bacterial Intra-Abdominal Infections. mBio. 2018;9:e01472-17.
27. Arendrup MC. Candida and candidaemia. Susceptibility and epidemiology. Dan Med J. 2013;60:B4698.
28. Amornphimoltham P, et al. Gut Leakage of Fungal-Derived Inflammatory Mediators: Part of a Gut-Liver-Kidney Axis in Bacterial Sepsis. Dig Dis Sci. 2019;64:2416-2428.
29. Khatib R, et al. Current trends in candidemia and species distribution among adults: Candida glabrata surpasses C. albicans in diabetic patients and abdominal sources. Mycoses. 2016;59:781-786.
30. Albac S, et al. Candida albicans is able to use M cells as a portal of entry across the intestinal barrier in vitro. Cell Microbiol. 2016;18:195-210.
31. Cheng S, et al. Profiling of Candida albicans gene expression during intra-abdominal candidiasis identifies biologic processes involved in pathogenesis. J Infect Dis. 2013;208:1529-1537.
32. Kronen R, et al. Invasive Fungal Infections Secondary to Traumatic Injury. Int J Infect Dis. 2017;62:102-111.
33. Rasilainen SK, et al. Microbial colonization of open abdomen in critically ill surgical patients. World J Emerg Surg. 2015;10:25.

34. Jabra-Rizk MA, et al. Candida albicans Pathogenesis: Fitting within the Host-Microbe Damage Response Framework. Infect Immun. 2016;84:2724-2739.
35. Montravers P, et al. Therapeutic management of peritonitis: a comprehensive guide for intensivists. Intensive Care Med. 2016;42:1234-1247.
36. Blumberg HM, et al. Risk factors for candidal bloodstream infections in surgical intensive care unit patients: the NEMIS prospective multicenter study. The National Epidemiology of Mycosis Survey. Clin Infect Dis. 2001;33:177-186.
37. Rajendran R, et al. A Prospective Surveillance Study of Candidaemia: Epidemiology, Risk Factors, Antifungal Treatment and Outcome in Hospitalized Patients. Front Microbiol. 2016;7:915.
38. Eggimann P, et al. Diagnosis of invasive candidiasis in the ICU. Ann Intensive Care. 2011;1:37.
39. Sandven P, et al. Significance of Candida recovered from intraoperative specimens in patients with intra-abdominal perforations. Crit Care Med. 2002;30:541-547
40. de Ruiter J, et al. The epidemiology of intra-abdominal flora in critically ill patients with secondary and tertiary abdominal sepsis. Infection. 2009;37:522-527.
41. León C, et al. Fungal colonization and/or infection in non-neutropenic critically ill patients: results of the EPCAN observational study. Eur J Clin Microbiol Infect Dis. 2009;28:233-242.
42. Solomkin JS, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. Clin Infect Dis. 2010;50:133-164.
43. Solomkin JS. Pathogenesis and management of Candida infection syndromes in non-neutropenic patients. New Horiz. 1993;1:202-213.
44. Solomkin JS, et al. The role of Candida in intraperitoneal infections. Surgery. 1980;88:524-530.
45. Eggimann P, et al. Candida colonization index and subsequent infection in critically ill surgical patients: 20 years later. Intensive Care Med. 2014;40:1429-1448.
46. Khanna K, et al. Hypoalbuminemia Is Associated With Septic Revisions After Primary Surgery and Postoperative Infection After Revision Surgery. Spine (Phila Pa 1976). 2018;43:454-460.
47. de Luis DA, et al. Surgical infection and malnutrition. Nutr Hosp. 2014;30:509-513.
48. McCall ME, et al. Maximizing Nutrition Support Practice and Measuring Adherence to Nutrition Support Guidelines in a Canadian Tertiary Care ICU. J Intensive Care Med. 2018;33:209-217.
49. Cahill NE, et al. Nutrition therapy in the critical care setting: what is "best achievable" practice? An international multicenter observational study. Crit Care Med. 2010;38:395-401.
50. Kizilarslanoglu MC, et al. Sarcopenia in critically ill patients. J Anesth. 2016;30:884-890.
51. Weimann A, et al. ESPEN guideline: Clinical nutrition in surgery. Clin Nutr. 2017;36:623-650.
52. Braga M, et al. ESPEN Guidelines on Parenteral Nutrition: surgery. Clin Nutr. 2009;28:378-86.
53. Livingston A, et al. If the gut works use it. Nurs Manage. 2000;31:39-42.
54. Yamashiro Y. Gut Microbiota in Health and Disease. Ann Nutr Metab. 2017;71:242-246.
55. Sam QH, et al. The Fungal Mycobiome and Its Interaction with Gut Bacteria in the Host. Int J Mol Sci. 2017;18:330.
56. Hostetter MK. Handicaps to host defense. Effects of hyperglycemia on C3 and Candida albicans. Diabetes. 1990;39:271-275.
57. Bader MS, et al. Hyperglycaemia and mortality of diabetic patients with candidaemia. Diabet Med. 2005;22:1252-1257.
58. Bader MS, et al. Candidemia in patients with diabetes mellitus: epidemiology and predictors of mortality. Scand J Infect Dis. 2004;36:860-864.
59. Rodrigues CF, et al. Candida sp. Infections in Patients with Diabetes Mellitus. J Clin Med. 2019;8:76.
60. Shahin J, et al. Predicting invasive fungal disease due to Candida species in non-neutropenic, critically ill, adult patients in United Kingdom critical care units. BMC Infect Dis. 2016;16:480.
61. Sganga G, et al. Surveillance of bacterial and fungal infections in the postoperative period following liver transplantation: a series from 2005-2011. Transplant Proc. 2013;45:2718-2721.

Chapter 137

Damage control surgery in managing severe intra-abdominal infections

Carlos A. Ordoñez
Division of Trauma and Acute Care Surgery, Department of Surgery. Fundación Valle del Lili. Cali, Colombia; Division of Trauma and Acute Care Surgery, Department of Surgery. Universidad del Valle, Cali, Colombia; Department of Surgery, Universidad Icesi, Cali, Colombia.

Yaset Caicedo
Department of Surgery, Universidad Icesi, Cali, Colombia.

Introduction

Damage control surgery (DCS), traditionally employed for managing critically ill patients with traumatic abdominal injuries, has been increasingly adapted for non-traumatic surgical emergencies. This approach aims to mitigate the progression of physiological failure—coagulopathy, acidosis, hypocalcemia and hypothermia—that can lead to mortality. DCS involves controlling the damage source, performing a limited index surgery, transferring the patient to the Intensive Care Unit for resuscitation, and deferring definitive surgery. This paradigm shift has significantly improved survival rates in critically ill patients. Studies have demonstrated promising outcomes in the application of DCS principles to non-traumatic conditions, including acute mesenteric ischemia, peritonitis secondary to hollow viscus perforation, post-surgical peritonitis, pancreatic surgery, necrotizing enterocolitis, hemorrhage, and abdominal compartment syndrome.

By implementing DCS, surgeons can stabilize patients, mitigate immediate threats, and strategically plan for a more definitive surgical intervention once the patient's physiological status has been optimized. This chapter explores the evolution of DCS principles as applied to non-traumatic emergencies, with a particular focus on severe intra-abdominal infections.

Principles of damage control surgery

The genesis of DCS can be traced back to the 1980s, a period characterized by a burgeoning discourse concerning the optimal management of severe abdominal traumas, particularly those involving the liver or spleen. Surgeons, seeking to mitigate the harmful effects of prolonged operative times and minimize postoperative complications, began exploring the feasibility of abbreviated surgical interventions. Early reports on these abbreviated procedures demonstrated promising outcomes, providing a catalyst for further investigation.

A pivotal milestone in the evolution of DCS occurred in 1993 when Rotondo and Schwab presented their series of 22 patients with abdominal vascular trauma. These patients underwent abbreviated procedures,

leading the duo to formally propose the concept of damage control surgery. This groundbreaking work, coupled with the accumulating evidence supporting the enhanced survival rates associated with DCS, ignited a surgical revolution. The paradigm shift ushered in by DCS marked a significant advancement in the care of critically ill patients with severe abdominal injuries.

The advent of DCS introduced novel challenges related to the temporary management of abdominal injuries. The deferred closure of the abdominal cavity necessitated the development of strategies to address the open wound. While the Bogotá bag, a plastic covering, was initially proposed as a temporary solution, its use was often associated with persistent hemodynamic instability due to abdominal compartment syndrome (ACS).

ACS, characterized by elevated intra-abdominal pressure, is a consequence of intestinal edema and mechanical organ compression. This condition significantly compromises organ perfusion and ventilatory dynamics. Negative pressure wound therapy (NPWT) emerged as a viable solution to these challenges. By applying negative pressure to the open abdomen, NPWT facilitates mechanical containment of the abdominal cavity, drainage of fluid and debris, and promotion of hemostasis.

Damage control applied in severe intra-abdominal infections

The application of DCS in non-traumatic abdominal emergencies has shown remarkable progress, underscoring its critical role in managing complex and life-threatening conditions such as generalized peritonitis, acute mesenteric ischemia, pancreatitis, necrotizing enterocolitis, and aortic dissection. These severe pathologies can precipitate rapid clinical decline, demanding an urgent and strategic surgical approach to stabilize patients and improve outcomes.

DCS is effective in addressing two major pathophysiological challenges: hemorrhagic shock and septic shock. Hemorrhagic shock, characterized by severe blood loss and reduced tissue perfusion, and septic shock, resulting from a profound dysregulation of the immune response due to systemic infection, both require prompt and targeted intervention.

In the context of septic shock, DCS plays a crucial role in modulating the immune response and managing microbial load. The physiological effects of DCS on septic shock involve several key mechanisms:

1. **Control of abdominal contamination**. By rapidly addressing abdominal contamination and limiting the spread of infectious agents, DCS reduces the burden of bacteria and toxins in the peritoneal cavity. This containment helps to prevent the exacerbation of systemic infection and mitigates the inflammatory response that contributes to septic shock
2. **Reduction of inflammatory cascade**. DCS minimizes extensive tissue damage and subsequent inflammatory responses by focusing on rapid stabilization rather than exhaustive surgical repair. This approach helps to limit the release of pro-inflammatory cytokines and other mediators that can drive the systemic inflammatory response associated with sepsis.
3. **Improved resuscitation and recovery**. Early intervention through DCS allows for more effective fluid resuscitation and stabilization of hemodynamic status. Enhanced early resuscitation helps restore physiological balance and improve organ perfusion, which is crucial for mitigating the effects of septic shock.
4. **Reduction in surgical stress**. By performing only the necessary interventions initially and deferring definitive surgery, DCS reduces the overall surgical stress on the patient. This approach helps to prevent the physiological strain that can worsen the immune response and exacerbate sepsis.
5. **Enhanced immune modulation.** DCS can indirectly modulate the immune response by improving systemic conditions and reducing the extent of infection-induced immune dysregulation. Stabilizing the patient's

condition and managing sepsis more effectively can lead to a more balanced immune response and better outcomes.

Early studies, such as those by Finlay *et al.* and Banieghbal *et al.*, demonstrated the benefits of damage control surgery (DCS) in improving survival rates and reducing complications in non-traumatic abdominal emergencies, including peritonitis and acute mesenteric ischemia. Recently, the ERAS (Enhanced Recovery After Surgery) guidelines have further refined the approach to emergency surgery, including recommendations for the application of DCS. The latest ERAS guidelines emphasize a multimodal approach to optimize patient care and outcomes in emergency settings. The integration of DCS into ERAS protocols represents a significant advancement in emergency surgical care, enhancing both the efficacy of surgical interventions and the overall recovery process for critically ill patients.

Evidence of damage control in severe Intra-abdominal infections

DCS for Hinchey II-IV complicated acute diverticulitis remains a promising approach. A meta-analysis published in 2021, encompassing nine studies, demonstrated that DCS achieved gastrointestinal continuity in over 60% of patients while maintaining a low rate of major anastomotic leaks and a mortality rate of 9.2%. Despite these encouraging findings, the study's limitations, including heterogeneity in inclusion criteria and potential selection bias, underscore the need for additional research to definitively establish DCS's clinical effectiveness and cost-benefit ratio.

A systematic review of eight studies published in 2020 found that DCS offers favorable outcomes, including a lower rate of definitive stoma compared to Hartmann's procedure. However, careful patient selection is crucial to avoid overtreatment. The study analyzed data from 359 patients with Hinchey III perforated acute colonic diverticulitis. Most patients underwent a limited resection with vacuum-assisted closure followed by primary resection anastomosis. The overall morbidity rate ranged from 23% to 74%, with a 30-day mortality rate of 0% to 20%. While the results are promising, further research is needed to refine patient selection criteria and establish DCS as a standard of care for perforated acute diverticulitis.

Kafka-Krish *et al.* conducted a randomized clinical trial to evaluate the efficacy of DCS *versus* conventional management for perforated diverticulitis with generalized peritonitis. Of the 56 patients screened, 21 were randomized to receive either DCS or conventional treatment. All participants had confirmed Hinchey stage III or IV disease. The primary outcome was the rate of reconstructed bowel continuity at discharge and six months postoperatively. The results of the trial demonstrated that DCS significantly increased the rate of bowel continuity at discharge compared to conventional management (92% *vs.* 63%). Additionally, patients in the DCS group were less likely to require a stoma at discharge (8% *vs.* 57%). Despite these advantages, the length of ICU and hospital stays were comparable between the two groups. This study provides compelling evidence that DCS is a viable and effective approach for managing perforated diverticulitis with generalized peritonitis, offering potential benefits in terms of bowel reconstruction and reduced stoma rates.

Rasslan *et al.* evaluated the prognostic value of SOFA, APACHE II, and Mannheinm Peritonitis Index scores in predicting outcomes for patients undergoing DCS in non-trauma settings. A retrospective analysis of 104 patients found that these scores, along with age and ASA classification, were significant predictors of mortality. Patients with higher scores had increased mortality risk. The study highlights the importance of using these scoring systems to assess patient prognosis and guide treatment decisions in DCS cases.

Faes *et al.* exposed their experience in the implementation of DCS for severe intra-abdominal infections. Of the 203 patients included, 26% died in the hospital, and 65% were stoma-free at discharge. Risk factors for

mortality included higher noradrenaline doses, abnormal blood gas analysis, male gender, higher ASA score, mesenteric ischemia, and type of resection. Additionally, higher ASA score, type of resection, and longer operation times were associated with a higher risk of stoma at discharge. The standardized DCS approach was feasible and safe in this tertiary teaching hospital, with early bowel reconstruction within 48 hours leading to reduced stoma rates.

Ordoñez *et al.* conducted a retrospective study to compare DCS with conventional surgical management in patients with severe non-traumatic peritonitis. The study included 290 patients who underwent urgent laparotomy at a trauma center in Colombia from 2003 to 2018, with 81 receiving DCS and 209 receiving conventional management. Despite worse preoperative conditions in the DCS group, measured by higher SOFA scores, there were no significant differences in hospital stay, mortality, or complication rates between the groups. Additionally, the ostomy rate was similar across both groups. The findings suggest that DCS is a feasible and safe strategy for managing severe non-traumatic peritonitis without increasing mortality or complications, and can be considered as an alternative to conventional management.

Smith *et al.* compared the outcomes of patients who underwent DCS for trauma or intra-abdominal sepsis. Their study revealed that patients in the intra-abdominal sepsis group had the poorest outcomes, including the lowest rates of primary fascial closure, the highest rates of intra-abdominal complications, and the longest time to definitive closure. Moreover, delayed closure beyond eight days was associated with a significantly higher risk of 90-day mortality across all groups. These findings emphasize that while DCS is vital in managing a variety of abdominal emergencies, prompt closure is crucial for improving survival, especially in non-traumatic cases like intra-abdominal sepsis.

Damage control surgery in severe intra-abdominal infections

The authors proposed the following algorithm that incorporates the principles of DCS and deferred anastomosis as the primary surgical approach for intestinal reconstruction (**Figure 1**).

Phase 0. Begin with crystalloid resuscitation and broad-spectrum antibiotics, using vasopressors if necessary. Diagnosis should be confirmed through lab results and diagnostic tools. Preparation for surgery includes central catheter placement, invasive monitoring, and reserving blood components.

Phase I. Perform peritoneal drainage and lavage, followed by debridement and resection of the damaged intestinal segment (**Figure 2**).

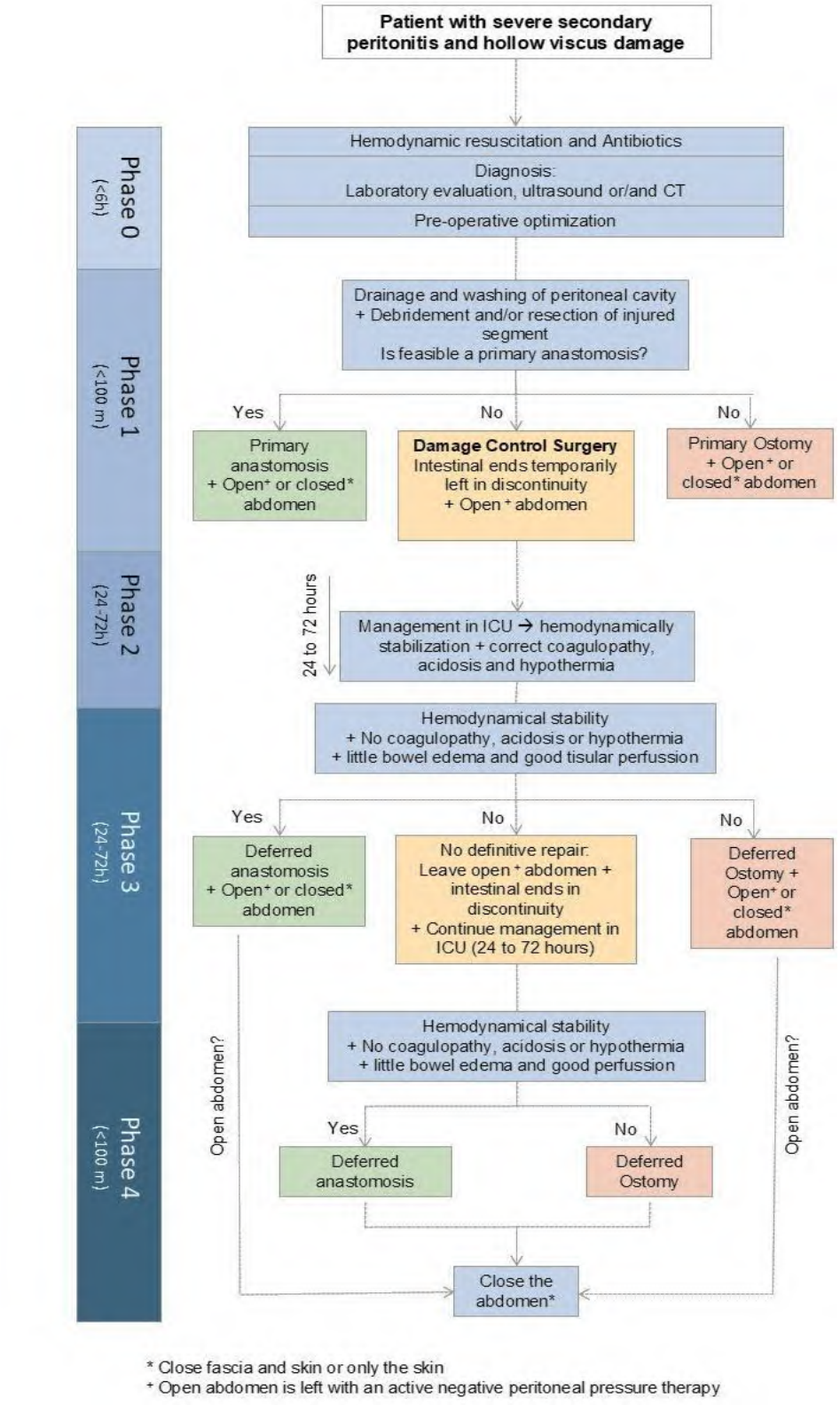

Figure 1. Damage control surgery algorithm for severe intra-abdominal infection.

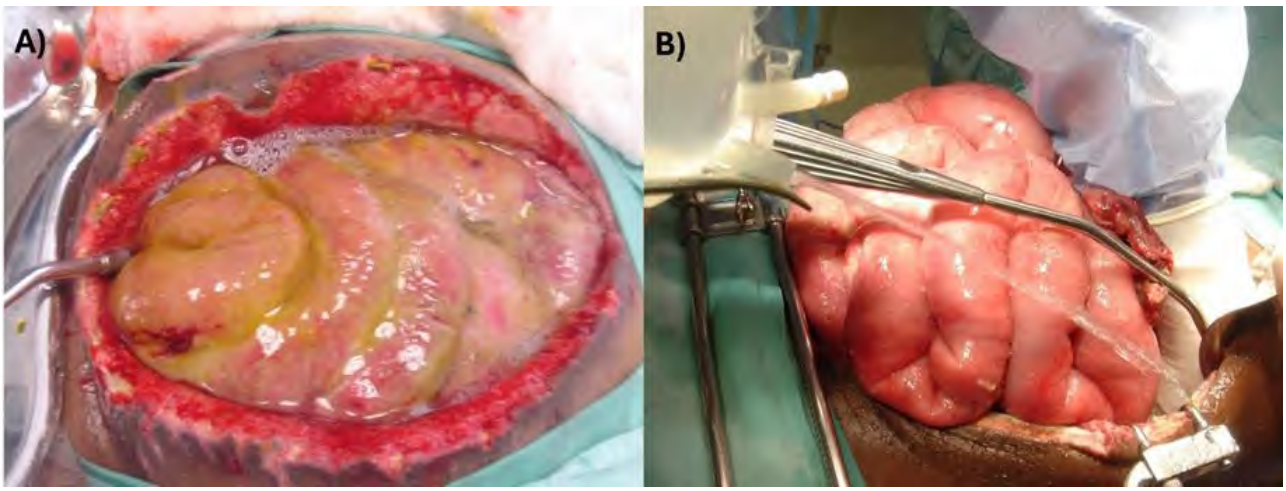

Figure 2. A) Peritoneal drainage; B) Peritoneal lavage.

If feasible, a primary anastomosis should be performed, with the abdomen left either open or closed. However, if the anastomosis is not possible due to factors such as edema, hypoperfusion, or hemodynamic instability, DCS can be applied by leaving the bowel in discontinuity, temporarily ligating the proximal and distal ends with an umbilical band or stapler and using a negative pressure dressing to allow for deferred abdominal closure (**Figure 3**).

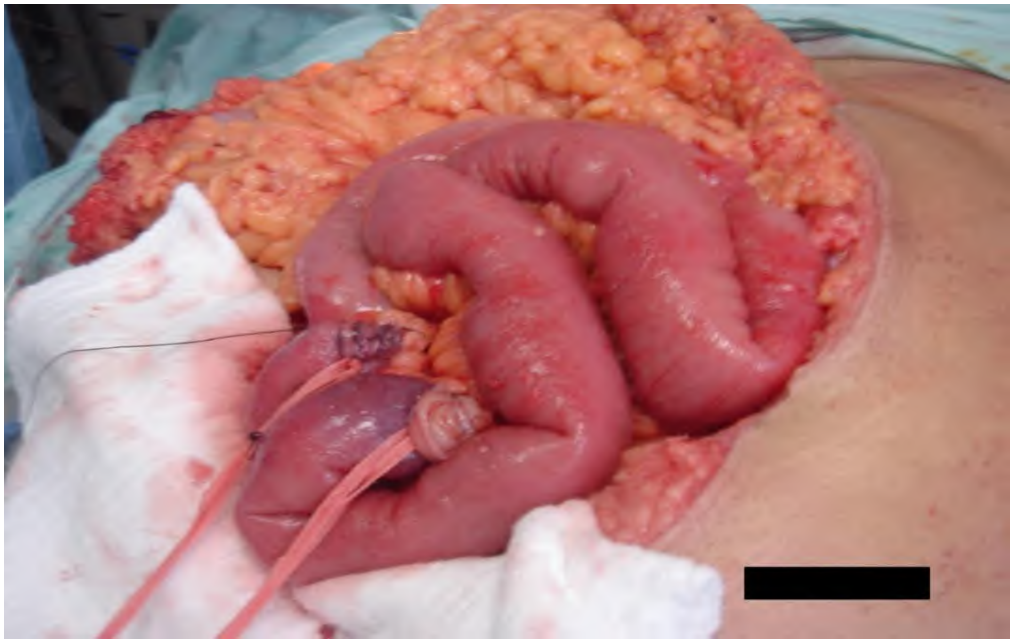

Figure 3. Leaving the bowel in discontinuity, temporally ligating both ends.

Alternatively, based on the patient's prognosis, the surgeon may opt for an ostomy with or without definitive abdominal wall closure.

Phase II. Transfer the patient to the ICU with ongoing hemodynamic support. Correct acidosis, hypothermia, and coagulopathy during this period, which typically lasts 24-48 hours, with a maximum of 72 hours.
Phase III. Conduct a second surgical procedure. If coagulopathy, acidosis, hypothermia, and intestinal edema have resolved and tissue perfusion is adequate, perform a hand-sewn or mechanical deferred anastomosis (**Figure 4**).

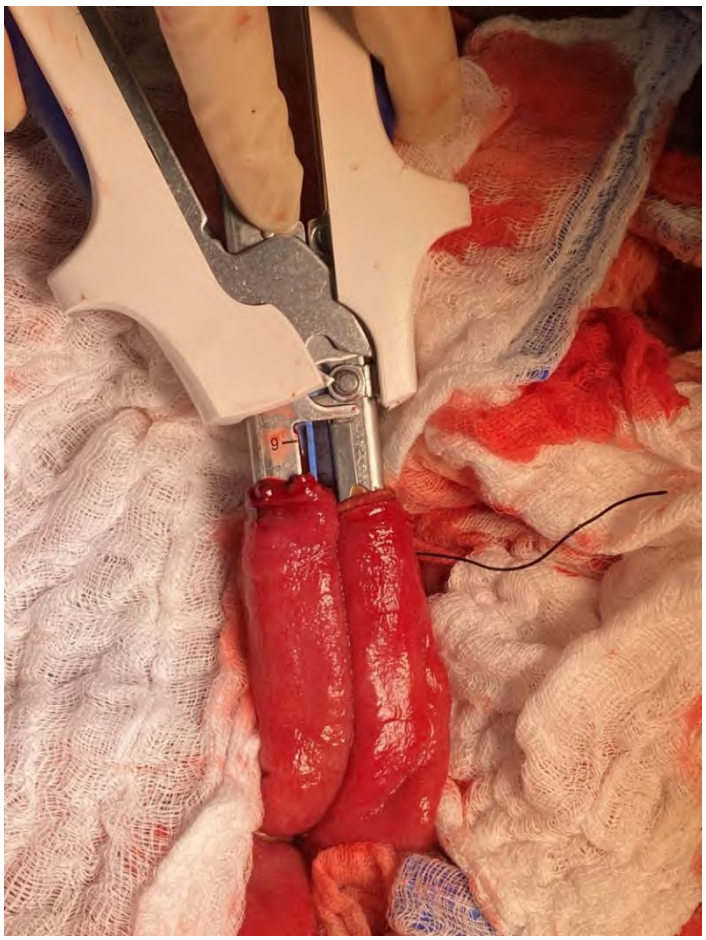

Figure 4. Reestablish bowel continuity with a Barcelona anastomosis.

If these criteria are not met, and no other options are available, the surgeon may opt for definitive ostomy management. Alternatively, if necessary, the intestinal ligatures can be released, the bowel contents emptied, and the bowel left in discontinuity, with a negative pressure dressing applied before returning the patient to the ICU for another 24-48 hours.
Phase IV. Reassess the patient's condition to decide on the final repair method. If the patient's condition has improved, a primary anastomosis is preferred; otherwise, an ostomy is required. In all cases, abdominal wall closure should occur within the first seven days, either with skin closure alone or both skin and fascial closure. Abdominal wall reconstruction can then be planned for 8-12 months post-closure.

Role of negative-pressure system in the control of severe intra-abdominal infections

Currently, negative-pressure systems play a crucial role in controlling infection and managing intra-abdominal pressure between procedures until abdominal closure can be achieved. Abdominal negative-pressure therapy is an effective intervention for managing intra-abdominal infections, particularly when conservative treatments fail and source control cannot be achieved in a single operation. In a cohort of 22 patients treated with commercial negative pressure systems, this technique demonstrated significant efficacy in controlling intra-abdominal pressure and managing severe sepsis. The median frequency of NPT system changes was every 4 days, and abdominal closure was feasible on the seventh postoperative day without the need for additional laparotomies. Despite some complications, including two instances of retroperitoneal bleeding and the development of intestinal fistulae and incisional hernias, the overall mortality rate was low at 4.5%. This study supports the potential of abdominal NPT as a promising strategy for controlling intra-abdominal hypertension and severe sepsis, warranting further research to optimize its application and refine its indications.

The World Society of Emergency Surgery (WSES) acknowledges that damage control resuscitation can lead to intra-abdominal hypertension or abdominal compartment syndrome, potentially resulting in severe physiological derangements and multiorgan failure if not addressed by abdominal decompression. The open abdomen approach is sometimes necessary when the abdomen cannot be closed due to visceral edema, persistent infection, or the need for further surgical intervention. While this approach can be effective in managing severe injuries or critical illness, it is resource-intensive and carries risks of complications. Therefore, its use should be reserved for patients who would benefit most. The WSES highlights that negative pressure systems, particularly those with dynamic components such as mesh-mediated fascial traction, generally provide better outcomes for delayed fascial closure compared to non-dynamic systems. Recent data suggest that negative pressure therapy is particularly beneficial in cases of severe peritonitis, while non-negative pressure methods may be more suitable for trauma patients.

Negative pressure systems and instillation is a novel therapeutic recently proposed. Brillantino *et al.* evaluate the effectiveness of a DCS using negative pressure wound therapy with instillation in treating generalized peritonitis from perforated diverticular disease in patients with severe preoperative conditions. The strategy involved a two-step procedure: initial peritoneal lavage, colon resection, and temporary abdominal closure with negative pressure wound therapy combined with instillation, followed by a second procedure 48 hours later to restore intestinal continuity if feasible. Among 30 patients, the use of negative pressure systems with instillation resulted in a high rate of successful colorectal anastomosis (80%) and a low stoma rate (23.3%), with primary fascial closure achieved in all cases. The approach demonstrated encouraging outcomes, including a manageable morbidity rate and a median hospital stay of 18 days, making it a viable option for patients with severe diffuse peritonitis.

Sibaja *et al.* performed a retrospective study of 48 patients treated with instillation revealed significant benefits, including a high rate of primary fascia closure (96%) within an average of 6 days, and no complications directly related to the therapy. This approach resulted in reduced mortality, shorter hospital and ICU stays, and overall promising outcomes compared to traditional methods like the Bogotá bag or Wittmann patch. Negative pressure systems with instillation present a valuable tool in managing complex septic abdomens, offering improved results in terms of infection control and patient recovery.

Conclusion

The principles of DCS can be effectively extended to non-traumatic abdominal emergencies, offering a feasible and safe approach without increasing mortality or morbidity. In critically ill patients facing metabolic decompensation from conditions like abdominal sepsis or massive hemorrhage, DCS provides a crucial intervention, stabilizing the patient and mitigating life-threatening factors such as hypothermia, acidosis, and coagulopathy. This approach creates a valuable time window, allowing for deferred intestinal reconstruction via anastomosis once the patient's condition has stabilized. The potential benefits of DCS include reduced risk of early postoperative complications, better control of physiological derangements, and improved long-term outcomes, as it minimizes the need for high-risk surgical procedures during the critical phase and enables tailored, staged interventions that optimize patient recovery.

Competing interests

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

References

1. Waibel BH, et al. Damage control for intra-abdominal sepsis. Surg Clin North Am. 2012;92:243–57, viii.
2. Waibel BH, et al. Damage control in trauma and abdominal sepsis. Crit Care Med. 2010;38:S421-430.
3. Ditzel RM, et al. A review of transfusion- and trauma-induced hypocalcemia: Is it time to change the lethal triad to the lethal diamond? J Trauma Acute Care Surg. 2020;88:434–439.
4. Girard E, et al. Damage Control Surgery for Non-traumatic Abdominal Emergencies. World J Surg. 2018;42:965–973.
5. Malgras B, et al. Damage control: Concept and implementation. J Visc Surg. 2017;154 Suppl 1:S19–29.
6. Beldowicz BC. The Evolution of Damage Control in Concept and Practice. Clin Colon Rectal Surg. 2018;31:30–35.
7. Stawicki SP, et al. The concept of damage control: extending the paradigm to emergency general surgery. Injury. 2008;39:93–101.
8. Morgan K, et al. Not just for trauma patients: damage control laparotomy in pancreatic surgery. J Gastrointest Surg Off J Soc Surg Aliment Tract. 2010;14:768–772.
9. Kafka-Ritsch R, et al. Damage control surgery with abdominal vacuum and delayed bowel reconstruction in patients with perforated diverticulitis Hinchey III/IV. J Gastrointest Surg Off J Soc Surg Aliment Tract. 2012;16:1915–1922.
10. Tartaglia D, et al. Damage control surgery for perforated diverticulitis with diffuse peritonitis: saves lives and reduces ostomy. World J Emerg Surg. 2019;14:19.
11. Banieghbal B, et al. Damage control laparotomy for generalized necrotizing enterocolitis. World J Surg. 2004 Feb;28(2):183–6.
12. Feliciano DV, Mattox KL, Jordan GL, Burch JM, Bitondo CG, Cruse PA. Management of 1000 consecutive cases of hepatic trauma (1979-1984). Ann Surg. 1986;204:438–445.
13. Stone HH, et al. Use of pedicled omentum as an autogenous pack for control of hemorrhage in major injuries of the liver. Surg Gynecol Obstet. 1975;141:92–94.
14. Feliciano DV, et al. Abdominal gunshot wounds. An urban trauma center's experience with 300 consecutive patients. Ann Surg. 1988;208:362–370.
15. Rotondo MF, et al. "Damage control": an approach for improved survival in exsanguinating penetrating abdominal injury. J Trauma. 1993;35:375–382;discussion 382-383.

16. Chovanes J, et al. The evolution of damage control surgery. Surg Clin North Am. 2012;92:859–875,vii–viii.
17. Quyn AJ, et al. The open abdomen and temporary abdominal closure systems--historical evolution and systematic review. Colorectal Dis Off J Assoc Coloproctology G B Irel. 2012;14:e429-e438.
18. Ribeiro MAF, et al. Comparative study of abdominal cavity temporary closure techniques for damage control. Rev Col Bras Cir. 2016;43:368–373.
19. Offner PJ, et al. Avoidance of abdominal compartment syndrome in damage-control laparotomy after trauma. Arch Surg Chic Ill 1960. 2001;136:676–681.
20. Cheng Y, et al. Negative pressure wound therapy for managing the open abdomen in non-trauma patients. Cochrane Database Syst Rev. 2022;5:CD013710.
21. Rodríguez-Holguín F, et al. Abdominal and thoracic wall closure: damage control surgery's cinderella. Colomb Medica Cali Colomb. 2021;52:e4144777.
22. Sartelli M, et al. The role of the open abdomen procedure in managing severe abdominal sepsis: WSES position paper. World J Emerg Surg. 2015;10:35.
23. Ordóñez CA, et al. Deferred primary anastomosis versus diversion in patients with severe secondary peritonitis managed with staged laparotomies. World J Surg. 2010;34:169–176.
24. Ordoñez CA, et al. Evolution of damage control surgery in non-traumatic abdominal pathology: a light in the darkness. Colomb Medica Cali Colomb. 2021;52:e4194809.
25. Weber DG, et al. Damage control surgery for abdominal emergencies. Br J Surg. 2014;101:e109-118.
26. Balogh ZJ. Damage Control Surgery for Non-Trauma Patients: Severe Peritonitis Management. World J Surg. 2021;45:1053–1054.
27. Bova R, et al. Source Control and Antibiotics in Intra-Abdominal Infections. Antibiot Basel Switz. 2024;13:776.
28. Finlay IG, et al. Damage control laparotomy. Br J Surg. 2004;91:83–85.
29. Scott MJ, et al. Consensus Guidelines for Perioperative Care for Emergency Laparotomy Enhanced Recovery After Surgery (ERAS®) Society Recommendations Part 2-Emergency Laparotomy: Intra- and Postoperative Care. World J Surg. 2023;47:1850–1880.
30. Cirocchi R, et al. The role of damage control surgery in the treatment of perforated colonic diverticulitis: a systematic review and meta-analysis. Int J Colorectal Dis. 2021;36:867–879.
31. Zizzo M, et al. Damage control surgery for the treatment of perforated acute colonic diverticulitis: A systematic review. Medicine (Baltimore). 2020;99:e23323.
32. Kafka-Ritsch R, et al. Prospectively Randomized Controlled Trial on Damage Control Surgery for Perforated Diverticulitis with Generalized Peritonitis. World J Surg. 2020;44:4098-4105.
33. Rasslan R, et al. Damage control surgery in non-traumatic abdominal emergencies: prognostic value of SOFA, APACHEII, and Mannheim peritonitis index. Updates Surg. 2024 Sep 13.
34. Faes S, et al. Rate of stoma formation following damage-control surgery for severe intra-abdominal sepsis: a single-centre consecutive case series. BJS Open. 2021;5:zrab106.
35. Ordoñez CA, et al. Damage Control Surgery may be a Safe Option for Severe Non-Trauma Peritonitis Management: Proposal of a New Decision-Making Algorithm. World J Surg. 2021;45:1043–1052.
36. Smith Jw, et al. Not All Abdomens Are the Same: A Comparison of Damage Control Surgery for Intra-abdominal Sepsis versus Trauma. Am Surg. 2016;82:427-432.
37. De Simone B, et al. Intraoperative surgical site infection control and prevention: a position paper and future addendum to WSES intra-abdominal infections guidelines. World J Emerg Surg WJES. 2020;15:10.
38. Coccolini F, et al. The open abdomen in trauma and non-trauma patients: WSES guidelines. World J Emerg Surg WJES World J Emerg Surg. 2018;13:7.
39. Brillantino A, et al. Advantages of Damage Control Strategy With Abdominal Negative Pressure and Instillation in Patients With Diffuse Peritonitis From Perforated Diverticular Disease. Surg Innov. 2019;26:656–661.
40. Sibaja P, Sanchez A, Villegas G, Apestegui A, Mora E. Management of the open abdomen using negative pressure wound therapy with instillation in severe abdominal sepsis: A review of 48 cases in Hospital Mexico, Costa Rica. Int J Surg Case Rep. 2017;30:26-30.

Chapter 138

Re-laparotomies in patients with intra-abdominal infections: when and how

Andrew W. Kirkpatrick
Departments of Critical Care Medicine and Surgery, University of Calgary, Alberta, Canada;
TeleMentored Ultrasound Supported Medical Interventions Research Group, Calgary, Alberta, Canada.

Spiros Delis
HPB Unit Konstantopouleio Hospital, Athens, Greece;
National and Kapodistrian University of Athens, Athens, Greece.

Federico Coccolini
General, Emergency and Trauma Surgery Department, Pisa University Hospital, Pisa, Italy.

Matti Tolonen
HUS Abdominal Center, Emergency Surgery, Helsinki University Hospital, Helsinki, Finland.

Introduction

Intra-abdominal sepsis (IAS) uniquely differs from most other forms of sepsis in requiring an invasive laparotomy to cure the most severe cases that typically arise from perforations or other disruptions to the gastrointestinal tract. Although such a surgical undertaking is a large insult to a patient, it is typically life-saving and cannot be avoided. In the current era of advanced pharmacologic and non-invasive therapeutic technologies that can safely permit non-operative management of some cases of IAS, it can be difficult for clinicians to know when however, a laparotomy is required, with errors of omission being associated with death, but errors of commission potentially associated without unnecessary morbidity. An even more difficult decision, however, is when to subject a patient to a repeat laparotomy, which again may be life-saving if appropriate, but the guidelines regarding this potential option are uncertain with little scientific evidence to guide clinicians. This question can be further conceptualized by accepting mandatory and discretionary reasons to perform a relaparotomy after an initial laparotomy for IAS. Mandatory reasons are simpler to define and include the planned closure of an abdomen initially left open, or alternatively, the mandatory exploration of a patient who has not improved, demonstrates ongoing leak or abscess on imaging, or has deteriorated and failed to recover after the initial laparotomy and those with an abdominal compartment syndrome (ACS) refractory to medical management. More complex, are discretionary reasons to perform a relaparotomy which can relate to the need to provide “surgical source” control and washout in an effort to improve outcomes from the risk of multiple organ dysfunction after severe IAS. The whole concept of surgical source control is critically important, yet nebulous due to difficulties in actually defining what “adequate source control” is or what it means in relation to any combination of patients and surgeons. It must be remembered that it is typically not

the bacteria related to IAS that cause deaths, but it is the bodies own biomediator response and potential devolution of the gut microbiome that are ultimately responsible for death in IAS, such that a balanced discussion of the timing and appropriateness of relaparotomy in IAS follows.

The burden of intra-abdominal infection

Sepsis is an ever-increasing cause of death worldwide, with a current incidence that is estimated at between 18 to 31 million cases worldwide per year. Mortality approaches 30-40% when shock is present, although this may be 80% in the developing world. It is also critical to recognize that it is not the actual bacteria or resultant infection that typically kills the patient, but the patient's own metabolic efforts to combat severe IAS with the massive propagation of inflammatory mediators that result in progressive organ failure which is ultimately lethal. The topic of bacterial antibiotic resistance and the huge risk of ever more multi-resistant organisms is a grave worldwide concern that is well covered in other chapters of this eBook. How much resistance will interact with the elaboration of toxic metabolites and biomediators is not truly known, and in less severe infections the concept of antibiotics being "anti-inflammatory" has been equated socioculturally with unnecessary antibiotic over usage and anti-microbial resistance. Thus, it becomes ever more important for clinicians to quickly respond to the sickest patients who require comprehensive surgical source control through a multimodal approach that effectively but not indiscriminately utilizes the right antibiotic for an appropriate clinical course and not longer.

Intra-abdominal sepsis (IAS) statistically constitutes the 2nd most common form of sepsis. It is also in the authors opinion, the most complex, as therapeutic decisions must understand and factor in the unique anatomic, physiologic, microbiologic, and pathobiologic characteristics of the abdominal cavity and its contained hollow viscera. Both the primary infectious process and inflammation related to resuscitation create swelling within the abdominal cavity which then may induce compartment physiology from increased compartment pressures that can induce reduced visceral perfusion synonymous with the ACS. Potentially more profound is that the majority of the human microbiome resides within the gut, which is primarily intra-abdominal and subject to physiologic and pathological stresses which likely dramatically affect human health in ways that are still superficially understood.

In 2016, the European Society of Intensive Care Medicine and the Society of Critical Care Medicine radically redefined the basic definitions of sepsis to emphasize that sepsis should be defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. This initiative was necessitated by important advances in understanding the advances that have since been made into the pathobiology (changes in organ function, morphology, cell biology, biochemistry, immunology, and circulation) of sepsis since the previous concepts of sepsis were promulgated two decades previously. However, even this effort to update sepsis guidelines to reflect modern science and understanding do not consider the profound implications of the human microbiome. Realistically, homo sapiens are superorganisms living in symbiosis with their microbiomes. Simply put, humans are simply life support systems for our microbiomes. This can be understood through the concept of the holobiont, which recognizes the importance of microbes in relation to individual organisms, best understood as a duality of the host and the symbionts within. The genetic material and cells of the commensal microbiota within a human greatly outnumber their host. The gut represents the largest body surface in contact with the external environment and constitutes a reservoir of more than 100 trillion bacteria. Symbiosis is critical and imbalances are associated with sepsis and shock occurs within just hours.

Severe complicated intra-abdominal sepsis (SCIAS) encompasses the most challenging situation physicians and surgeons encounter. IAS is defined as severe when associated with organ dysfunction, and as complicated

when the inflammation or contamination spreads beyond a single organ, causing either localized or diffuse peritonitis. SCIAS, typically resulting from secondary peritonitis, may be distinguished from other causes of severe sepsis through a requirement for surgical abdominal exploration to surgically address the disruption in the gastrointestinal (GI) tract. Patients with SCIAS require early hemodynamic support, source control, and antimicrobial therapy. However, despite advances in diagnosis, surgery, and antimicrobial therapy, mortality rates associated with complicated intra-abdominal infections and IAS remain exceedingly high. Even with prompt appropriate therapy, SCIAS may progress to septic shock and multiple organ dysfunction, largely because of peritoneal and systemic inflammation. There is great variability in the human immune response to an infectious focus, and some individuals greatly overreact to an inciting infection and produce a massive biomediator storm that propagates multi-system organ failure and death whereas other individuals have little or no response to the same stimuli. The failure to obtain adequate source control is often the driving cause of SCIAS and has been identified as an independent predictor of mortality in those with this condition.

Indications for relaparotomy in intra-abdominal infection

In terms of when to reoperate, we consider the indications to be mandatory and discretionary, recognizing that decision-making is difficult and should be individualized to every patient's physiology and expressed health wishes if known.

Mandatory relaparotomy in intra-abdominal infection

The easiest decision regarding performing a relaparotomy in patients with intra-abdominal infections is in those patients in whom a previous decision was made to leave the abdominal fascia open at the index operation for IAS. Such patients should be returned to the operating room as soon as they have stabilized with the intention of completing the definitive surgical procedure. The Guidelines of the World Society of Emergency Surgery (WSES) state the open abdomen re-exploration should be conducted no later than 24-48 hours after the index and any subsequent operation, with the duration from the previous operation shortening with increasing degrees of patient non-improvement and hemodynamic instability (Grade 1C Grade Recommendation). Further, early fascial and/or abdominal definitive closure was recommended by the WSES for management of the open abdomen once any requirements for ongoing resuscitation have ceased, the source control has been definitively reached, no concern regarding intestinal viability persists, no further surgical re-exploration is needed and there are no concerns for abdominal compartment syndrome (Grade 1B Grade Recommendation). Each of these later exceptions to this recommendation will be considered further below. Primary fascial closure rates may be improved by returning to the operating room as early as possible after the index laparotomy (and ideally within 24 hours); preventing and/or treating IAH, enteric fistulae, and intra-abdominal collections after surgery; and by limiting the use of crystalloid fluids and fluid-related weight gain during the surgical interval. In general, however, if the abdomen cannot be closed within the first week after its creation, it becomes increasingly difficult to do so as the abdominal musculature lateralizes and the inability to close typically reflects an association with some other adverse complication. Further, cohort studies of trauma patients with an OA suggest that, delaying re-exploration may reduce the primary fascial closure rate by 1.1% for each hour after the first 24 h after the index operation in trauma patients), and increased complication rates were observed in patients having the first re-operation after 48 hours.

Another group of patients who mandate relaparotomy are those for whom intra-abdominal hypertension (IAH), which is nearly ubiquitous in all critically ill patients, cannot be avoided and becomes unmanageable through medical and percutaneous techniques. The World Society of the Abdominal Compartment Syndrome (WSACS) has created consensus guidelines for the stepwise management of IAH with the goal of avoiding progression to the Abdominal Compartment Syndrome (ACS). Although the Society attempted to rebrand for the purposes of broadening and refining its scientific focus regarding abdominal compartment physiology, anatomy, and pathobiology, the track record of this organization justifies continued reference to the WSACS. For practical reasons, severe IAH can be operationalized as being unacceptable when consistently above 20 mmHg of pressure when associated with new organ failure. Ideally, medical management or minimally invasive techniques such as the percutaneous drainage of intra-peritoneal fluid could reduce IAP until the patient improves and can be "de-resuscitated". However, when ACS occurs, it is associated with adverse outcomes and is fatal if not quickly treated. It affects nearly every organ system in the body physically and humorally by inducing ischemia and the familiar biomediators storm associated with shock. Even if the abdominal cavity is open already with a vacuum-mediated temporary abdominal dressing the ACS can occur if the IAP and other vital signs are not carefully watched and cared for.

Conceptually, a patient should be taken back to the operating room whenever a surgeon is seriously concerned that the patient has failed initial attempts at source control, which practically means there is a concern for ongoing leakage or ischemia. This most frequently will arise from a missed perforation, iatrogenic perforation, new perforation, or anastomotic breakdown of a previous anastomosis. We suggest that if any of these conditions are suspected whether the abdominal fascia has been formally closed or not should not greatly influence the timing or threshold to reoperate. In those randomized to expectant management after laparotomy with the intention of NOT performing a relaparotomy for intra-abdominal sepsis, a remarkable 42% still required relaparotomy for suspected or proven persistent peritonitis in a large Dutch multicenter randomized controlled trial (RCT) conducted by Van Ruler *et al*.

Computed Tomography (CT) scanning can facilitate this decision-making and should be liberally used to provide knowledge regarding intra-abdominal pathology and complications. However, even in current practice in specialized centres, some patients are too sick and unstable to tolerate the delay in obtaining a CT and should undergo immediate reoperation. Such patients will often be hemodynamically unstable or unsupportable or have obvious peritonitis, or overt evidence of enteric leakage visible in the wounds or drain, although drains are less frequently utilized in contemporary practice. However, the need for individualization in patient care is again seen, as some patients who are hemodynamically stable may occasionally be exceptionally managed with percutaneous or non-operative therapies as the exception to the rule regarding mandatory relaparotomy. In such a case there will always be a low threshold to admit failure of the non-operative approach and a low threshold to reoperate. The primary reason to perform a mandatory relaparotomy in patients with IAS is any concern for ongoing pathology that was not definitively corrected at the index operation. If there is a missed anatomic disruption of the integrity of the gastrointestinal tract or persistent ischemia/necrosis then this is a simpler concept to understand and communicate that these problems must be surgically and definitively corrected. If there is such a concern, such patients should be reoperated promptly even if they just left an operating room. The occasional cases where advanced medical/percutaneous therapies in conjunction with healthy physiology are again the exception to the rule in this discussion.

Ideally, relaparotomy should be conducted in a formal operating room, but there will be occasions when the patient is too sick or complex for transport and reoperation must be conducted in the ICU with appropriate logistical support.

Discretionary relaparotomy for IAS and "source control"

The most complex topic to discuss concerns performing or making the decision to necessitate a relaparotomy by purposefully leaving an abdomen open with the intention of a future relaparotomy, in order to optimize surgical "source control". We have previously described obtaining adequate surgical source control as the "holy grail" of managing severe complicated intra-abdominal sepsis, however, we fully acknowledge that there is no consensus as to exactly what surgical source control actually is. For example, no conclusive definition of source control technique or even adequacy has been universally accepted. We will thus challenge all engaged surgeons to consider "What do you mean by source control'? Surprisingly, no unified definition of source control technique or adequacy has been universally adopted or validated. As Coccolini *et al.* have outlined, source control encompasses numerous factors including the causative event, source of infection bacteria, local bacterial fora, patient condition, and his/her eventual comorbidities. The current authors contend that despite our limited understanding of the intricacies of the true pathways related to the pathobiology of sepsis and the profound implications of the abdominal compartment containing human microbiome, adequate source control is no longer only a surgical issue, but one that requires a multidisciplinary, multimodality approach. Thus, as discussed above, any gross macroscopic gastrointestinal tract leakage must be controlled, but also, we propose that the source control concept should also be broadened to encompass attempts to control the generation and propagation of the systemic biomediators and symbiotic influences on the microbiome that perpetuate multi-system organ failure and death.

Currently, there is no magic bullet or pharmacological therapy for controlling the bioburden of propagating inflammation from intra-abdominal sepsis. There are no currently proven adjuncts to ameliorate the synthesis and systemic effects of biomediators beyond prompt resuscitation, antibiotic therapy and surgery to control anatomic disruptions or remove necrosis, followed by supportive critical care. Pharmacologic approaches, while very expensive, have proven ineffective in improving patient outcomes and are not currently indicated. Thus, surgeons need to explore further basic and applied scientific approaches and topics involved in understanding the inflammation generated by intra-abdominal infection. These topics might involve studying the intersection of coagulation, inflammation, and inflammation), or using hemofiltration to remove biomediators as early as possible after generation, or potentially using negative pressure peritoneal therapy to remove biomediators directly from the peritoneal cavity before they have any chance to act systemically.

Leaving open or reopening an abdomen to attempt better surgical source control

The basic premise that theoretically provides guidance to instruct surgeons to leave the abdomen open as an adjunct to surgical source control is that it will "optimize source control" and thus the patient will have a better outcome. Although this conceptually appeals to surgeons that our operating room skills will help patients and this approach is often promoted, scientific support for this is circumstantial and not proven.

In a previous era, relaparotomy was routinely practiced with the goal of enhancing surgical source control even when it involved formally closing the fascia at an index laparotomy and then formally reopening it multiple times thereafter. Such a strategy was termed Planned Relaparotomy (PRL). In such a strategy, re-laparotomy with fascial closure was routinely performed every 36-48 hours in order to inspect, drain, and lavage the abdominal cavity until the intra-operative findings were negative for peritonitis. A very influential multi-centre randomized trial that effectively ended this practice of formal relaparotomy was published in 2007. Van Ruler *et al.* conducted a prospective randomized trial comparing PRL with laparotomy on demand (LOD) which

mandated repeat laparotomy only in those patients in whom the lack of clinical improvement or clinical deterioration suggested ongoing peritonitis from either persistent peritonitis or a new infectious focus. The relative merits of either approach were widely debated previously, until the conclusion of the above RCT. Although this trial noted no difference in mortality between the two approaches, the LOD strategy reduced direct medical costs by 23%. The equivalence in outcomes, coupled with apparent cost-savings, resulted in the generation of consensus guidelines recommending that LOD after laparotomy for peritonitis be adopted as the standard of care.

We contend, however, that this trial very well indicates why questions related to whether an open abdomen might still benefit critically ill patients with severe intra-abdominal infection has NOT been definitively answered. In this seminal study, the mortality in both groups was still alarming, and well illustrates the catastrophic nature of severe intra-abdominal infection, noting the associated mortality of approximately one-third of all patients in the study regardless of treatment allocation. No matter which cohort is considered, such a dismal outcome demands surgeons to seek something better for their patients. This study did not find that one method was better or worse, just less money was spent. Further, the study did not offer patients an OA and thus did not utilize modern negative peritoneal pressure therapy (NPPT) or mitigate IAH in either therapy. To restate, although often misunderstood, the Van Ruler RCT did not utilize a contemporary "open abdomen" (OA) approach in either arm in that the abdominal fascia was formally closed in both arms. Increasingly, the OA is being recommended as an attractive option to provide better control of intraperitoneal contamination. This approach is perceived to be a safer option now than in previous decades due to the development of advanced temporary abdominal closure (TAC) devices that offer greater safety in protecting the viscera, and potentially profound benefits in ameliorating the propagation of inflammatory bio-mediators in SCIAS (46-48), but all with minimal evidence to support these contentions. And notably, compared to trauma patients, patients undergoing OA management for intra-abdominal sepsis have a greater risk of OA complications, including entero-atmospheric fistula (EAF) and intra-abdominal abscess formation, and a lower rate of primary fascial closure (i.e., fascia-to-fascia closure within the index hospitalization).

The authors believe that the critical concept that might potentially benefit patients with severe intra-abdominal infection is that of using NPPT for a period of time after index source control laparotomy. Animal studies and in-silica modeling of these animal studies suggest that NNPT provides a greater degree of negative pressure throughout the peritoneum, which may reduce plasma bio-mediator levels when compared to more passive peritoneal drainage. Systemic inflammation (TNF-α, IL-1β, IL-6) in one study was significantly reduced in the ANPPT group and was associated with significant improvement in intestine, lung, kidney, and liver histopathology. Our research group has conducted the only prospective randomized controlled trial partially addressing the potential of NPPT in severe intra-abdominal infection, the Intraperitoneal Vacuum Trial (46). This RCT was conducted in Calgary, Alberta, and in addition to numerous physiological variables, bio-mediator levels were also measured. Although standard systemic bio-mediator levels were not statistically different nor was peritoneal fluid drainage, the 90-day survival rate was improved in the ANPPT group (hazard ratio, 0.32; 95% confidence interval, 0.11–0.93; p=0.04). A valid critique of this trial was there was a mix of trauma and non-trauma patients. Thus, although unexplained, significantly improved survival with ANPPT seems to warrant further exploration of an open abdomen with NPPT. The authors believe that the global clinical equipoise as to whether the abdomen should be left open or closed after laparotomy in patients with severe intra-abdominal infection warrants a carefully conducted multicenter RCT.

There was a now historical RCT conducted prior to 2006 that randomized patients to a closed or open strategy, but the techniques of OA management used are not directly comparable to contemporary ones as the management of an OA has undergone dramatic improvements in technology and technique. Robledo *et al.* randomized patients with severe secondary peritonitis to an open or closed strategy using a non-absorbable

prosthetic mesh interposed position between the open fascia and viscera, thus exposing the underlying bowel to great risk of enterocutaneous or enteroatmospheric fistula formation). Although there was no statistical mortality difference, the risk of death was higher with the OA, interposed non-absorbable polypropylene mesh strategy and the trial was stopped early.

The Closed or Open after Laparotomy (COOL) for Severe Complicated Intra-abdominal sepsis trial is currently studying this same question although the intervention arm has been updated in detail to reflect current practice. This trial randomizes the very sickest cohort of patients with intra-abdominal infections to either primary closure if they can be safely closed compared to a cohort who are allocated to a modest period of an open abdomen with NPPT. The goal is to detect a mortality difference, and the trial is being conducted on 4 continents in 28 different hospitals. Although current enrollment is almost three times greater than the historical trial mentioned above, enrolment is expected to continue despite the previous commercial sponsor (3M Corporation) reneging on signed research contracts. The investigators are determined not to let a medical corporation suppress the search for better patient care and thus are determined to finish this trial.

Conclusion

All surgeons should be aware of and cautioned that leaving an abdomen open with the intention of an intentional relaparotomy or choosing to reopen it at a subsequent time is very physiologically unnatural and in the most contemporary work published is being discouraged. Mandatory reasons to perform a relaparotomy are closing an existing open abdomen, relieving refractory abdominal compartment syndrome, and excluding ongoing ischemia or uncontrolled contamination, especially if the patient is clinically deteriorating. Discretionary reasons to perform a relaparotomy or to commit to the need for a relaparotomy are to potentially improve source control of macroscopic contamination, reduce the bioburden on abdominal infection, and theoretically avoid dysbiomic changes in the gut flora. This last discretionary indication is not established however as best practice and requires further scientific study before it can be widely recommended. Thus, we leave practising surgeons with the advice to NOT use an OA technique in any case of severe intra-abdominal sepsis when it is possible to physically close the abdominal cavity UNLESS that patient is enrolled in a controlled scientific study to learn whether such a strategy might benefit other patients.

Competing interests

Andrew W. Kirkpatrick serves as the PI of the COOL trial, which previously was partially supported by the 3M/Acelity Corporation until Aug 2022. AW Kirkpatrick is also a member of the Canadian Forces Medical Services and has consulted for the 3m/Acelity Corporation, Zoll Medical, Innovative Trauma Care, and CSL Behring. He is the Director of the TeleMentored Ultrasound Supported Medical Interventions (TMUSMI) Research group and serves in the Canadian Forces Medical Services.

References

1. Coccolini F, et al. What do we mean by source control and what are we trying to accomplish with an open abdomen in severe complicated intra-abdominal sepsis? J Trauma Acute Care Surg. 2024;96:e39-e40.

2. Coccolini F, et al. Source control in emergency general surgery: WSES, GAIS, SIS-E, SIS-A guidelines. World J Emerg Surg. 2023;18:41.
3. Jawad I, et al. Assessing available information on the burden of sepsis: global estimates of incidence, prevalence and mortality. J Glob Health. 2012;2:010404.
4. Fleischmann C, et al. Assessment of Global Incidence and Mortality of Hospital-treated Sepsis. Current Estimates and Limitations. Am J Respir Crit Care Med. 2016;193:259-272.
5. Angus DC, et al. Epidemiology of severe sepsis in the United States: analysis of incidence, outcomes, and associated costs of care. Crit Care Med. 2001;29:1303-1310.
6. Slade E, et al. The surviving sepsis campaign: raising awareness to reduce mortality. Critical Care. 2003;7:1-2.
7. Dellinger RP, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. Intensive Care Med. 2008;34:17-60.
8. Dellinger RP, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. Crit Care Med. 2008;36:296-327.
9. Singer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315:801-810.
10. Sartelli M, et al. Global validation of the WSES Sepsis Severity Score for patients with complicated intra-abdominal infections: a prospective multicentre study (WISS Study). World journal of emergency surgery. World J Emerg Surg. 2015;10:61.
11. Szakmany T, et al. Sepsis Prevalence and Outcome on the General Wards and Emergency Departments in Wales: Results of a Multi-Centre, Observational, Point Prevalence Study. PLoS One. 2016;11:e0167230.
12. Clements TW, et al. Secondary Peritonitis and Intra-Abdominal Sepsis: An Increasingly Global Disease in Search of Better Systemic Therapies. Scand J Surg. 2021;110:139-149.
13. Coccolini F, et al. What do we mean by source control and what are we trying to accomplish with an open abdomen in severe complicated intra-abdominal sepsis? J Trauma Acute Care Surg. 2024;96:e39-e40.
14. GBD 2021 Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance 1990-2021: a systematic analysis with forecasts to 2050. Lancet. 2024;404:1199-1226.
15. Lambert H, et al. Antimicrobial resistance, inflammatory responses: a comparative analysis of pathogenicities, knowledge hybrids and the semantics of antibiotic use. Palgrave Communications. 2019;5:85.
16. Roberts DJ, et al. Increased pressure within the abdominal compartment: intra-abdominal hypertension and the abdominal compartment syndrome. Curr Opin Crit Care. 2016;22:174-185.
17. Roberts DJ, et al. The open abdomen in trauma, acute care, and vascular and endovascular surgery: comprehensive, expert, narrative review. BJS Open. 2023;7.
18. Kirkpatrick AW, et al. Do we have the guts to go? The abdominal compartment, intra-abdominal hypertension, the human microbiome and exploration class space missions. Can J Surg. 2020;63:E581-E93.
19. Alverdy JC, et al. The gut microbiome and the mechanism of surgical infection. Br J Surg. 2017;104:e14-e23.
20. Hurst GDD. Extended genomes: symbiosis and evolution. Interface Focus. 2017;7:20170001.
21. Patel JJ, et al. The gut in trauma. Curr Opin Crit Care. 2016;22:339-346.
22. Clark JA, et al. Intestinal crosstalk: a new paradigm for understanding the gut as the "motor" of critical illness. Shock. 2007;28:384-393.
23. Sartelli M, et al. The role of the open abdomen procedure in managing severe abdominal sepsis: WSES position paper. World journal of emergency surgery. World J Emerg Surg. 2015;10:35.
24. Sartelli M, et al. Complicated intra-abdominal infections worldwide: the definitive data of the CIAOW Study. World J Emerg Surg. 2014;9:37.
25. Sartelli M, et al. Complicated intra-abdominal infections in a worldwide context: an observational prospective study (CIAOW Study). World J Emerg Surg. 2013;8:1.
26. Sartelli M, et al. 2013 WSES guidelines for management of intra-abdominal infections. World journal of emergency surgery. World J Emerg Surg. 2013;8:3.
27. Tellor B, et al. Inadequate Source Control and Inappropriate Antibiotics are Key Determinants of Mortality in Patients with Intra-Abdominal Sepsis and Associated Bacteremia. Surg Infect (Larchmt). 2015;16:785-793.

28. Coccolini F, et al. The open abdomen in trauma and non-trauma patients: WSES guidelines. World J Emerg Surg. 2018;13:7.
29. Pommerening MJ, et al. Time to first take-back operation predicts successful primary fascial closure in patients undergoing damage control laparotomy. Surgery. 2014;156:431-438.
30. Coccolini F, et al. The role of open abdomen in non-trauma patient: WSES Consensus Paper. World J Emerg Surg. 2017;12:39.
31. Kirkpatrick AW, et al. Intra-abdominal hypertension and the abdominal compartment syndrome: updated consensus definitions and clinical practice guidelines from the World Society of the Abdominal Compartment Syndrome. Intensive care medicine. 2013;39:1190-1206.
32. Kirkpatrick AW, et al. WSACS--The Abdominal Compartment Society. A Society dedicated to the study of the physiology and pathophysiology of the abdominal compartment and its interactions with all organ systems. Anaesthesiol Intensive Ther. 2015;47:191-194.
33. Malbrain ML, et al. Fluid overload, de-resuscitation, and outcomes in critically ill or injured patients: a systematic review with suggestions for clinical practice. Anaesthesiology Intens Ther. 2014;46:361-380.
34. Ouellet JF, et al. Recurrent abdominal compartment syndrome induced by high negative pressure abdominal closure dressing. J Trauma. 2011;71:785-786.
35. van Ruler O, et al. Comparison of on-demand vs planned relaparotomy strategy in patients with severe peritonitis: a randomized trial. JAMA. 2007;298:865-872.
36. Lee AJ, et al. The abdomen in "thoracoabdominal" cannot be ignored: abdominal compartment syndrome complicating extracorporeal life support. Case Rep Crit Care. 2014;2014:351340.
37. Kirkpatrick AW, et al. The unrestricted global effort to complete the COOL trial. World J Emerg Surg. 2023;18:33.
38. Lonsdale DO, et al. Infection, Sepsis and the Inflammatory Response: Mechanisms and Therapy. Front Med (Lausanne). 2020;7:588863.
39. Opal SM, et al. The next generation of sepsis clinical trial designs: what is next after the demise of recombinant human activated protein C?*. Crit Care Med. 2014;42:1714-1721.
40. Moller MH, et al. The Magic Bullet in Sepsis or the Inflation of Chance Findings? Chest. 2017;152:222-223.
41. Costantini TW, et al. The intersection of coagulation activation and inflammation after injury: What you need to know. J Trauma Acute Care Surg. 2024;96:347-356.
42. Supady A, et al. Extracorporeal haemoadsorption: does the evidence support its routine use in critical care? Lancet Respir Med. 2022;10:307-312.
43. Nathens AB, et al. Therapeutic options in peritonitis. Surg Clin North Am. 1994;74:677-692.
44. Bosscha K, et al. Surgical management of severe secondary peritonitis. Br J Surg. 1999;86:1371-1377.
45. Kirkpatrick AW, et al. Closed Or Open after Source Control Laparotomy for Severe Complicated Intra-Abdominal Sepsis (the COOL trial): study protocol for a randomized controlled trial. World J Emerg Surg. 2018;13:26.
46. Kirkpatrick AW, et al. Active Negative Pressure Peritoneal Therapy After Abbreviated Laparotomy: The Intraperitoneal Vacuum Randomized Controlled Trial. Annals Surg. 2015;262:38-46.
47. Cheatham ML, et al. Prospective study examining clinical outcomes associated with a negative pressure wound therapy system and Barker's vacuum packing technique. World J Surg. 2013;37:2018-2030.
48. Malig MS, et al. High Mobility Group Box-1 Protein and Outcomes in Critically Ill Surgical Patients Requiring Open Abdominal Management. Mediators Inflamm. 2017;2017:6305387.
49. Coccolini F, et al. The open abdomen, indications, management and definitive closure. World journal of emergency surgery. World J Emerg Surg. 2015;10:32.
50. Atema JJ, et al. Systematic review and meta-analysis of the open abdomen and temporary abdominal closure techniques in non-trauma patients. World J Surg. 2015;39:912-925.
51. Quyn AJ, et al. The open abdomen and temporary abdominal closure systems--historical evolution and systematic review. Colorectal Dis. 2012;14:e429-38.
52. Kubiak BD, et al. Peritoneal negative pressure therapy prevents multiple organ injury in a chronic porcine sepsis and ischemia/reperfusion model. Shock. 2010;34:525-34.

53. Emr B, et al. Removal of inflammatory ascites is associated with dynamic modification of local and systemic inflammation along with prevention of acute lung injury: in vivo and in silico studies. Shock. 2014;41:317-323.
54. Roberts DJ, et al. Efficacy and safety of active negative pressure peritoneal therapy for reducing the systemic inflammatory response after damage control laparotomy (the Intra-peritoneal Vacuum Trial): study protocol for a randomized controlled trial. Trials. 2013;14:141.
55. Person B, et al. Abbreviated emergency laparotomy in the non-trauma setting. World J Emerg Surg. 2009;4:41.
56. Khan A, et al. Damage-control laparotomy in nontrauma patients: review of indications and outcomes. J Trauma Acute Care Surg. 2013;75:365-368.
57. Robledo FA, et al. Open versus closed management of the abdomen in the surgical treatment of severe secondary peritonitis: a randomized clinical trial. Surg Infect (Larchmt). 2007;8:63-72.
58. Huang J, et al. 2023 updates on the closed or open after-source control for severe complicated intraabdominal sepsis (COOL) trial. World J Surg Infect. 2022;1:47-9.
59. Kao AM, et al. Outcomes of open abdomen versus primary closure following emergent laparotomy for suspected secondary peritonitis: A propensity-matched analysis. J Trauma Acute Care Surg. 2019;87:623-629.
60. Proano-Zamudio JA, et al. Delayed fascial closure in nontrauma abdominal emergencies: A nationwide analysis. Surgery. 2022;172:1569-1575.

Chapter 139

Infections in trauma

Laura Bloom
Department of Acute Care Surgery, Los Angeles General Medical Center, Los Angeles, CA, USA.

Anaar Siletz
Department of Acute Care Surgery, Los Angeles General Medical Center, Los Angeles, CA, USA.

Kenji Inaba
Department of Acute Care Surgery, Los Angeles General Medical Center, Los Angeles, CA, USA.

Introduction

Trauma is the leading cause of death worldwide in people under 40 years old. This is associated with immense human tragedy and socioeconomic impact on society. Most immediate and early deaths are due to neurologic injury or hemorrhage. Up to 60% of mortalities due to trauma occur in the pre-hospital setting. For patients who arrive alive at the hospital, an additional 60% of mortalities occur within the first few hours after arrival. For those who survive the initial resuscitation and operative care of their acute injuries, the next major risk to the patient is infection. Infection is associated with a nearly 30% mortality rate in this population. Reestablishing homeostasis to prevent infection within the first approximately 100 hours after injury is of pivotal importance. Infection in patients impacted by trauma often occurs within the first four days after injury and is associated with the dysfunction of multiple organs. Risk factors for infection specific to the trauma patient include the destruction of mechanical barriers; contamination from exogenous bacteria; and invasive interventions. Antimicrobial resistance and antimicrobial stewardship are important considerations in the treatment of trauma patients. In addition to antimicrobials, trauma patients also often require surgical intervention to minimize contamination and obtain source control. This chapter provides a guide for the use of antimicrobials and procedural source control in the prevention and treatment of infection associated with trauma. Included are recommendations specific to injuries affecting the central nervous system, maxillofacial and scalp regions, thorax, and abdomen, as well as for orthopedic fractures, burns, and isolated soft tissue wounds including bites.

Definitions and principles

Antimicrobial prophylaxis in the setting of trauma is the use of antimicrobials to prevent surgical site infection and/or infection at the site of injury. As for all patients, evidence-based indications for antimicrobial prophylaxis decrease the risk of infection while minimizing the risk of adverse effects and antimicrobial resistance.
Antimicrobial therapy is defined as the use of antimicrobials to treat infection by inhibiting the growth of or killing the involved microorganism. Therapy must be administered only when infection is present. Evidence-

based indications in conjunction with antimicrobial stewardship programs must be implemented at all levels – locally, nationally, and internationally.
Surgical source control is defined as a surgical intervention that removes contaminated tissue or fluid to prevent or control infection.
Polytrauma in common usage refers to a patient who has sustained multiple injuries, often blunt, but can be more strictly defined as the presence of injury to three or more points in two or more distinct anatomic regions in conjunction with one or more of the following five physiologic factors: hypotension (systolic blood pressure ≤90 mm Hg), decreased level of consciousness (Glasgow Coma Scale score ≤8), acidosis (base excess ≤−6.0), coagulopathy (international normalized ratio ≥1.4 or partial thromboplastin time ≥40 s), and age (≥70 years).

Identifying infection and sepsis

Identifying infection and sepsis in the trauma population can be challenging. Trauma initiates a systemic inflammatory response which can mask a developing infection, leading to a delay in initiation of treatment. Infection, particularly untreated infection, can progress to sepsis, defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. Early recognition and treatment of infection are critical to limit the progression to sepsis, septic shock, and mortality. Once sepsis is diagnosed, immediate action is essential. Blood cultures and serum lactate level should be obtained, and immediate treatment with antimicrobials and crystalloid resuscitation initiated. Late administration of antimicrobials is associated with a significant increase in mortality, especially when associated with hypotension. Even very short delays adversely impact patient outcomes. All patients must be thoroughly evaluated to determine whether source control surgery is indicated.
As sepsis progresses to septic shock, the patient is now at risk for multisystem organ failure. For each organ system that fails, the mortality rate increases by 15–20%; once four or more organ systems are in failure, the mortality rate exceeds 90%. This highlights the critical importance of recognition and expedited treatment of infection.

Central nervous system trauma

The majority of central nervous system traumatic injuries are due to blunt trauma. However, rates of penetrating injury are increasing in some areas of the world in association with rising firearm violence and suicide attempts. The indications for antimicrobial prophylaxis in central nervous system trauma is narrow. Blunt traumatic brain injuries managed nonoperatively do not warrant antimicrobial prophylaxis. This includes closed or open basilar skull fractures even with evidence of pneumocephalus and/or leakage of cerebrospinal fluid. Blunt traumatic brain injuries managed operatively warrant antimicrobial prophylaxis at the time of surgery to prevent surgical site infection. In general, penetrating traumatic brain injury is a medical emergency associated with high mortality rates and antimicrobial prophylaxis is indicated. Penetrating spine injuries, including transperitoneal injuries with gastrointestinal involvement, warrant antimicrobial prophylaxis for a maximum of 48 hours.

Maxillofacial and scalp trauma

The extensive colonization of the oral cavity is believed to contribute to the high rates of infection in patients who sustain maxillofacial trauma. For superficial lacerations and abrasions to the face and scalp, local wound care is the mainstay of treatment, and antimicrobial prophylaxis is not recommended. Antimicrobial prophylaxis is warranted for the following: through-and-through lacerations from the face to the oral cavity; extensive tissue loss; extensive contamination; contaminated fractures; open mandible fractures; frontal sinus fractures involving the posterior table; mammalian bites to the face and hand; and any maxillofacial trauma undergoing open fracture reduction. Prolonged antimicrobial prophylaxis after the first 24 hours should only be considered when open fracture reduction is performed in the setting of a contaminated wound and should be individualized to the patient and their specific injury.

Thoracic trauma

Thoracic trauma is common, and a significant proportion of patients who suffer moderate-to-severe thoracic trauma will require tube thoracostomy. For blunt and penetrating trauma, antimicrobial prophylaxis is conditionally recommended at the time of tube thoracostomy insertion to reduce the incidence of empyema. Whether the injury is blunt or penetrating in nature, patients undergoing surgical exploration should be given antimicrobial prophylaxis at the time of surgery to prevent surgical site infection. In patients with retained hemothorax, the rate of empyema is as high as 25%. These patients warrant antimicrobial prophylaxis in addition to surgical evacuation of the hemothorax to obtain source control.

Abdominal trauma

In the setting of blunt abdominal trauma managed nonoperatively, antimicrobial prophylaxis is not indicated. Antimicrobial prophylaxis in blunt abdominal trauma is indicated when there is concern for hollow viscus injury for which the patient is undergoing surgical exploration to identify the injury and obtain source control. In penetrating abdominal trauma, particularly in patients undergoing surgical exploration, antimicrobial prophylaxis is indicated. Whether from blunt or penetrating mechanisms, hollow viscus injury with contamination of the abdominal cavity warrants a short course of antimicrobial therapy with aerobic and anaerobic bacterial coverage. The current recommendation is to continue antibiotics for 4±1 days.

Traumatic orthopedic fractures

The prevention and treatment of infection associated with traumatic orthopedic fractures depends on whether the fracture is closed or open and the degree of associated soft tissue injury. In closed traumatic orthopedic fractures managed nonoperatively, antimicrobial prophylaxis is not indicated. Closed traumatic orthopedic fractures undergoing operative intervention warrant antimicrobial prophylaxis at the time of surgery for the prevention of surgical site infection. In open traumatic orthopedic fractures, antimicrobial prophylaxis reduces rates of wound infection and should be administered as soon as possible. The choice of antimicrobial agent for open fractures depends on the grade of injury. Gustilo-Anderson Grade I and II injuries

(without gross contamination or extensive tissue damage) merit prophylaxis against Gram-positive bacteria. Broader coverage against both Gram-positive and Gram-negative bacteria is indicted for Gustilo-Anderson Grade III injuries (extensive soft tissue injury, contamination, or associated vascular injury). There is no role for prolonged antimicrobial prophylaxis in open traumatic orthopedic fractures. Rather, a delay in fracture care should be avoided. Irrigation and debridement should be performed within 24 hours to mitigate the risk of local infectious complications; nonunion; hardware failure; and prolonged length of stay. Antimicrobial coverage should not continue beyond 24 hours after tissue coverage. In patients with a higher injury burden, expeditious external fixation may be an appropriate temporizing measure, with a delay in formal fixation until after the patient has stabilized. For the patient presenting with a mangled extremity, surgical treatment options include amputation and limb salvage reconstruction. Antimicrobial therapy should be tailored to the procedure being performed and the risk of infection in the remaining tissue and wound bed. Immediate amputation is reserved for patients who are unstable, for extremities that have transected nerves not suitable for reconstruction, and for crushed extremities with more than six hours of ischemia time. If the patient is physiologically unable to tolerate immediate removal of non-viable tissue, consideration should be given to antimicrobial prophylaxis once the other life-threatening issues have been treated.

Burns

Patients who sustain burns are at high risk for infection due to loss of the skin's mechanical barrier. These patients are typically afflicted by multidrug-resistant organisms. The cornerstone of infection prevention in burn patients is early debridement of contaminated tissue with removal of all foreign material and coverage of the affected site. There is no indication for the routine administration of antimicrobial prophylaxis. For patients who sustain severe burns requiring endotracheal intubation and mechanical ventilation, antimicrobial prophylaxis may be indicated to reduce rates of pneumonia.

Traumatic soft tissue wounds including bites

Traumatic skin and soft tissue wounds can be present in isolation and are also common in polytrauma patients. For all skin and soft tissue injuries, irrigation and debridement of devitalized tissue is of the utmost importance. Understanding the indications for antimicrobial prophylaxis is also critical, as sepsis-related mortality is associated with delays in the initiation of appropriate therapy. If not administered within the past five years, all patients with traumatic skin and soft tissue wounds or bite wounds should be considered for tetanus immunization. For patients with uncomplicated traumatic skin and soft tissue wounds, including stab wounds limited to the skin and soft tissue, antimicrobial prophylaxis is not indicated. For deeper injuries and stab wounds, the decreased risk of infection must be weighed against the increased risk of morbidity from sedation and/or extension of the laceration. Stab wounds in communication with deeper cavities and/or structures should be managed based on the underlying injury. For gunshot wounds that are complex, to specific anatomical locations such as hands and feet, and/or are due to high-velocity weapons, antimicrobial prophylaxis is recommended in addition to local wound care. For gunshot wounds with less extensive tissue injury and/or due to low-velocity weapons, the role of antimicrobial prophylaxis remains unclear.

For bites from snakes, spiders, and scorpions, antimicrobial prophylaxis is discouraged unless there are signs of active secondary infection. Mammalian bites typically do not require antimicrobial prophylaxis but should prompt consideration of prophylaxis against contractable viral diseases such as rabies. The exceptions are mammalian bites to the face and hand, which have higher rates of infectious complications. Human bites, however, warrant the routine use of antimicrobial prophylaxis to reduce rates of infection. Source control with irrigation and debridement of devitalized tissue is indicated for all skin and soft tissue wounds including bite wounds. For moderately and severely contaminated wounds, surgical source control and antimicrobial prophylaxis have a synergistic effect on reducing rates of infection.

Conclusion

Patients sustaining trauma experience complex physiologic derangements. Those who survive the initial injury and resuscitation phase often exhibit immune dysregulation that can both mask the onset of infection and simultaneously put the patient at risk for it. While each trauma patient is unique, the recommendations herein may serve as a guide to the appropriate use of antimicrobial prophylaxis (**Table 1**), antimicrobial therapy, and surgical source control for the treatment of trauma patients around the globe.

Table 1. Summary of recommendations.

Anatomical location	**No antimicrobial prophylaxis**	**Antimicrobial prophylaxis/Therapy**	**Duration of antimicrobials** (in the absence of infectious complications)
Central nervous system trauma	Blunt traumatic brain injury managed nonoperatively – including closed or open basilar skull fracture regardless of the presence of pneumocephalus and/or cerebrospinal fluid leak	Blunt traumatic brain injury managed operatively	Single dose preoperatively
		Penetrating traumatic brain injury	<72 hours
		Penetrating spine injury – including transperitoneal injuries with gastrointestinal involvement	≤48 hours

(cont.)

Table 1. Summary of recommendations *(cont.)*

Anatomical location	**No antimicrobial prophylaxis**	**Antimicrobial prophylaxis/Therapy**	**Duration of antimicrobials** (in the absence of infectious complications)
Maxillofacial trauma	Superficial laceration/ abrasion to face and scalp	Through-and-through laceration from face to oral cavity	≤24 hours
		Extensive contamination	≤24 hours
		Contaminated fracture	≤24 hours
		Open mandibular fracture	≤24 hours
		Frontal sinus fracture involving posterior table	≤24 hours
		Mammalian bite to face (consider rabies vaccination)	≤24 hours
		Maxillofacial trauma undergoing open fracture reduction	≤24 hours
		Open fracture reduction in the setting of a contaminated wound	>24 hours (duration individualized to the patient and specific injury)
Thoracic trauma		Tube thoracostomy	Single dose prior to insertion
		Thoracic surgical exploration	Single dose preoperatively
		Retained hemothorax	Single dose prior to surgical evacuation
Abdominal trauma	Blunt abdominal trauma managed nonoperatively	Blunt abdominal trauma undergoing surgical exploration in the setting of concern for hollow viscous injury	Single dose preoperatively; 4±1 days if hollow viscous injury identified
		Penetrating abdominal trauma	Single dose preoperatively; 4±1 days if hollow viscous injury identified
		Hollow viscous injury with contamination of peritoneal cavity	4±1 days

(cont.)

Table 1. Summary of recommendations *(cont.)*

Anatomical location	No antimicrobial prophylaxis	Antimicrobial prophylaxis/Therapy	Duration of antimicrobials (in the absence of infectious complications)
Traumatic orthopedic fractures	Closed traumatic orthopedic fractures managed nonoperatively	Closed traumatic orthopedic fractures managed operatively	Single dose preoperatively
		Open traumatic orthopedic fractures: • Gustilo-Anderson Grade I/II: Gram-positive coverage • Gustilo-Anderson Grade III: Gram-positive and Gram-negative coverage	Administer as soon as possible, stop ≤24 hours after tissue coverage
Burns	All burns with the exception of severe burns require endotracheal intubation and mechanical ventilation	Severe burns requiring endotracheal intubation and mechanical ventilation (may be indicated to reduce rates of pneumonia)	4 days
Traumatic soft tissue wounds including bites	Uncomplicated traumatic skin and soft tissue wounds, including stab wounds limited to the skin and soft tissue Bite from a snake, spider, or scorpion (unless there is a sign of active secondary infection) Mammalian bite (except to face or hand; consider rabies vaccination)	Complex gunshot wound	≤24 hours
		Gunshot wound to specific anatomical locations such as hands and feet	24-72 hours
		High-velocity gunshot wound	24-72 hours
		Mammalian bite to face or hand (consider rabies vaccination)	3-5 days
		Human bites	3-5 days

Competing interests

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

References

1. Pape HC, et al., The definition of polytrauma revisited: An international consensus process and proposal of the new 'Berlin definition'. J Trauma Acute Care Surg. 2014;77:780-786.
2. Dickmann P, et al. Sepsis 2019 - New Trends and Their Implications for Multiple Trauma Patients. Z Orthop Unfall. 2020;158:81-89.
3. Mas-Celis F, et al. Sepsis in Trauma: A Deadly Complication. Arch Med Res. 2021;52:808-816.

4. Chung S, et al. Timing and Associated Factors for Sepsis-3 in Severe Trauma Patients: A 3-Year Single Trauma Center Experience. Acute Crit Care. 2018;33:130-134.
5. Stengel D, et al. Systematic review and meta-analysis of antibiotic therapy for bone and joint infections. Lancet Infect Dis. 2001;1:175-188.
6. WHO Guidelines Approved by the Guidelines Review Committee, in Global Guidelines for the Prevention of Surgical Site Infection. 2016. Available at: https://iris.who.int/bitstream/handle/10665/277399/9789241550475-eng.pdf?sequence=1. Last accessed: 4 October 2024.
7. Coccolini F, et al. Antibiotic prophylaxis in trauma: Global Alliance for Infection in Surgery, Surgical Infection Society Europe, World Surgical Infection Society, American Association for the Surgery of Trauma, and World Society of Emergency Surgery guidelines. J Trauma Acute Care Surg. 2024;96:674-682.
8. Sartelli M, et al. The "Torment" of Surgical Antibiotic Prophylaxis among Surgeons. Antibiotics (Basel). 2021;10:1347.
9. Dhingra S, et al. Microbial Resistance Movements: An Overview of Global Public Health Threats Posed by Antimicrobial Resistance, and How Best to Counter. Front Public Health. 2020;8:535668.
10. Sartelli M, et al. Antimicrobial Stewardship: A Call to Action for Surgeons. Surg Infect (Larchmt). 2016;17:625-631.
11. Chung CY, et al. Damage control surgery: old concepts and new indications. Curr Opin Crit Care. 2023;29:666-673.
12. Ciriello V, et al. Biomarkers predicting sepsis in polytrauma patients: Current evidence. Injury. 2013;44:1680-1692.
13. Wang J, et al. Cytokine Biomarker Phenotype for Early Prediction and Triage of Sepsis in Blunt Trauma Patients. J Surg Res. 2023;283:824-832.
14. Koch C, et al. Comparison of qSOFA score, SOFA score, and SIRS criteria for the prediction of infection and mortality among surgical intermediate and intensive care patients. World J Emerg Surg. 2020;15:63.
15. Evans L, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Intensive Care Med. 2021;47:1181-1247.
16. Pruinelli L, et al. Delay Within the 3-Hour Surviving Sepsis Campaign Guideline on Mortality for Patients With Severe Sepsis and Septic Shock. Crit Care Med. 2018;46:500-505.
17. Ganga A, et al. Antibiotic prophylaxis in penetrating traumatic brain injury: analysis of a single-center series and systematic review of the literature. Acta Neurochir (Wien). 2023;165:303-313.
18. Ratila, B, et al. Antibiotic prophylaxis for preventing meningitis in patients with basilar skull fractures. Cochrane Database Syst Rev. 2006:Cd004884.
19. Appelbaum RD, et al. Antibiotic prophylaxis in injury: an American Association for the Surgery of Trauma Critical Care Committee clinical consensus document. Trauma Surg Acute Care Open. 2024;9:e001304.
20. Pasupuleti LV, et al. Is extended antibiotic prophylaxis necessary after penetrating trauma to the thoracolumbar spine with concomitant intraperitoneal injuries? Surg Infect (Larchmt). 2014;15:8-13.
21. Brooke SM, et al. A Multidisciplinary Evaluation of Prescribing Practices for Prophylactic Antibiotics in Operative and Nonoperative Facial Fractures. J Craniofac Surg. 2015;26:2299-2303.
22. Freeman JJ, et al. Antibiotic prophylaxis for tube thoracostomy placement in trauma: a practice management guideline from the Eastern Association for the Surgery of Trauma. Trauma Surg Acute Care Open. 2022;7:e000886.
23. Bradley M, et al. Risk factors for post-traumatic pneumonia in patients with retained haemothorax: results of a prospective, observational AAST study. Injury. 2013;44:1159-1164.
24. Maxwell RA, et al. Use of presumptive antibiotics following tube thoracostomy for traumatic hemopneumothorax in the prevention of empyema and pneumonia--a multi-center trial. J Trauma. 2004;57:742-748;discussion 748-749.
25. Sims EH, et al. How many antibiotics are necessary to treat abdominal trauma victims? Am Surg. 1997;63:525-535.
26. Sawyer RG, et al. Trial of short-course antimicrobial therapy for intraabdominal infection. N Engl J Med. 2015;372:1996-2005.
27. Gaudias J. Antibiotic prophylaxis in orthopedics-traumatology. Orthop Traumatol Surg Res. 2021;107:102751.
28. Grigorian A, et al. Antibiotic administration within 1 hour for open lower extremity fractures is not associated with decreased risk of infection. J Trauma Acute Care Surg. 2023;94:226-231.

29. Hoff WS, et al. East Practice Management Guidelines Work Group: update to practice management guidelines for prophylactic antibiotic use in open fractures. J Trauma. 2011;70:751-754.
30. Garner MR, et al. Antibiotic Prophylaxis in Open Fractures: Evidence, Evolving Issues, and Recommendations. J Am Acad Orthop Surg. 2020;28:309-315.
31. Srour M. et al. Prospective evaluation of treatment of open fractures: effect of time to irrigation and debridement. JAMA Surg. 2015;150:332-336.
32. Scalea TM, et al. External fixation as a bridge to intramedullary nailing for patients with multiple injuries and with femur fractures: damage control orthopedics. J Trauma. 2000;48:613-21;discussion 621-623.
33. Bumbaširević M, et al. Mangled extremity- Modern concepts in treatment. Injury. 2021;52:3555-3560.
34. Avni T, et al. Prophylactic antibiotics for burns patients: systematic review and meta-analysis. BMJ. 2010;340:c241.
35. Lee C, et al. The polytrauma patient: Current concepts and evolving care. OTA Int. 2021;4:e108.
36. Raju R. Immune and metabolic alterations following trauma and sepsis - An overview. Biochim Biophys Acta Mol Basis Dis. 2017;1863:2523-2525.
37. Cummings P, et al. Antibiotics to prevent infection of simple wounds: a meta-analysis of randomized studies. Am J Emerg Med. 1995;13:396-400.
38. Brenes-Chacon H, et al. Use of Antibiotics following Snakebite in the Era of Antimicrobial Stewardship. Toxins (Basel). 2024;16:37.
39. Wilson JL, et al. Venom Hypersensitivity. Prim Care. 2023;50:305-324.
40. Gerhardt RT, et al. The effect of systemic antibiotic prophylaxis and wound irrigation on penetrating combat wounds in a return-to-duty population. Prehosp Emerg Care. 2009;13:500-504.

Chapter 140

Infections and surgeons

Mikayla Moody
Department of Surgical Services, Western Michigan University Homer Stryker MD School of Medicine, Kalamazoo, USA.

William Wames
Department of Surgical Services, Western Michigan University Homer Stryker MD School of Medicine, Kalamazoo, USA.

Desmond Zeng
Department of Surgical Services, Western Michigan University Homer Stryker MD School of Medicine, Kalamazoo, USA.

Robert G. Sawyer
Department of Surgical Services, Western Michigan University Homer Stryker MD School of Medicine, Kalamazoo, USA.

Introduction

Surgeons have been intimately involved in the treatment of infection for millennia. Even in the time of the ancient Egyptians, there is documentation of surgeons using various instruments to open abscesses or debride septic wounds. These wounds would then be drained with linen and poultice supplied as antimicrobials, although it is unclear whether that was the understanding of the practitioners at the time. In many ways, our practice as surgeons regarding infection has not advanced much further. The goal in treating infection is to limit the number of offending bacteria, to prevent further bacteria from gaining a foothold, and to use adjuncts to control whatever bacteria remain. The tools have changed such that we no longer use poultices and now use antibiotics with greater efficacy, but these tools also bring about new challenges.

In modern times, a surgeon must have an appropriate understanding of antibiotic use from pre-procedure through completion of treatment. Decisions must be made regarding the appropriate antibiotic treatment in each scenario, whether this is for antimicrobial prophylaxis or a chronically infected wound. These decisions must be made considering the specific pathogens at play and their susceptibility patterns. Surgeons must also be cognizant of the growing concern for antimicrobial resistance and what role our use of antibiotics plays in promoting this amongst the most virulent pathogens we face.

It is important to also contemplate the effect of these antimicrobials on patients directly. Growing research has shown the importance of gut health in overall health as it relates to nutritional status, healing, mental health, and susceptibility to further infection. Each antibiotic that we give influences a patient's microbiome and this must be weighed against the benefit of an additional dose of antibiotics.

In the following chapter, we will examine the role of surgical prophylaxis, surgical antimicrobials, source control, and antibiotic stewardship. In each case, we will consider historic and recent data to present a foundation by which we hope that the reader can build their own best practices.

Surgical prophylaxis

Initiating our discussion with surgical prophylaxis allows us to start at somewhat of a beginning. Antimicrobial prophylaxis is common practice in almost all surgical procedures from the common inguinal hernia repair to the most complex pancreaticoduodenectomy. For many in the surgical subspecialties it is common practice to prescribe cefazolin to be given approximately 30 minutes prior to incision for almost all procedures. This is rarely questioned unless the patient has an allergy to penicillin or cephalosporins, but the rationale for this decision also needs to be examined.

What is the goal of antimicrobial prophylaxis? During which procedures is prophylaxis necessary? What is the appropriate antimicrobial to be given and is it different for different procedures? What is the appropriate dosing, if there is one, for a standard patient? And does that dosing need to be repeated at any point?

When discussing surgical antimicrobial prophylaxis, we are focused primarily on what would be described as primary perioperative prophylaxis. This implies that our goal is to prevent a new perioperative infection, largely from the native skin flora of our patient. The first step in preventing many of our perioperative infections is cleansing of the patient themselves reducing their bacterial load. In our facility, this is done using a chlorhexidine wash dubbed “nose to toes”. Furthermore, once the patient is positioned in the operative area is cleansed with a 2% chlorhexidine solution, although a recent randomized control trial showed that there was a noninferiority between povidone iodine and chlorhexidine gluconate for preventing surgical site infections in cardiac and abdominal surgeries. Additionally, the patient will receive two grams of cefazolin, if they weigh less than 120 kilograms, to be redosed at four-hour intervals, based upon guidelines set forth by the Surgical Infection Society.

With that in mind, the question that remains is “In which procedures is antimicrobial prophylaxis necessary?" One method for this determination is to rely on wound classification as set forth by the National Healthcare Safety Network. In this method, wounds are classified as clean, clean-contaminated, contaminated, or dirty/infected. By their nature, contaminated or dirty wounds require antibacterial treatment, not prophylaxis; therefore, they are excluded from this conversation. Clean wounds are defined as “uninfected operative wounds in which no inflammation is encountered and the respiratory, alimentary, genital, or uninfected urinary tracts are not entered”. Current guidelines suggest that in these “clean” procedures, barring substantial infection risk due to patient comorbidities or risk of infecting a prosthetic implant, antimicrobial prophylaxis may be withheld.

Conversely, clean-contaminated procedures involve entering those same tracts without unusual contamination. In these procedures, antimicrobial prophylaxis should be centered around native skin flora as well as Gram-negative rods and enterococci. The specific choice of antibiotic for surgical prophylaxis depends on the details of the surgical procedure, as well as the local antibiogram of the surgical population, and is beyond the scope of this chapter. However, the previously mentioned guidelines provide a strong foundation.

Once the determination has been made that a patient requires anti-microbial prophylaxis and which agent is best, we then need to discuss the dosing and potential redosing of that agent. A recently published review article examining the role of pharmacokinetics and pharmacodynamics in dosing of surgical prophylaxis showed that the standard two-gram dose of cefazolin maintained sufficient tissue concentrations out to the

four-hour redosing threshold whether given 60 minutes or 15 minutes before incision in patients ranging from 60 kg to 180 kg.

Similarly, a randomized control trial from Switzerland in 2017 stratified over 5500 patients into two groups for either early (n=2,798) or late (n=2,782) infusion of preoperative prophylaxis. The median infusion time for the early group was 42 minutes before incision, whereas the late group was 16 minutes before incision. The overall rate of surgical site infection was 5.1% with no statistically significant difference shown between early and late administration.

The goal of any prophylactic dosing regimen is to maintain tissue concentration of the antibiotic greater than MIC throughout the procedure from first incision to closure. The exact dosing and re-dosing regimen will require acknowledgement of the specific pharmacokinetics of the antibiotic chosen, the patient's weight/BMI, the patient's renal function, and certain milestones during a procedure such as initiation of cardiopulmonary bypass.

These studies show that in the overwhelming majority of procedures that single dose surgical prophylaxis is sufficient. If it is felt that single-dose prophylaxis is not sufficient, the recommendation is to keep any regimen to less than 24 hours. Multiple studies have shown the adverse effects related to prolonged antibacterial therapy, the most well-known being increased antibiotic resistance, but also opportunistic infections and side effects of the antibiotics themselves.

Branch Elliman *et al.* published the results of a national cohort study that included over 79,000 patients who had undergone surgical procedures in the United States Veteran's Affairs healthcare system. They showed that increasing the duration of surgical prophylaxis was not only ineffective at reducing surgical site infection but was associated with increased rates of acute kidney injury and *Clostridioides difficile* infections. Patients were stratified across multiple areas with resulting analysis showing that there was no association between surgical site infection rate and duration of prophylaxis. At the same time, the adjusted odds ratio of an acute kidney injury increased with each additional day of prophylaxis from an odds ratio of 1.13 for dosing less than 48 hours to an odds ratio of 1.79 for dosing greater than 72 hours in non-cardiac procedures; a similar pattern was found in cardiac procedures. Additionally, the risk of *C. difficile* infection demonstrated a non-significant odds ratio of 1.08 for less than 48 hours of prophylaxis but an odds ratio of 3.65 for a duration greater than 72 hours.

This study, as well as many others, reinforces the concept that antibiotic stewardship is not only related to which antibiotic is given but also the duration of treatment. The consequences of overuse include not only poorer patient outcomes but also increased healthcare costs.

As it pertains to surgical prophylaxis, the goal as with every endeavor in medicine is to maximize the benefit while reducing the risk. In this regard, that means using appropriate antibiotics, if necessary, for a given type of procedure in dosing that allows for concentrations above the MIC, with redosing as necessary, and cessation of therapy as early as possible in a patient's clinical course.

Surgical antimicrobials

Pre-emptive antimicrobials are appropriate in patients with some characteristics, including chronic UTIs, immunosuppression, necrotizing pancreatitis, positive fungal markers, massive aspiration events, and ascites. The factors involved in surgical antimicrobial therapy are multipronged. Appropriate therapy must be composed of the proper agent, proper dosing, proper timing, microbiological evaluation, appropriate de-escalation, and proper duration. Without appropriate parameters, antibiotic treatment can prove to be detrimental

for the patient through increased length of stay, acquisition of resistant infection, or side effects from escalated antibiotic regimens.

Obtaining cultures not only reduces inappropriate antibiotic treatment but also has mortality benefits for the patient. Recent studies conducted in Japan demonstrate that patients with complicated intra-abdominal infection (CIAI) who underwent a source control procedure with intra-abdominal cultures taken had significantly lower mortality than those who did not (4.0% *versus* 5.7%, OR 1.44 95% CI). This trial included 44% of institutions certified by the Japanese Surgical Society. Patients with appendicitis and upper gastrointestinal perforation had the largest differences in mortality. In addition, patients with high-risk CIAI and healthcare-associated CIAI had statistically significant associations between obtaining intra-abdominal cultures and lower in-hospital mortality. Patients without cultures taken were also more likely to have an escalation of antimicrobial agents on day five (OR 1.56, CI 1.42-1.72 95% CI).

However, guidelines on de-escalation of antibiotic treatment remain nebulous. Meta-analysis demonstrates that there are no universally accepted consensus definitions for antibiotic de-escalation (ADE), defined as a decrease in the number of antibiotics used in a treatment regimen or as a shortening in the duration of the therapy. However, it has also been defined as stopping combination therapy or switching the route of antibiotics (e.g. from intravenous to oral). There has been previous research into the duration of adequate antibiotic therapy. Granacho-Montero *et al.* demonstrated significantly reduced mortality in intensive care unit (ICU) patients with sepsis or septic shock when ADE strategies were employed. Postoperative source control recommendations vary from trial to trial, with recommendations usually ranging from 4-8 days.

One such trial is the DURAPOP trial, conducted in 21 French intensive care units from May 2011 to February 2015. The trial itself compared the efficacy and safety rates between an 8-day and a 15-day regimen in patients with postoperative intra-abdominal infections who were also critically ill. ICU patients with adequate source control, intraoperative cultures yielding positive microbial cultures, and empirical antibiotic therapy initiation within 24 hours after completion of surgery were eligible. Empiric treatment was guided by the French Guidelines for postoperative intra-abdominal infections. The primary endpoint was the number of antibiotic-free days from day 8 to day 28; if a patient died before day 28 it was counted as no antibiotic-free days. Secondary endpoints were equivalence in terms of 45-day mortality as well as superiority analyses of death at day 28 from any cause, length of ICU and hospital stay, need for reoperation for any reason, need for additional drainage, superinfection or recurrent infection (assessed by microbial sample), and another course of antibiotic therapy for any reason. Overall survival was estimated with Kaplan-Meier curves and the log-rank test, and all other secondary analysis was performed with Student's t-test, Fisher's or Wilcoxon's test as appropriate. Linear and logistic regression were fitted for elucidation of antibiotic-free days, 45-day mortality, and the emergence of MDR bacteria.

410 patients were included in the study and 249 were randomized on day 8 post-operatively, with analysis conducted on a total of 236 patients. 28 patients overall underwent reoperation, with an equivalent amount (14) in each group. The number of antibiotic-free days was higher in the 8-day arm (median 15 [6-20] days) than in the 15-day arm (12 [6-13] days). 45-day mortality rates did not differ between the two groups, with mortality rates from day 8 to day 28 in the intent-to-treat population amounting to 7.5% in the 8-day arm and 11.2% in the 15-day arm (p=0.37, OR 0.64). Kaplan-Meier survival probability estimates at day 45 for the 8-day arm were 0.89 and 0.85 for the 15-day arm, demonstrating no survival benefit for longer antibiotic courses. No significant difference was demonstrated for the emergence of MDR bacteria, but there was low-level evidence in logistic regression demonstrating a slightly higher prevalence of multidrug-resistant *Pseudomonas* in the 15-day group than in the 8-day group. Overall, the reduction of the duration of antibiotic timing proved beneficial, even in the setting of critical illness.

The standard surgeon also has several tools that do not involve antimicrobial interventions. These include diagnostics, source control, and system involvement. When an infection is definitively diagnosed, antibiotics are begun immediately. If a patient presents with likely septic shock (vasoactive agent requirement) and an infection is suspected, treatment is also begun immediately. However, if infection is suspected but not proven and the patient is hemodynamically stable and not on vasoactive medications, antibiotics should be selectively utilized. However, the question arises of appropriate treatment while waiting for cultures, and the debate on whether antibiotics should be started in the interim rages on.

However, there are promising data recommending caution in starting antibiotics. In a recent Surgical Infection Society cluster-randomized, multicenter pilot, a protocol of specimen-initiated antibiotic initiation was utilized in hopes that there would be similar outcomes to an immediate initiation protocol. A total of four tertiary care surgical ICUs participated, and a total of 186 patients with suspected ventilator-associated pneumonia who were not on vasoactive agents were included. There was no difference in demographics, comorbidities, sequential organ failure assessment, APACHE II score, or ISS score between the two groups. Patients were randomized to an immediate culture group (antibiotics started as soon as cultures were sent) or a specimen-initiated culture group, in which antibiotics were withheld until Gram stain or culture returned demonstrating infection. Secondary outcomes included mortality, length of stay, duration of therapy, and subsequent pneumonia.

In the specimen-initiated arm, antibiotics were started significantly later, with 19.4% of patients avoiding antibiotics (0 *versus* 9.3 hours, $p<0.0001$). Between the two groups, there were no differences in the rate of protocol adherence, 30-day mortality, or ventilator-free alive days at 30 days. While waiting for cultures can be agonizing for a clinician, patients had no worse outcomes when hospital-acquired pneumonia was suspected. Thus, culture-driven treatment can be implemented, further driving home the need for procedures that may allow for source control

Source control

Source control is a key concept in surgical infections, particularly in patients with sepsis. It is typically discussed in the context of intra-abdominal infection and general surgery but also applies to non-abdominal infectious contexts involving other surgical specialties, such as neurosurgery and urology. A recent set of guidelines released by the World Society of Emergency Surgery, Global Alliance for Infections in Surgery, Surgical Infection Society Europe, and Surgical Infection Society America aimed to define the concept of source control and outline its key principles. Source control is defined as “the set of all physiological/pharmacological/interventive measures adopted to control a focus of infection, to modify factors in the infectious milieu promoting microbial growth or impair host antimicrobial defenses, and to allow the organism to recover the homeostasis”. This definition includes not only surgical or procedural interventions, but also antibiotics and other supportive measures to modulate the systemic response to infection.

Surgical source interventions can be either open surgery, laparoscopic surgery, or minimally invasive procedures, such as image-guided aspiration drain placement or endoscopic procedures. With open or laparoscopic surgery, the goal is the removal of infected or necrotic tissue as well as the control of sources of contamination. With minimally invasive intervention, the goal is to create a route for infectious fluid collections to evacuate and decrease the infectious burden. This highlights the fact that surgical source control and antibiotics/supportive interventions are complementary processes in the management of sepsis.

In severe intra-abdominal sepsis, intervention may need to take the form of a damage control surgery. Situations in which this is necessary include patients with severe physiologic abnormalities or with severe injuries

in which emergent intervention is necessary to help correct the underlying pathology. Examples of this include bowel ischemia, abdominal compartment syndrome, or gastrointestinal perforation with uncontrolled contamination. The key principles of damage control surgery include control of contamination, control of bleeding, and expeditious exit from the operating room with an open abdomen or temporary abdominal closure. The advantages of the open abdomen include ease of access for repeat evaluation of the abdomen and a pathway to manage severe injuries in critically ill patients. However, there are multiple disadvantages including a hypermetabolic state potentially leading to malnutrition, intraperitoneal fluid and protein losses, enterocutaneous/enteroatmospheric fistula formation, and potential loss of domain. Many of the current methods for temporary abdominal closure methods are also resource-intensive, such as negative pressure therapies. Subsequent re-laparotomy is performed as indicated to ensure control of contamination with a shift toward fascial closure once that has been ensured.

One key factor for surgical source control is the timing of the intervention. The general guiding principle is to intervene as soon as possible with multiple studies demonstrating that delays in intervention lead to increased mortality. The ideal timing of source control intervention appears to be within 6 to 12 hours of presentation; however, the exact timing often depends on the clinical status of the patient. In the 2021 Surviving Sepsis international guidelines, source control interventions should be pursued “as soon as medically and logistically practical”15. The combination of the patient’s current clinical status and underlying medical comorbidities will ultimately dictate the timing of a source control intervention. The 2023 guidelines outlined by Coccolini and colleagues break down the timing to emergent (in need of intervention as soon as possible), urgent (intervention needed within 1-24 hours after appropriate fluid resuscitation and antibiotic initiation), and delayed (intervention after the infectious process has demarcated). Ultimately, though, it will come down to clinician judgement, the patient’s clinical status, and available resources to dictate patient care.

Source control interventions have provided a pre-requisite for the de-escalation of antibiotic therapy. This is perhaps best demonstrated in the landmark STOP-IT trial, which demonstrated that patients with complicated intra-abdominal infection who received a fixed course of antibiotics for 4 calendar days after adequate source control did not have worse outcomes in a composite of surgical-site infection, recurrent intraabdominal infection, or death within 30 days after the index source-control procedure when compared to patients who received antibiotics until 2 days after resolution of fever, leukocytosis, and ileus. Subsequent studies, such as the previously discussed DURAPOP study which studied outcomes of critically ill patients based on post-source control antibiotic duration, have similarly sought to use operative source control in different patient populations as a marker to guide antibiotic duration with the goal of decreasing excessive use of antibiotics and antibiotic resistance.

Antibiotic stewardship

Antibiotic stewardship is a topic that has progressively become more popular. It first appeared in a published article in 1996 but was quickly adopted by major infectious disease organizations as a term to highlight the importance of judicious use of antibiotics. This spearheaded initiatives and programs aimed at minimizing excessive antibiotic use. Current antibiotic stewardship programs involve multidisciplinary teams including surgeons, infectious disease physicians, and pharmacists. Surgeons play a particularly special role in antibiotic stewardship given their frequent work with intra-abdominal infections and their role as the individuals often responsible for source control interventions. The goal is to not only decrease excessive antibiotic use but also to ensure that infected patients get adequate antibiotic coverage if their current regimen is not sufficient. The benefits of an antibiotic stewardship program include reduced antibiotic use, improved outcomes,

reduced antibiotic resistance, and lower healthcare costs. In that regard, it becomes even more important to support antibiotic stewardship programs.

Robinson and colleagues described how surgeons can work together with the typical antibiotic stewardship program consisting of clinical pharmacists and infectious disease practitioners to optimize patient care. They note that pharmacists often can act as a bridge between infectious disease physicians and surgeons to help implement best practices and ensure adherence to these principles with daily medication reviews. They are also able to make non-critical suggestions regarding antibiotic regimens based on pharmacokinetics and pharmacodynamics and local antibiograms. The idea of a daily “antibiotic time out” to review the antibiotic regimen of each patient can help define an endpoint for antibiotic therapy and decrease excessive antibiotics. It also encourages de-escalation to more narrow-spectrum antibiotics to decrease potential resistance development.

Surgeons typically have three major domains in which they play a significant role in stewardship: the use of prophylactic antibiotics, initiation of broad-spectrum antibiotics when infection is suspected, and the definitive treatment of an infection when it has been defined and culture data is available. If they are involved in a source control intervention, they are also able to collect culture data which can help guide antibiotic therapies.

Clear communication is pivotal to antibiotic stewardship given the multidisciplinary team involved. This is even more crucial when considering that the Infectious Disease Society of America and Society for Healthcare Epidemiology of America guidelines focus on pre-prescription authorization and post-prescription review with feedback as two evidence-based antibiotic stewardship strategies. The success of these types of interventions relies on constant assessment and feedback to refine antibiotic choices. When frustrations mount, it may be crucial to reinforce that the goal of antibiotic stewardship is to deliver ideal care to the patient under the mutual care of all parties involved.

Conclusion

Though surgeons may not be thought of as key players in infectious diseases, many aspects of surgery have major implications in the care of infections. Surgeons make daily decisions on the type and duration of prophylactic antibiotics which can dramatically increase morbidity by increasing the risk of *C. difficile* infection. They are often the ones performing important source control interventions to treat foci of infections and collecting intraoperative cultures that are crucial in guiding antibiotic therapies. Source control interventions are critical in infection treatment as they not only directly treat infection but also augment antibiotic treatments and help define antibiotic treatment durations. Surgeons are key members of antibiotic stewardship programs given the multiple roles they play in infection treatment. Given that intra-abdominal sepsis is the second most common cause of sepsis and sepsis-related deaths, even though surgeons are not infectious disease specialists, they do play a pivotal role in treating infections. Therefore, surgeons have an obligation to carry out and contribute to best practices in the treatment of infections in their patients to optimize outcomes.

Competing interests

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

References

1. Widmer AF, et al. Povidone Iodine vs Chlorhexidine Gluconate in Alcohol for Preoperative Skin Antisepsis: A Randomized Clinical Trial. JAMA. 2024;332:541-549.
2. Bratzler DW, et al. Clinical Practice Guidelines in Antimicrobial Prophylaxis in Surgery. Surgical Infections. 2013;14:73-156.
3. Zelenitsky. Effective Antimicrobial Prophylaxis in Surgery: The Relevance and Role of Pharmacokinetics-Pharmacodynamics. Antibiotics. 2023, 12, 1738
4. Weber WP, et al. Timing of surgical antimicrobial prophylaxis: a phase 3 randomised controlled trial. Lancet Inf Dis. 2017;17:605-614.
5. Branch-Elliman W, et al. Association of Duration and Type of Surgical Prophylaxis with Anti-Microbial Associated Adverse Events. JAMA Surgery. 2019;154:590-598.
6. Montravers P, et al. Short-course antibiotic therapy for critically ill patients treated for postoperative intra-abdominal infection: the DURAPOP randomised clinical trial. Intensive Care Med. 2018;44:300-310.
7. Tsuchiya A, et al. Nationwide observational study of mortality from complicated intra-abdominal infections and the role of bacterial cultures. Br J Surg. 2019;106:606-615.
8. Garnacho-Montero J, et al. Antibiotic de-escalation in the ICU: how is it best done? Curr Opin Infect Dis. 2015;28:193-198.
9. Vallicelli C, et al. Antibiotic De-Escalation in Emergency General Surgery. Antibiotics (Basel). 2022;11:1148
10. Guidry CA, et al. Trial of antibiotic restraint in presumed pneumonia: A Surgical Infection Society multicenter pilot. J Trauma Acute Care Surg. 2023;94:232-240.
11. Coccolini F, et al. Source control in emergency general surgery: WSES, GAIS, SIS-E, SIS-A guidelines. World J Emerg Surg. 2023;18:41.
12. Risinger WB, et al. Damage control surgery in emergency general surgery: What you need to know. J Trauma Acute Care Surg. 2023;95:770-779.
13. Reitz KM, et al. Association Between Time to Source Control in Sepsis and 90-Day Mortality. JAMA Surg. 2022;157:817-826.
14. Azuhata T, et al. Time from admission to initiation of surgery for source control is a critical determinant of survival in patients with gastrointestinal perforation with associated septic shock. Crit Care. 2014;18:R87.
15. Evans L, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Intensive Care Med. 2021;47:1181-1247.
16. Sawyer RG, et al. Trial of short-course antimicrobial therapy for intraabdominal infection. N Engl J Med. 2015;372:1996-2005.
17. Dyar OJ, et al. What is antimicrobial stewardship? Clin Microbiol Infect. 2017;23:793-798.
18. Robinson ED, et al. Collaborative Antimicrobial Stewardship for Surgeons. Infect Dis Clin North Am. 2020;34:97-108.

Chapter 141

Issues in managing surgical infections in low resource settings in Asia

Suman Baral
Mediplus Hospital and Trauma Center Ltd, Mahendrapool, Pokhara, Nepal.

Shrinit Babel
University of South Florida Morsani College of Medicine, Florida, USA.

Pradeep Rajbhandari
Department of Internal Medicine, Yale School of Medicine, New Haven, Connecticut, USA.

Shasi Poudel
Department of Emergency Medicine, Fewacity Hospital and Research Center Ltd, Pokhara, Nepal.

Introduction

Surgical infections are broadly defined as any infectious process requiring operative intervention or any infections caused by an operative process. Such clinical conditions can be attributed to intraabdominal infections like appendicitis, helicobacter-associated infections, liver abscess, hepatitis, and diverticulitis; skin and soft tissue infections include necrotizing life-threatening infections; healthcare-associated infections like surgical site infections; and other medical-associated infections like tuberculosis, empyema, Chagas disease, Rheumatic heart disease, etc. The burden of surgical infections has been poorly defined in low-economy nations due to a lack of adequate data and failed registry mechanisms compared to high-income countries. The best estimates indicate that 5 billion people lack access to safe surgical care on time worldwide, while around 65% of the poorest countries have sites with only 6.5% of all operations performed. A low quantity of surgeries performed detrimentally potentiates low-resource settings that often compromise the quality and safety of the surgical cases. This is evidenced by the data mainly in low-income countries, which accounts for perioperative and anesthetic mortality to be over twice that of high-income countries (HICs), and this has been largely attributed to common procedures like cesarean sections, surgical injuries, and anesthesia-related complications. Post-operative infections are also a major concern in low-income countries as reports from WHO narrate a pooled incidence of 11.8%, while this value corresponds to around 2% in HICs, which warrants emergency attention to combat this serious issue. The primary objective of this narrative is to provide a comprehensive overview of the status of surgical infections, both preoperatively and postoperatively, describing the incidence and burden associated with various surgically treatable diseases, such as acute appendicitis and peptic ulcer disease, and highlighting the need for urgent measures to combat this critical issue. These measures are particularly crucial in low-middle-income countries (LMICs) in South Asia, where the burden of surgical infections is disproportionately high.

Surgical infections and their burden

Intrabdominal infections

Acute appendicitis is one of the most common surgical emergencies worldwide, with a global incidence of 19 million. Various studies have noted geographical variation in the incidence of appendicitis, with higher rates in high-income countries and lower rates in low-income and middle-income countries (LMICs). However, a systematic review published by Ferris and colleagues highlights an upward trend in appendicitis incidence in LMICs but steady incidence rates in many high-income countries. The late presentation, along with complicated appendicitis, predisposes to increased chances of post-operative surgical site infections with documented incidence of 17.9%, along with mortality and morbidity. In 2019, the global prevalence of peptic ulcer disease (PUD) was approximately 8.09 million, representing a 25.82% increase from 1990, while South Asia had the highest age-standardized prevalence rate of 156.62 per 100,000 population. PUD is one of the leading causes of disability and death, with 85% of such deaths occurring in LMICs. In many developing countries, the prevalence of infection with *H. pylori* exceeds 50% by five years of age, and by adulthood, infection rates exceeding 90% are not unusual, as evidenced by the study from Bangladesh and China. Overall, the pooled worldwide prevalence of gallstones remained at 6.1%, with 5.1% in Asia. A lower incidence leading to low morbidity and mortality rates of gallstone disease could be due to high-fiber diets and low cholesterol intake; regardless, trend reversal can be anticipated due to changes in lifestyles and Western diets, even in South Asian countries.

Typhoid fever is the most common bloodstream infection in South Asia. The incidence in this region is about 500 per 100,000 people, which is more than half of worldwide cases. Annually, around 7 million people are affected, with about 75,000 deaths. The most serious complication is typhoid intestinal perforation (TIP), observed in 0.8% to 39%, with a significant rate difference between high-income and low-middle-income countries. The annual incidence rate of pyogenic liver abscess is about 2.3 cases per 100,000 people in the USA. At the same time, there has been an abrupt rise in incidence in Taiwan, 275 cases per 100,000 people. Predominantly, *Klebsiella pneumoniae* is the causative agent in countries like Korea and Taiwan, accounting for 80% of the cases. Amoebic liver abscess, primarily caused by *Entamoeba histolytica*, is globally distributed; however, poor sanitation and unsafe, contaminated drinking water facilitate a higher incidence of 21 per 100,000 inhabitants per year in LMICs, especially in Asia.

Thailand is the most prevalent country with echinococcosis in humans, followed by very low incidence in Indonesia, Malaysia, Vietnam, the Philippines, Cambodia, India, Pakistan, Nepal etc. Low prevalence could be due to underreporting and lack of surveillance. Potential cure is seen in around 30% of the cases, while 70% benefit from surgical intervention. In the Southeast Asia Region, 39 million people are affected by chronic hepatitis B, 10 million by hepatitis C, and nearly 410,000 people die from viral hepatitis each year, while 81% of the deaths are due to hepatitis B and C. Estimates show that by the year 2030, approximately 4.5 million premature deaths could be averted through the implementation of vaccination programs, diagnostic tests, medication availability and educational campaigns targeting hepatitis. A study by Silver *et al.* in their systematic review identified a prevalence rate of 18% with ascariasis, where the articles published by SAARC and ASEAN countries regarding soil-transmitted helminths were analyzed. Diverticulitis may not be seen often in LMICs, which is quite rare. However, trends may increase due to lifestyle and dietary habits changes these days.

Soft tissue and bone infections

There exists no definite valid data regarding soft tissue and bone infections from LMICs; however, reports claim mortality with soft tissue infections to be 1.5 times that of HICs. More than 4 million fatalities occur

annually from trauma, with 88% of injury-related deaths along with SSIs occurring three times higher than HICs in open fractures surgical repairs. The estimated incidence of necrotizing soft-tissue infections varies between geographical areas worldwide from 0.2 to 6.9 per 100,000 person-years, with peak incidence reported in Thailand reaching 15.5 per 100,000 person-years. The prevalence of peripheral arterial disease has been documented as low as 3.2% in South India, which increases with risk factors of diabetes mellitus. The number of patients affected worldwide is expected to double by 2030, with an anticipated 485 million people affected, with nearly 2/3rd of cases originating in LMICs. Similarly, leishmaniasis, insect bites, lymphatic filariasis, etc., are also a few of the diseases that need consideration in LMICs; however, sparse data are only available in this domain.

Surgical site infections

Healthcare-associated surgical site infections (SSIs) are a significant public health issue challenge in low-resource settings across Asia. Indeed, their incidences and prevalence vary contextually, depending on factors like healthcare infrastructure, the type of surgery performed, and the availability of infection control methods. Regardless, SSIs are among the most common types of healthcare-associated infections, contributing to increased mortality, extended hospital stays, and agglomerated burden on the healthcare system.

In a meta-analysis of healthcare-associated infections in developing Asian countries, the pooled prevalence of SSIs was estimated at 5.6 per 100 surgical procedures, a figure notably higher than in higher-income countries. For example, studies based in Nepal have reported SSI rates ranging from 2.86% to 22.66%, contingent on the type of surgery and patient demographics. A study from a tertiary care center in Kathmandu found an SSI prevalence of 2.86% following cesarean deliveries, while another study reported a 12.6% prevalence following cesarean sections at another hospital. Likewise, a meta-analysis based in China reported an SSI incidence of 4.5%, with similar regional and procedural stratifications. In Vietnam, 10.9% of general surgeries developed an SSI at a time, with higher rates observed in cardiothoracic surgery. In South Asia, particularly in Bangladesh, a study in a tertiary care hospital in Dhaka reported a 14.2% SSI prevalence, with a significant proportion of these caused by multidrug-resistant organisms. In Pakistan, the incidence of SSIs following various surgeries ranged from 9.3% to 33.6% across multiple subspecialties. The general trend in SSIs across various regions of Asia documented in the literature is illustrated in **Figure 1**.

A myriad of patient-related, surgical, and environmental factors precipitate the rates of SSIs observed in low-resource settings in Asia. It is well-established that at a patient level, malnutrition, diabetes, anemia, obesity, and prolonged preoperative hospital stays serve as a risk factor. In Nepal, patients with anemia or diabetes were observed to have a significantly elevated risk of developing SSIs following cesarean section or any other major surgery. Surgical factors such as the type and duration of surgery, emergency *versus* elective status, and the use of prophylactic antibiotics are also key in precipitating an SSI. Emergency surgeries, especially those conducted with inadequate preoperative preparation, are associated with higher SSI rates. This has been documented in various studies across Asia, including those from Nepal, India, and Bangladesh. Similarly, external and environmental factors, including the lack of proper surgical instruments, inadequate sterilization techniques, and limited access to clean water and sanitation, exacerbate the risk of developing SSIs in low-resource settings. The paradigm of surgical site infection development in resource-limited settings in Asia has been summarized in **Figure 2**.

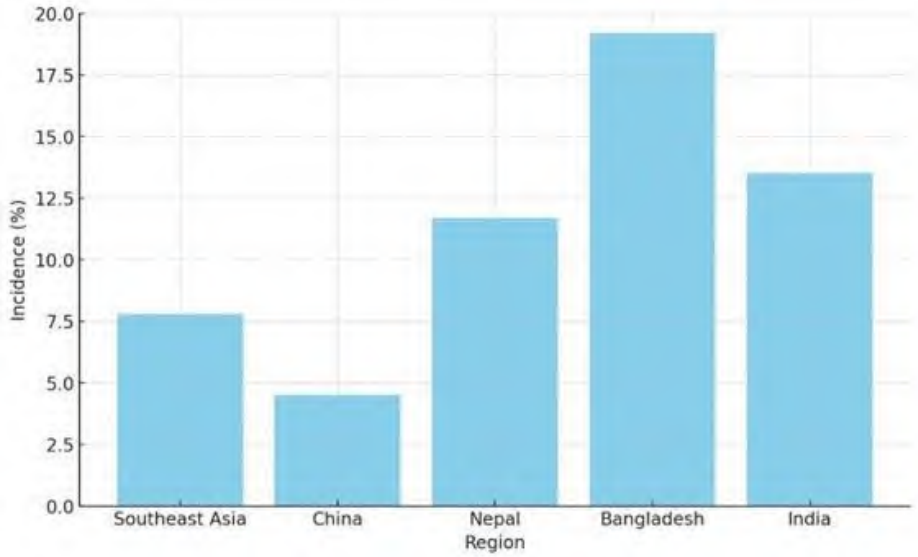

Figure 1. Incidence of surgical site infections in different regions of Asia as documented in the literature.

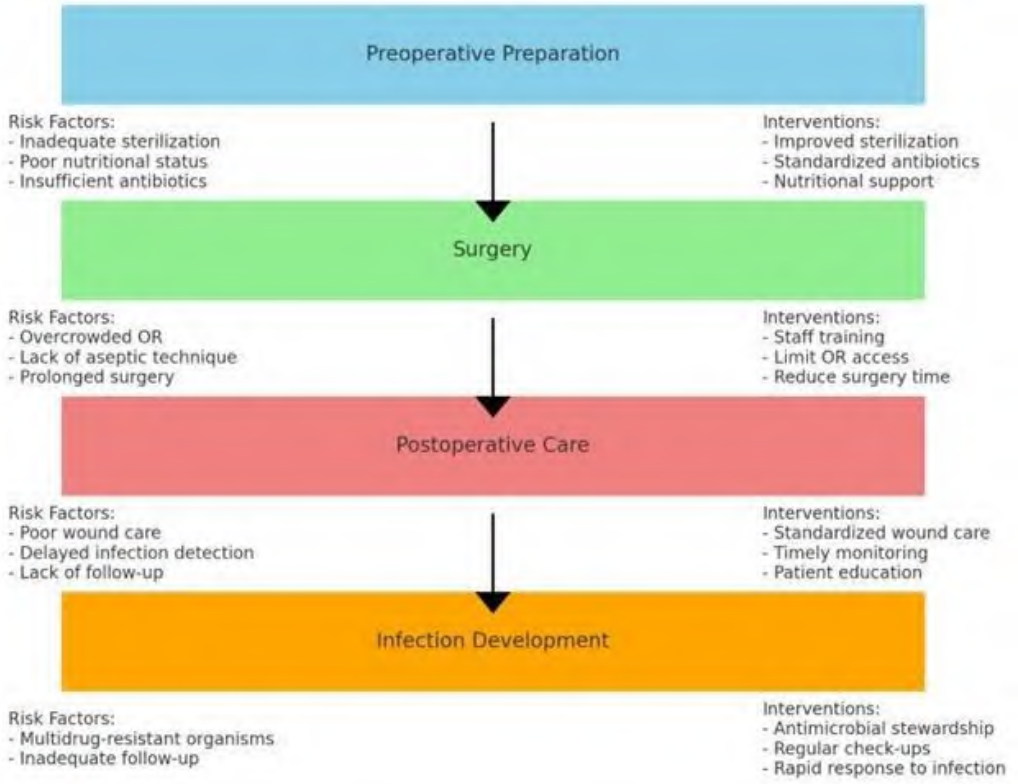

Figure 2. The paradigm of surgical site infection development in resource-limited settings in Asia.

Surgeries and infection types

The most common surgeries associated with SSIs in Asia include cesarean sections, abdominal surgeries, and procedures otherwise involving the gastrointestinal tract in some form. Cesarean sections are a significant

contributor to the burden of SSIs, with studies from Nepal and India reporting rates ranging between 3.1% and 24.2% following these procedures.

Multidrug-resistant pathogens often drive the microbial profile of SSIs in these settings. *Staphylococcus aureus*, including the methicillin-resistant *Staphylococcus aureus* (MRSA), and Gram-negative bacteria such as *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* are commonly isolated in SSIs. For instance, in a study based in Bangladesh, MRSA and other multidrug-resistant organisms were found to be significant contributors to SSIs, exceptionally complicating the treatment and increasing the risk of adverse outcomes.

The growing prevalence of antibiotic-resistant bacteria becoming the infectious agent in SSIs further complicates patient trajectories. In general, studies across various Asian countries have reported the development of significant resistance patterns, especially among Gram-negative organisms. For example, a study in Pakistan highlighted the high incidence of multidrug-resistant *Acinetobacter* species in SSIs, which poses a severe challenge to effective infection control.

Global surgical ecology

The need for surgery extends across countries at all stages of development, the largest area of unmet need exists within LMICs. Around 5 billion people do not have access to safe, affordable surgical and anesthesia care when needed, while 9 of 10 people cannot access basic surgical care in LMICs. Of the 313 million procedures undertaken worldwide each year, only 6% occur in the poorest countries, where over a third of the world's population lives. These unmet needs are greater in eastern, western, and central sub-Saharan Africa and South Asia.

Devries and Rosenberg documented surgery as an ecosystem that incorporates a network of personnel, processes, and materials necessary for rendering surgical services in a local environment. A safe surgery to be performed not only involves an incision and surgical expertise but incorporates holistic approaches inside the theatre and outside the surgical parameter, including surgical workforce, infrastructures, supply chain, wound care supplies, infection surveillance, antibiotics stewardship, adequately stuffed laboratory with ancillary support with wound care nurses, nutritionist, physical therapist, and infectious disease specialist.

Surgical workforce and auxiliary support

A growing surgical workforce and appropriate mobilization are the keys to increasing surgical capacity. Worldwide, there are an estimated 1.1 million specialist surgeons, 550,134 anesthesiologists, and 483 357 obstetricians, while low-income and lower-middle-income countries, which represent 48% of the global population, have 20% of this workforce, or 19% of all surgeons, 15% of anesthesiologists, and 29% of obstetricians. Trained non-physician providers also contribute to minor surgical procedures in areas of need where specialist services are unattainable. Multidisciplinary support from infectious disease specialists, adequate nursing staff providing good nursing care, physical therapists, and nutritionists play an important role in the perioperative period that helps combat surgical infections. Antibiotic sensitivity tests with bacterial culture facilities need to be made available, which help develop evidence and look for local microbiological susceptibility patterns.

Antimicrobial resistance (AMR) and surveillance of surgical infection

AMR is one of the most commonly encountered public health concerns throughout the world due to the rampant use of antibiotics, which shows 20% - 50% unessential application in acute care models. This issue is accentuated in LMICs like South Asia, where overprescribing, along with the over-the-counter availability of antibiotics, makes easy access to the community. Data from the SEA region show that 4 million people died in 2019 due to sepsis as an immediate or intermediate cause of death, among which 62% were caused by bacterial infections, which included 0.39 to 1.41 million people who died because of bacterial AMR. Nosocomial and hospital-associated infections are increased in LMICs, where ICU prevalence is twice and thrice that of Europe and the United States, respectively. Infection surveillance and the development of antimicrobial stewardship are equally challenging due to compounding population density, limited data on local resistance patterns, fragmented health systems that include public and private institutes, and a dearth of policies and regulations while inappropriate or no use of existing ones. AMR driving factors include lack of access to appropriate drugs, lack of sanitation, underuse of diagnosis, medicated animal feed, easy access to antibiotics, self-medication, financial gain to sellers, poor hygiene and infection control, etc.

Infrastructure and supply chains

The subsystems that contribute to the surgical ecosystem include hospital buildings, electricity supply, waste management, supply chains, pharmacy, and biomedical engineering. The supply chain includes resources like surgical gauze, adhesive tapes, saline and dressing supplies, surgical instruments, sterilization methods, hand hygiene solutions, and disinfectants, which have a significant impact on surgical infection management. These parameters' availability holistically can improve across all surgical domains, including surveillance and global surgical infection management.

Solutions and interventions

Alleviating the burden of surgical infections

The most important method to curtail SSI is by adopting methods to reduce the burden of surgical infection. There are numerous strategies for treatment and prevention to lessen the impact of the diverse variety of surgical infections that occur worldwide. These approaches should be fundamentally focused on either patient factors, surgical procedures, or both.

In recent years, there has been a big push for patient involvement and education in medication management. In LMICs, where patients frequently reside far from hospitals and health facilities, patient participation can be an extremely high-yield idea. An outreach training program to teach general practitioners and nurses of health centers, as well as patients, about the signs and symptoms of postoperative infections can be an effective method. Involving important parties, like Ministries of Health, is essential to guaranteeing the longevity of the initiative. Financial burden, long hospital stays, and worse clinical outcomes due to SSIs can be reduced by these strategies.

The availability of surgical site preparation, awareness about hand washing methods, use of pre-operative antibiotics, infection surveillance, incision management systems, and peri-operative serum glucose control are examples of environmental and resource issues that are the potential ways to reduce the burden of SSIs.

Similarly, clean water and improved sanitation can be very instrumental in stopping Typhoid fever transmission. Additionally, early diagnosis and treatment of typhoid fever may prevent intestinal perforation.
Attempts have been made in recent years to come up with guidelines for the prevention of SSIs. WHO has introduced guidelines for SSIs and made recommendations; however, it is challenging to implement the strategies to follow these guidelines in low and low-middle-income countries (LMICs) as some of these guidelines are not readily deliverable.

Surgical infection surveillance and antimicrobial stewardship

Amid a rise in antimicrobial resistance (AMR), monitoring the frequency of antibiotic usage should be the first step in improving antibiotic use. Carrying out antimicrobial surveillance concurrently with surgical infection surveillance, with data being documented via the creation of a centralized registry or sophisticated database technologies, is considered the best way. Creating nationwide databases with participating hospitals and health facilities can enhance surveillance. However, this is challenging when there are no computerized health records in hospitals. For review and analysis, automated data collection and central deposition might be especially useful.
Antimicrobial medication provided, dosage, mode of administration, duration of treatment, and organisms treated should all be included in the paperwork. The next objective should be to establish national or regional antibiotic stewardship programs (ASPs). Since most of these initiatives were started during the previous ten years, even for High-Income countries (HICs), they are still considered relatively new. When accessible, carefully recording microbiologic culture data from low- and middle-income countries (LMICs) is essential to deciding whether or not antibiotic use is appropriate. Discouragement of the careless use of antibiotics can be achieved with the help of an antibiotic selection optimization tool.
Collecting data on the use and duration of antibiotics for the microbiological or SSIs that have been diagnosed will make up the majority of the first work in generating ASPs. Though it might not be possible to implement an ASP program everywhere, the principles of antibiotic stewardship should be focused on LMICs. The active form of lectures and participation rather than passive teaching can be an effective way to improve antibiotic stewardship and achieve optimal outcomes. Additionally, effective training programs to reassure surgeons and clinicians on the best practices that involve more judicious and selective use of antibiotics can be helpful.

Enhancing the management of surgical infections

Early detection of SSIs can lead to improvements in the management of postoperative infection. Once infections are identified, a uniform protocol to provide treatment ideally involves basic surgical concepts, including dressing care, source control, antibiotic regimens chosen carefully, and meticulous follow-up.
Due to a lack of qualified peers, surgeons in LMICs frequently handle far heavier workloads and treat more patients across bigger geographic areas. Using technology to facilitate communication between surgeons and outpatient doctors may also help detect surgical infections earlier. Teaching surgeons, general practitioners, and nurses of health centers about the symptoms and indicators of postoperative infections can be an effective method. Workers at health centers should receive training on how to identify the telltale signs and symptoms of common surgical problems such as soft tissue infections, obstructions, and peritonitis. Similarly, mobilization and education of healthcare workers, such as operating room technicians, hospital staff, and patients, can result in significant improvements. Through an outreach program, surgeons or physicians can train other health personnel once a week or once a month to treat patients and instruct general practitioners on how to manage SSIs.

Conclusion

The rising incidence of AMR and surgical infection is a potentially challenging issue and is growing as a substantial global health burden, with LMICs bearing a disproportionate share of this burden. One of the biggest obstacles to management in LMICs is the lack of financial and skilled resources. The creation of programs for infection control, antimicrobial stewardship, and surveillance are the first steps in the right direction. Education is essential, and it should start early in the training process, be in a dynamic format, and be continued with periodic educational initiatives and require commitments at multiple levels. Identifying the challenges and implementation of strategies to combat SSIs should be broadly understood and supported by stakeholders at the global level.

Competing interests

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

References

1. Vincenzo N. Introductory Chapter: Surgical Infections. In: Vincenzo N, editor. Infectious Process and Sepsis. Rijeka: IntechOpen; 2020. Ch. 1.
2. Rickard J, et al. Surgical Infections in Low- and Middle-Income Countries: A Global Assessment of the Burden and Management Needs. Surg Infect (Larchmt). 2020;21:478-494.
3. Monahan M, et al. Surgical site infection and costs in low- and middle-income countries: A systematic review of the economic burden. PLoS One. 2020;15:e0232960.
4. Alkire BC, et al. Global access to surgical care: a modeling study. Lancet Glob Health. 2015;3:e316-23.
5. Santhirapala V, et al. Towards high-quality peri-operative care: a global perspective. Anesthesia. 2020;75 Suppl 1:e18-e27.
6. World Health Organization. Global guidelines for the prevention of surgical site infection. 2016. Available at: https://iris.who.int/bitstream/handle/10665/277399/9789241550475-eng.pdf?sequence=1. Last accessed: 24 September 2024.
7. GBD 2021 Appendicitis Collaborator Group. Trends and levels of the global, regional, and national burden of appendicitis between 1990 and 2021: findings from the Global Burden of Disease Study 2021. Lancet Gastroenterol Hepatol. 2024 Sep;9:825-858.
8. Frenck RW Jr, et al. Helicobacter in the developing world. Microbes Infect. 2003;5:705-713.
9. Wang X, et al. Global Epidemiology of Gallstones in the 21st Century: A Systematic Review and Meta-Analysis. Clin Gastroenterol Hepatol. 2024;22:1586-1595.
10. Contini S. Typhoid intestinal perforation in developing countries: Still unavoidable deaths? World J Gastroenterol. 2017;23:1925-1931.
11. Khim G, et al. Liver abscess: diagnostic and management issues found in the low resource setting. Br Med Bull. 2019;132:45-52.
12. Akhondi H, et al. Liver Abscess. 2023 Jul 3. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2024 Jan–.
13. Ambar Garjito T, et al. Echinococcosis: Past and Present Situation in Southeast Asia. Overview on Echinococcosis. IntechOpen; 2020.
14. Ramasamy S, et al. Eliminating Viral Hepatitis from India and Southeast Asia by 2030: Challenges and Ways Forward. Preventive Medicine Research & Reviews. 2024;1:84-89.

15. Wiktor SZ, et al. The global burden of viral hepatitis: better estimates to guide hepatitis elimination efforts. Lancet. 2016;388:1030-1031.
16. Silver ZA, et al. Geographical distribution of soil-transmitted helminths and the effects of community type in South Asia and South East Asia - A systematic review. PLoS Negl Trop Dis. 2018;12:e0006153.
17. Hua C, et al. Necrotizing soft-tissue infections. Lancet Infect Dis. 2023;23:e81-e94.
18. Allegranzi B, et al. The burden of endemic health-care-associated infection in developing countries: systematic review and meta-analysis. Lancet. 2011;377:228-241.
19. Koirala P, et al. Postoperative Surgical Site Infection among Patients with Caesarean Delivery in the Department of Obstetrics and Gynaecology in a Tertiary Care Centre: A Descriptive Cross-sectional Study. JNMA J Nepal Med Assoc. 2023;61:526-530.
20. Shrestha S, et al. Incidence and risk factors of surgical site infection following cesarean section at Dhulikhel Hospital. Kathmandu Univ Med J (KUMJ). 2014;12:113-116.
21. Fan Y, et al. The incidence and distribution of surgical site infection in mainland China: a meta-analysis of 84 prospective observational studies. Sci Rep. 2014;4:6783.
22. Nguyen D, et al. Incidence and predictors of surgical-site infections in Vietnam. Infect Control Hosp Epidemiol. 2001;22:485-492.
23. Sickder HK, et al. Prevalence of surgical site infection in a tertiary level hospital in Bangladesh. Int J Nat Soc Sci. 2017;4: 63-68.
24. PakSurg Collaborative. PakSurg 1: determining the epidemiology and risk factors of surgical site infections in Pakistan-a multicentre, prospective cohort study. BMJ Open. 2023;13:e070831.
25. Mishra RT, et al. Surgical site infection following cesarean section and its associated risk factors at a tertiary care hospital in Chitwan. J Chitwan Med Coll. 2020;10:47-51.
26. Basany K, et al. A prospective cohort study of surgical site infections following single-dose antibiotic prophylaxis in cesarean section at a tertiary care teaching hospital in Medchal, India. PLoS One. 2024;19:e0286165.
27. Meara JG, et al. Global Surgery 2030: evidence and solutions for achieving health, welfare, and economic development. Int J Obstet Anesth. 2016;25:75-8.
28. deVries CR, et al. Global Surgical Ecosystems: A Need for Systems Strengthening. Ann Glob Health. 2016 ;82:605-613.
29. Sihombing B, et al. Response to antimicrobial resistance in South-East Asia Region. Lancet Reg Health Southeast Asia. 2023;18:100306.
30. Zellweger RM, et al. A current perspective on antimicrobial resistance in Southeast Asia. J Antimicrob Chemother. 2017;72:2963-2972.
31. Spiegel DA, et al. World Health Organization Global Initiative for Emergency and Essential Surgical Care: 2011 and beyond. World J Surg. 2013;37:1462-1469.
32. World Health Organization. Global Guidelines for the Prevention of Surgical Site Infection. 2018. Available at: https://www.ncbi.nlm.nih.gov/books/NBK536404/. Last accessed: 24 September 2024.
33. Berrevoets MA, et al. Monitoring, documenting and reporting the quality of antibiotic use in the Netherlands: a pilot study to establish a national antimicrobial stewardship registry. BMC Infect Dis. 2017;17:565.

Chapter 142

Issues in managing surgical infections in low resource settings in Africa

Vihar R. Kotecha
Department of General Surgery, Weill-Bugando School of Medicine, Catholic University of Health and Allied Sciences, Bugando, Mwanza, Tanzania;
Department of General Surgery, Bugando Medical Centre Bugando, Mwanza, Tanzania.

Jeremiah Seni
Department of Microbiology and Immunology, Weill-Bugando School of Medicine, Catholic University of Health and Allied Sciences, Bugando, Mwanza, Tanzania;
Central Pathology Laboratory, Clinical Microbiology Unit, Bugando Medical Centre, Bugando, Mwanza, Tanzania.

Introduction

United Nations Economic Commission for Africa, reports that the continent harbours a population of almost 1.5 billion people, and most Sub-Saharan African (SSA) countries fall into low-income to low- to middle-income countries (LMICs). Falling into the latter economic development category creates several challenges to healthcare provision due to the country's swinging development priorities. The growing need for safe affordable health care becomes a priority but offering it to the fullest capacity remains a challenge due to a multitude of issues. A staggering 93.0% of the African population lacks access to timely, safe and affordable surgical care. Surgical care is no longer a luxury but a necessity, as reported by Meara *et al.*, yet surgery is unsafe in many African countries. When surgery cannot be reliably offered, the complication rate could be as high as 50%. One of the largest contributors to morbidity and death is developing postoperative surgical site infection. Surgical infection is noted to be up to 10 times higher in SSA when compared to high-income countries. Caesarean section is the most prevalent surgical procedure in Africa. This life-saving operation is associated with significant post-operative SSI rates, ranging from 3.5 – 12%. Isolated factors such as the performance of surgery in a rural setting, age, the urgency of surgery, and ASA status have been attributed to the development of infection. Still, the overall dysfunctional quality of care has been attributed as the major problem contributing to infection. Like other public health measures, offering safe surgery has been associated with low cost to the health system and ensuring its delivery with quality should be equally prioritised. Surgical infection is here to stay in Africa, it will continue hindering the deliverance of quality health services unless concerted efforts at individual patients, communities, healthcare systems and governments at large are made to combat the "Inverse care law" stated by Tudor Hart. This law states that "disadvantaged population needs more health care than the advantages but receive less". In Africa getting to a health facility on time is a luxury, and if one makes it there, they are not guaranteed prompt, effective treatment. Disruptive yet frugal ideas with collaboration may solve this complex problem that pushes the health care system and individuals to

significant costs. We implore several challenges related to surgical infection in SSA, shedding pertinent potential solutions which are reflective of local context to sustain gains that have been shown in a few countries and showcase reciprocity in the countries lagging.

Socioeconomic factors hindering delivery of surgery; a cornerstone in source control of surgical infection

In SSA, there is a huge discrepancy in the delivery of surgery. The Lancet Commission stated that 5 billion people lack access to surgery in SSA, while 143 million additional surgical procedures are needed to save lives and prevent morbidity. Surgery can be the most important modality of source control in several surgical infections, however, there are several overarching barriers to obtaining this care. The three-tier model of delay is most commonly used in healthcare, i.e. delay in seeking, reaching and receiving care. Socioeconomic factors are often elemental to the delay in presentation to health care. Such barriers are lack of formal education, prior poor experience with health care, distance from a health care facility, more trust in traditional health care, and inability to finance treatment. In Rwanda, delays in health care presentation were associated with visiting a traditional health care provider, monthly income, lack of health care insurance and distance of > 2 hours. Lancet Commission further mentions that health facilities should be within a 2-hour reach. In SSA, this gap is decreasing as governments invest in health care. The question remains if these hospitals can offer reliable surgical care. Surgical infection can be catastrophic with the uncertain availability of surgical care in health facilities.

Patients' and healthcare systems' issues

Unattended surgical infection would consume into the patient's physiologic reserves one system after the other thereby contributing to death if no counter interventions are offered. If Mother Nature selects those who reach a health facility, receiving appropriate surgical care may be uncertain due to several reasons ranging from lack of skilled human resources to lack of diagnostic equipment or availability of correct treatment options such as availability of medications, critical care facility or unconducive environment for provision of surgery. In some facilities, diagnosis can be achieved, but surgery delivery is impossible. Acute appendicitis is frequently an emergent surgical cause of peritonitis; life can be saved even if it is complicated, provided it reaches the hand of a competent surgeon in an adequate health facility.

Surgical infection; propagation in the setting of comorbidity in SSA

SSA have a prevalence of Human Immunodeficiency Virus (HIV) infection ranging between 0 - 40%. Approximately 67% of the total global population of people with HIV live in SSA. This illness has drawn public health attention for almost two decades with some success in capping the prevalence. Only after the Lancet Commission report has the shift to looking at surgery become slightly equalized. Curbing HIV has been resource-intensive leading to diversion from strengthening surgical care. Lessons and modalities used to combat HIV could be partly borrowed to elevate control of surgical infection in SSA. Stage four of an HIV-infected individual can present to the surgeons with aggressive surgical infections such as necrotizing fasciitis which makes

the situation more complex since such individuals could often be malnourished with some having organ dysfunction from their primary illness. Multidisciplinary care that is required is rarely available even if the patient is within 2 hours of a rural health facility. In many African settings multidisciplinary care if nested in the urban settings, a location which would be miles away for several. As we combat HIV in SSA, there is now an outburst of non-communicable diseases (NCDs), such as Type 2 diabetes mellitus (DM), and hypertension. The global prevalence of DM is 10.5%, while the prevalence of DM and Hypertension are 0 - 16% and 6 - 48% respectively in SSA. Chronic illnesses add another layer of complexity in managing severe surgical infections due to the requirements of highly integrative and multidisciplinary healthcare systems with the availability of critical care services. In SSA where rural healthcare systems are still rudimentary combating severe surgical infection remains a healthcare challenge. Treating severe surgical infections with underlying comorbid conditions is often resource-intensive, in the absence of critical care services the outcomes may be fatal. To address this, most countries are venturing into universal health coverage (UHC) to partly cater for the availability of essential medicines, diagnostics and health care services (including emergency surgical care services) at all levels in the cascade of referral health care systems. The UHC is also envisioned to address the health services interruptions posed by epidemics, pandemics and unforeseen health threats, which most often have deleterious effects on patients requiring emergent surgical services.

Shortage of healthcare workers

Controlling surgical infection in its early stages is a proven strategy to prevent undue outcomes and requires skilled healthcare providers vested with proactiveness rather than reactiveness in the provision of comprehensive services in the surgical pathways pre-operatively, intra-operatively and post-operatively. The scarcity of surgeons in LMICs is a reality, with only 6.2 surgeons per 100,000 population in comparison to 56.9 in High-income countries HIC. Despite having such short numbers, most of these skilled personnel are positioned in the urban setting there by virtually increasing the real distance of receiving definitive care to beyond 2 hours. In the rural setting, task-shifting to junior doctors and medical officers is a norm in LMIC these individuals are dampening deficiency, while in reality, they possess limited skills. Unpublished experiences from tertiary referral centres receive highly complicated patients who have undergone operations by “junior doctors”, such individuals, without doubt, mean good faith for the patient but the undertaking may be beyond their ability. Lacking mentorship and guidance on what they should do in complex situations is an existing gap in SSA. Public sectors must focus on the availability of a critical mass of specialists up to the district level. They should foster healthcare policies to streamline human resource distribution in line with recommendations by the Lancet Commission. Controlling surgical infection requires a well-orchestrated play, surgeons, anaesthesia providers, nurses, laboratory technicians, pharmacists, microbiologists, etc. The scarcity of surgeons has been demonstrated, but the rest of the team echoes similar shortages. For instance, it is assumed that 90% of the nurse shortage occurs in Africa, Southeast Asia and the eastern Mediterranean region, only 3% of the nurse population lives in Africa. Having such high shortages leads to a nurse-to-patient ratio of 1 to 2000 population in LMICs. Nurses are critical players in health care provision, including care for surgical infections. Close monitoring and early detection of patients’ physiologic deviation is the narrow window of opportunity in reversing the pathologic process, and nurses have a significant role to play in this. An increment in mortality was noted from 7 to 14% when the nurse-to-patient ratio increased from 1:6 to 1:8 this can safely be tagged as increasing nurses could potentially influence patient outcomes. The nurse-to-population ratio hasn’t been standardised as of yet, but in LMICs, recommendations are divided according to shift hours, for example, morning shifts require the majority of nurses, one nurse for four patients. It is recommended that in centres with an Intensive

care unit (ICU) Nurse to patient ratio should be 1:2 for patients who are not ventilated and 1:1 for patients on mechanical ventilation. We have seen that surgical infection is the highest contributor to mortality in surgical patients, a team approach is required to handle this delicate situation when the patient's life is on the edge. Unpublished data from Tanzania shows a nurse-to-patient ratio can be as high as 1:10 within regular wards and 1:4 in ICUs. Nurses hold a huge responsibility to patients, some of which include wound care, delivery of timely medications, and ensuring a clean environment. In a surgical ward, most patients are being nursed for some kind of wound, be it from recent surgery, trauma, a complication surgery, soft tissue infection or cancer. These wounds differ, they range from clean operation wounds to dirty wounds. Clean wounds have the potential to become contaminated or contaminated wounds to spread further if wound care and delivery of medication is not offered timely. Studies have demonstrated multiple factors associated with missed nursing care such as, bed making, turning a patient to delivery of medication to wound dressing. The highest trending reason was nursing staff a shortage, followed by an unexpected rise in patients and a lack of supporting staff.

We often forget other individuals in the health care setting who play a critical supportive role in the care of patients with surgical infections. Laboratory scientists, microbiologists, and radiologists are often forgotten. Over the last decade role of radiologists has been realised as the availability of radiologic imaging has grown to and radiologists skill to offer radiology-guided interventions have matured. It is estimated in rural Uganda that 500 out of 1000 patients seen require sonography or plain radiography. The number of radiologists varies significantly within and across countries. Such high demands for radiological services are an unmet need in the absence of radiological care providers. Radiology is a quickly evolving field as more and more radiologic investigation facilities are available, and so is the opportunity to grow in image-guided interventions. Interventional radiology is a highly skilled field suggested to be available in centres with functioning computed tomography (CT) scanners and ultrasound machines. Ultrasound-guided interventions for several abdominal infections are now acceptable modalities of treatment in situations of draining and abdominal/pelvic abscesses. For example, a clinical concern for organ space infection may require some sort of radiologic imaging, that can help in the diagnosis of brewing infections. In SSA organ space infection would require an operating theatre visit again for the majority, but with the upcoming radiologic-guided interventions such visits can be reduced more particularly in developed centres where the availability of interventional radiologists in bigger cities in SSA is becoming a normal trend. A secondary operation to clear an organ space infection may be lifesaving but it doesn't leave the patient with a potentially higher rate of morbidity and delayed recovery. Radiologic-guided procedures are effective and prevent additional complications/morbidity from the second or third operation. To curb surgical infection and its propagation the availability of appropriately numbered human resource is utterly important in the provision of surgical services to complement appealing healthcare systems infrastructures (buildings, equipment and medicines) that countries like Tanzania have invested in to foster "value for money" which translate into favourable medical and surgical patients' outcomes.

Challenges in healthcare systems

Africa is a breeding ground for old and new infectious diseases, with 30 new emerging infectious diseases diagnosed since 1960. Communicable disease outbreaks occur regularly on the continent, and such outbreaks derail an already crippling health system. These challenges are complex and multifaceted, spanning across poor infrastructure, resulting in a weak health system, high disease burden, health system corruption, poor leadership and administration, and poor quality of healthcare services. Africa has the highest number of endemic diseases, and it is estimated that 10 million lives are lost to epidemics, which contributes to $ 800

billion loss in productivity. When global pandemics hit, international collaborations with Africa quickly become fragile this was clear in the SARS-COV-2 pandemic where SSA was quickly pushed last on the list for access to rapid tests and vaccines. Learning from the recent pandemic African leaders need to develop ways of collaborating within the continent, think in the interest of the inhabitants and hold accountable corrupt systems and individuals that lead to ongoing failures in the health care systems.

Weak governance is another critical factor that contributes to these challenges in Africa such as lack of political will, non-use of evidence-based interventions, weak training and education, weak health information management systems, and poor integration of programmes. Public healthcare facilities are poorly equipped with medical supplies, medication, and surgical equipment not forgetting short staffing both in number and diversity. Furthermore, the infrastructure is old in many settings, with additional problems accessing clean water or constant electricity supply. New hospital structures are equipped with the bare minimum of medications and equipment and staff, medication and consumables are frequently out of stock. This is aggravated by meagre health budgets and a lack of clear health system delivery plans. African health budgets heavily depend on donor funding which adds another layer of complexity since these funds come with specific rules to address specific goals. Such funds may also consume the time of the meagre human resources which exist while dangerously shelving other priority plans that countries may have established.

Shortage of medical equipment and drug supply in SSA, propagating surgical infection

From reaching a health facility to receiving appropriate care is a trial that a patient with a surgical infection goes through in SSA. Surgical infection can be rapidly progressive, necessitating some urgent/emergent surgical interventions, followed by close monitoring. Delivery of the surgical procedure is dependent on several types of equipment broadly categorised as hospital consumables, reusables, and machines to offer anaesthesia and safe surgery. The World Health Organization estimates that between 50 to 80% of medical equipment in developing countries is not functioning. These countries furthermore lack technology-guided assessment systems and regulatory controls to prevent the importation of inferior medical equipment which could malfunction quickly. Critical shortages of medical equipment in African settings pushing compelled healthcare providers to cut shortcuts to save a life. The aftermath resulting from their intervention may be the next combat if the patient survives to see the sunlight. Medical equipment needs to be available in abundance in the rural hospitals, this is where the population is, yet these are the least stocked setups. Healthcare providers further complain of poor-quality medical equipment that hinders the delivery of quality care. One hospital nurse mentioned that they needed to use three patient monitors to get all the vital signs. No single monitor had functioning all parts. Such shortfalls frustrate and overworked nurses even further. Nurses from one study mention that the quality of medical equipment they use is inferior, they become non-functional in no time. Anecdotal experiences echo similar experiences, for example, buying a monitor may require permission from a centralised financing system, which could take several months for approval and once approved, another few months to receive the equipment. More frequently, the quantity has been cut by half, and quality is often poor. Maintenance is often lacking due to few or no biomedical technicians, yet equipment's malfunctions more frequently. This breakdown would trigger another cycle of procurement, and gathering the strength to initiate another cycle is not for flail leaders, slowly, healthcare providers accept this situation in despair. How can surgical infection, which has the potential of being treated, be salvaged with such crippling systems? Foreign global Surgical missions have been thought to be a saviour to a handful of healthcare facilities when

surgical teams come in with high-quality medical supplies, often some items remain behind after a mission. These are thought to help the failing system for a short time until things fall back to the status quo.

Apart from source control, the utility of antimicrobial agents forms the backbone of managing surgical infection. Usually, a combination of antimicrobial classes limits the growing microbial burden in the patient, however, antimicrobial availability in the SSA setting is limited. Most countries have a central supply of drugs and medical equipment, and meeting the nationwide requirements for medical supplies and medication is often difficult. For example, in Tanzania, the top five most-utilized classes of antibiotics are tetracycline, sulfonamides and trimethoprim, quinolones, aminoglycosides, and beta-lactam antibiotics like penicillins and cephalosporins. Certain groups of Antimicrobials are over-utilized, due to the limited availability of the full range of antimicrobial classes. To concur with surgical infection the availability of life-saving antibiotics and the different variety of antimicrobial classes is another angle that SSA needs to combat. In the setting of surgical infection, intravenous formulation of antimicrobial agents should be initiated as soon as an infection is suspected, mostly, a third-generation cephalosporin is the initial drug of choice. A study looking at antimicrobial utility reports that 45% of all the antimicrobial prescriptions in Tanzania were from the Beta-lactam group of antibiotics. This group has become the wonder drug, and its availability has become so frequent that it can be dispensed over the counter without a prescription. As a result, there is an alarming progressive evolution of multidrug-resistant bacterial pathogens (MDR) due to antimicrobial selective pressure covered by misuse or overuse of beta-lactam antibiotics leading to predominance of two AMR phenotypes prototypes namely methicillin-resistant *Staphylococcus aureus* (MRSA) and Extended-spectrum beta-lactamase producing (ESBL) Gram-negative bacteria. Furthermore, the prescription pattern is not geared toward hospital antibiograms since most of the hospitals do not have microbial culture and susceptibility facilities. This growing problem may quickly convert a controllable surgical infection into an uncontrollable situation at an individual patient level. Infection prevention teams are available in hospitals, but governance and administrative support may usually be slacking to allow meaningful quality improvement changes in AMR-responsive practices. Developing antimicrobial stewardship (AMS) programs could help control this cropping pandemic. Worldwide Antimicrobial Resistance National/International Network Group (WARNING) Collaborators published a guide to hospital prescription of antimicrobial agents; such efforts need to be embraced by local AMS and Infection prevention care teams or committees to foster multidisciplinary collaborative and responsive efforts teams where they exist.

Conclusion

Surgical services in Africa are slowly progressing but are counteracted by a multitude of factors hindering these gains. Surgical site infections are the highest cause of complications in SSA, contributing to the economic burden on individuals and healthcare systems. The problem is large and multifaceted. Research has availed some data, such as the unmet compelling needs for the provision of quality surgical services through addressing human resource challenges, the escalating burden of AMR, limited laboratory diagnostic infrastructures to guide prudent use of antimicrobial therapies, and uncertain funding mechanisms. Available data are compelling to health ministries to accept this challenge as a real threat and break it down into sizeable chunks. Formulating multidisciplinary teams at hospitals, regional, national and global levels, to generate more electronic data-gathering tools would allow more in-depth insights suitable to address the country's specific needs. Data-driven projects may generate reliable strategic plans that could culminate in meaningful outcomes but should also be strategically designed considering the local context. Fostering hospital-academia partnerships, private-public engagements, and government-implementing partner linkages should be used as

"low-hanging fruit" to realise the quality of surgical services leading to favourable patient outcomes. The challenge ahead is huge but huge challenges create huge opportunities.

Competing interests

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

References

1. (Blog) As Africa's Population Crosses 1.5 Billion, The Demographic Window Is Opening; Getting The Dividend Requires More Time And Stronger Effort. United Nations Economic Commission for Africa. Available at: https://www.uneca.org/stories/%28blog%29-as-africa%E2%80%99s-population-crosses-1.5-billion%2C-the-demographic-window-is-opening-getting. Last accessed: 31 August 2024.
2. World Bank Group. Economic data Africa. Available from: https://data.worldbank.org/country. Last accessed: 31 August 2024.
3. Meara JG, et al. Global Surgery 2030: Evidence and solutions for achieving health, welfare, and economic development. Lancet. 2015;386(9993):569–624.
4. Biccard BM, et al. Perioperative patient outcomes in the African Surgical Outcomes Study: a 7-day prospective observational cohort study. Lancet. 2018;391(10130):1589–1598.
5. Biccard B. Enhanced postoperative surveillance versus standard of care to reduce mortality among adult surgical patients in Africa (ASOS-2): a cluster-randomised controlled trial. ancet Glob Health. 2021;9:e1391-e1401.
6. Wondmeneh TG, et al. The incidence of surgical site infection and its predictors among women delivered via cesarean sections in Ethiopia: a systematic review and meta-analysis. Front Med (Lausanne). 2024;11:1395158.
7. Grimes CE, et al. Cost-effectiveness of surgery in low- and middle-income countries: A systematic review. World J Surg. 2014;38:252–263.
8. Hart JT. The inverse care law. Lancet. 1971;1:405-412.
9. Lancet T. 50 years of the inverse care law. Lancet. 2021;397:767.
10. Munyaneza M, et al. Factors Influencing Seeking and Reaching Care in Patients With Peritonitis in Rwanda. J Surg Res. 2020;246:236–242.
11. Juran S, et al. Geospatial mapping of access to timely essential surgery in sub-Saharan Africa. BMJ Glob Health. 2018;3:e000875.
12. Louw J, et al. Factors Contributing to Delays to Accessing Appendectomy in Low- and Middle-Income Countries: A Scoping Review. World J Surg. 2023;47:3060.
13. Mabewa A, et al. Etiology, treatment outcome and prognostic factors among patients with secondary peritonitis at Bugando Medical Centre, Mwanza, Tanzania. World J Emerg Surg. 2015;10:47.
14. McCord C, et al. General Surgical Emergencies. In: Debas HT, et al., editors. Essential Surgery: Disease Control Priorities, Third Edition (Volume 1). Washington (DC): The International Bank for Reconstruction and Development / The World Bank; 2015. Chapter 4.
15. Haeuser E, et al. Mapping age- and sex-specific HIV prevalence in adults in sub-Saharan Africa, 2000-2018. BMC Med. 2022;20:488.
16. Millar AJW, et al. Surgical implications of HIV infection. Pediatr Surg Int. 2022;39:39.
17. Sun H, et al. IDF Diabetes Atlas: Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. Diabetes Res Clin Pract. 2022;183:109119.
18. Dalal S, et al. Non-communicable diseases in sub-Saharan Africa: what we know now. Int J Epidemiol. 2011;40:885–901.

19. Spencer SA, et al. A health systems approach to critical care delivery in low-resource settings: a narrative review. Intensive Care Med. 2023;49:772.
20. Kapologwe NA, et al. Development and upgrading of public primary healthcare facilities with essential surgical services infrastructure: a strategy towards achieving universal health coverage in Tanzania. BMC Health Serv Res. 2020;20:218.
21. Price R, et al. World Health Assembly Resolution WHA68.15: "Strengthening Emergency and Essential Surgical Care and Anesthesia as a Component of Universal Health Coverage"—Addressing the Public Health Gaps Arising from Lack of Safe, Affordable and Accessible Surgical and Anesthetic Services. World J Surg. 2015;39:2115–2125.
22. Okoroh JS, et al. Strengthening Health Systems of Developing Countries: Inclusion of Surgery in Universal Health Coverage. World J Surg. 2015;39:1867–1874.
23. Sartelli M, et al. It is time to define an organizational model for the prevention and management of infections along the surgical pathway: a worldwide cross-sectional survey. World J Emerg Surg. 2022;17:17.
24. Holmer H, et al. Global distribution of surgeons, anaesthesiologists, and obstetricians. Lancet Glob Health. 2015;3:S9–S11.
25. Imam A, et al. Nurse staffing and patient care outcomes: Protocol for an umbrella review to identify evidence gaps for low and middle-income countries. Wellcome Open Res. 2021;6:363.
26. Speaking of Medicine and Health. Pp. 9-113. Available at: https://speakingofmedicine.plos.org/page/9/. Last accessed: 20 September 2024.
27. Rassin M, et al. Trends in nursing staff allocation: the nurse-to-patient ratio and skill mix issues in Israel. Int Nurs Rev. 2007;54:63–69.
28. Sharma S, et al. Nurse-to-patient ratio and nurse staffing norms for hospitals in India: A critical analysis of national benchmarks. J Family Med Prim Care. 2020;9:2631.
29. Kawooya MG. Training for Rural Radiology and Imaging in Sub-Saharan Africa: Addressing the Mismatch Between Services and Population. J Clin Imaging Sci. 2012;2:37.
30. Omosigho PO, et al. Multiple burden of infectious disease outbreaks: Implications for Africa healthcare system. J Taibah Univ Med Sci. 2023;18:1446.
31. Nkengasong JN, et al. Africa Needs a New Public Health Order to Tackle Infectious Disease Threats. Cell. 2020;183:296.
32. Moyimane MB, et al. Experiences of nurses on the critical shortage of medical equipment at a rural district hospital in South Africa: a qualitative study. Pan Afr Med J. 2017;28:100.
33. Sangeda RZ, et al. National antibiotics utilization trends for human use in Tanzania from 2010 to 2016 inferred from Tanzania medicines and medical devices authority importation data. Antibiotics. 2021;10:1249.
34. Worldwide Antimicrobial Resistance National/International Network Group (WARNING) Collaborators. Ten golden rules for optimal antibiotic use in hospital settings: the WARNING call to action. World J Emerg Surg. 2023;18:50.

Chapter 143

Artificial intelligence in preventing and managing infections in surgery

Andrey Litvin
Gomel State Medical University, University Clinic, Gomel, Belarus.

Introduction

Artificial intelligence (AI) has emerged as one of the essential means in the further development of medicine, notably in surgery, where major functions of ensuring safety for patients and the success rate of operations are performed by prevention and treatment for infection. Given the vast amounts of data available in clinical practice, AI can provide new ways to analyze information and make decisions that will improve treatment outcomes and reduce the risk of postoperative infections.

Among the technologies of modern AI are machine learning (ML) and big data analysis; they help accurately predict infection risks, optimize preoperative preparation, and control compliance with hygiene standards. Implementing such developments not only improves the effectiveness of preventive measures but also speeds up infection identification and treatment, reducing the number of complications and improving patients' quality of life.

The use of AI technologies in surgery opens up new opportunities in the implementation of approaches for personalizing treatment, taking into account the features of each patient and also adjusting methods for infection control and prevention in each surgical practice. AI is fundamentally connected to contemporary surgical procedures, as it is included to improve safety and efficacy in healthcare delivery.

The basic application areas of artificial intelligence are early prediction, timely prevention, early diagnosis, and targeted personalized treatment of surgical infections. Other applications of artificial intelligence, such as successful improvement of surgical procedures, analysis of medical images of surgical infections, and selection of effective antibiotics to treat surgical infections, are also promising.

AI and early prediction of surgical infections

AI has shown great promise in improving the accuracy of predicting surgical site infections by applying ML models to analyze complex data and identify patterns that are not easily detected using traditional methods. In a study of planned abdominal surgery, an AI model with gradient boosting was shown to be very effective. In this model, 19 predictors (including demographics, comorbidities, and laboratory results) were used to predict postoperative infections.

It has been reported that postoperative infections can be predicted using artificial neural networks (ANNs) with promising results. It had an AUROC value equal to 0.905. The model was based on the “clean” class operation, indicative of the potential of neural networks for early infection detection. Besides, in the case of

colorectal surgery operations, ANN indicators outperformed those of other models: the AUROC value was 0.769, which allows key factors to be identified, such as operation time and surgical access. Another neural network model has shown the best performance in spinal surgery—its AUROC value was 0.950 on ML-based algorithms in contrast to surgical site infections (SSI), reflecting a more powerful prediction ability.

Artificial intelligence-based models have been critical in recognizing surgical infection risk. Among such factors are age, body mass index, smoking, and preoperative albumin levels, which were identified as independent predictors of postoperative complications in spine surgery. Another study achieved high accuracy in predicting postoperative complications following several gynecological surgeries by ML models, such as gradient boosting and random forests, with AUROC values equal to 0.991. An AI model for predicting postoperative infection cases after total hip replacement based on MRI findings has also shown good preliminary results.

AI and prevention of surgical infection

AI is rapidly becoming an important tool for preventing surgical infections and opening up new opportunities for improving patient safety. AI systems might be expected to provide personalized recommendations for preoperative preparation, considering the individual characteristics of the patient and the type of upcoming surgery, which may include antibiotic prophylaxis as well as recommendations on skin preparation and others.

AI can monitor compliance with infection prevention protocols in the operating room and ICU: specifically, the proper use of personal protective equipment, instrument sterilization, and aseptic technique. This way, it identifies potential violations and helps prevent them. ML algorithms can analyze postoperative patient data to identify the first signs of infection. This provides timely initiation of treatment and prevents the development of severe complications.

It is noteworthy that AI aids in the selection of optimal antibiotic prophylaxis, taking into account the individual features of the patient, surgery type, and local information about microorganism resistance, which is more efficient in preventive measures for infections and reduces the risk of antibiotic resistance. AI systems can analyze data from cameras and sensors to check how medical personnel comply with hygiene standards in healthcare institutions: handwashing frequency and correctness.

An AI-based epidemiological surveillance system has therefore been proven to be an effective tool for hospital-acquired infection (HAI) surveillance through accurate case identification and increased surveillance efficiency. Besides, AI optimizes the processes of providing medical care, which also contributes to infection control. AI-based training and surveillance programs are developed, which will optimize the use of personal protective equipment and reduce the prevalence of hospital-acquired infections.

AI and the diagnosis of surgical infections

AI has shown a lot of promise in diagnosing surgical infections, with enhanced levels of accuracy and timely detection of surgery infections. In the context of infectious endocarditis, AI and ML models are applied for the purpose of increasing diagnostic accuracy and risk stratification. The diagnostic accuracy was good, and so was the patient's effective outcome in the efficiency of these models compared with traditional manners. For example, some AI models have achieved high sensitivity and specificity in diagnosing prosthetic valve endocarditis and predicting postoperative mortality.

Likewise, AI has been applied to enhance the pathological diagnosis of periprosthetic joint infections. The sensitivity and specificity of diagnostics of the infection around the arthroplasty increase in AI-based models, contributing to more precise and faster treatment decision-making. Artificial intelligence applications include automatic wound infection recognition using computer vision and machine learning algorithms. These systems demonstrate high accuracy compared to classical methods in identifying signs of wound infection and provide reliable diagnostic assistance. Neural networks were trained to recognize patterns in postoperative infections to make accurate forecasting video high-percentage and timely interventions to prevent infection development.

AI and personalized treatment, improving surgical procedures and postoperative monitoring

AI is increasingly integrated into healthcare for better personalized treatment, especially in surgical infections. The role of AI in infection control is to recommend an alternative treatment for multidrug resistance based on genomic profiles, as well as further personalizing treatment to enhance loyalty and patient engagement. It permits the use of algorithms for extremely accurate predictions of surgical tactics, second opinions for doctors from narrow specialists, and standardization of treatment approaches in complex cases. This property is crucial in the treatment of infections that require surgical intervention: it ensures the effectiveness of treatment and adapts the therapy to the specific needs of the patient.

AI is certainly of increasing assistance for the perfection of surgical interventions, creating new prospects for making operations more precise, safe, and efficient. With AI technologies being integrated into robotic surgery, da Vinci, for instance, it results in better accuracy and less damage to the tissue; henceforth, the risk of infections developed after healing decreases. Technologies that allow for hard-to-reach surgery with minimal trauma are also infection-resistant because of the procedure's low error rate and accuracy. AI-controlled surgical robots would be able to quickly analyze large volumes of patient data, including medical images and vital signs, and make recommendations to the surgeon aimed at identifying and reducing the risk of infection during surgery. Such technologies are already vigorously executed in practice, with scientific research taking place all over the world.

AI plays a critical role in preoperative planning. This includes anticipating likely perioperative complications and recommending suitable surgical approaches, thereby reducing the risk of infection. By generating highly detailed 3D models of anatomy, AI enables surgical planning with much detail, hence avoiding likely impending complications that could cause infections. Diminished risk of infection through reduced invasiveness is further attained with AI-enabled increased visualization and surgical navigation that boosts accuracy in conducting surgical interventions. Furthermore, AI participation in surgical coaching through virtual and added reality imitation improves surgeon training and certification, which in some ways, but not directly, leads to a reduction in postsurgical infections due to better general surgical competency.

AI can model surgical outcomes and create detailed 3D models of a patient's anatomy. It helps to accurately plan surgical interventions and may reduce the risk of complications. At present, an AI model has been developed to combine preoperative and intraoperative risk factors with vital signs observed during surgery to predict postoperative infections.

Another potential use of AI is in continuously monitoring the post-surgery patient for any signs of infection development, which can help to timely identify such and quickly take appropriate actions. Nowadays, with the technological boom, digital technologies like smartphone-based monitoring systems are already in place

for the surveillance of surgical wounds after a patient is discharged from the hospital. These systems have achieved a high degree of precision in antibiotic use with reductions in readmission rates and duration of hospital stay, suggesting that value-based service delivery could improve patient treatment outcomes and reduce health care costs.

AI and the optimization of antibiotic use

AI can assist in the optimal selection of antibiotic therapy based on individual patient features and the infectious agent's properties. This, in turn, ensures this treatment will be more effective and less risky in terms of inducing antibiotic resistance. Antibiotic stewardship through the improvement of antibiotic management includes enhancing the accuracy of drug prescriptions and customizing methods of treatment based on specific drug treatment outcomes. This would serve to reduce not only the unnecessary use of antibiotics but also eliminate the risk of resistance that, in turn, would lead to improved outcomes of treatment and reduced health service costs. Furthermore, AI could facilitate the transition from intravenous antibiotic therapy to oral treatment, reducing the associated complications as well as the cost of a prolonged intravenous application. This is crucial today since scientific evidence proves that short courses are as effective as long-term ones.

One of the most important areas of research is the development of new antibiotics for surgical-infection treatment, especially with the increase in resistance to current antibiotics. Identification of new antibiotic candidates is another critical aspect of antibiotic development. This AI uses ML algorithms in searching for new antibacterial compounds. For instance, one of the systems studied 130 thousand chemical compounds and was able to find 25 thousand potential candidates to fight resistant bacteria.

Another molecular image-based platform has been developed that can be used to search through an extensive library of drug-like molecules and identify 340 molecules with antibacterial properties that are unique compared to known antibiotics. This approach accelerates the process of discovery and, at the same time, is a cost-effective solution to the problem related to antibiotic resistance. Besides, AI methods are used to create new substances and identify potential antibiotics, which sharply reduces the preclinical phase of drug development.

Problems and limitations of using AI

AI integration for better predicting surgical infections improves diagnostic accuracy personalizes treatment plans, and ensures effective monitoring systems. However, much as AI is used in this field, it has its problems and limitations that need to be taken into account. From the problems related to data to ethical issues and the necessity for trustworthy validation of AI models.

Quality and accessibility of data

The data provided should be of the highest quality for the efficient performance of AI models. But then many health systems have poorly balanced datasets and a lack of data, which can mislead AI predictions and decrease model accuracy. For instance, a lack of data in training datasets could cause errors, leading to a lack of reliability in AI models for postoperative infection predictions.

Heterogeneity of data

Data about SSIs is frequently heterogeneous, making it difficult to make accurate predictions. The variety of data sources and formats may impede the advance of effective AI models for infection management.

Issues in ethics and confidentiality. The use of AI in healthcare has raised serious concerns about patient data privacy. Often, AI models need to work with information that is classified and private, which later can be a source of misuse or lead to breaches.

Bias and fairness. This is crucial since AI algorithms can perpetrate existing biases present in the data on the outcomes of discrimination. Particularly in surgical institutions, where decisions might lead to disastrous outcomes.

*Model validation and interpretability***.** Most AI models in surgical infection treatment are not externally validated, which is a prerequisite for model trustworthiness and generalization to different clinical settings. Without independent validation studies, it is difficult to have confidence that decisions based on AI will be correct.

Interpretability of AI models. Leading to the situation where many AI algorithms are "black boxes," the understanding and trust of AI recommendations become difficult for clinicians. Improving transparency must be one of the ways to enhance the adoption of AI in clinical workflow, as provided with a lack of idea on how to integrate on your side, noted health workers may be inadequately prepared to surrender after an error made by the AI.

Problems of implementation and integration. Implementing AI tools in surgical facilities demands that workflows and infrastructure be drastically changed to ensure compatibility with AI systems, electronic medical records, and other clinical systems.

Questions of regulation and accountability. The use of AI in surgery results in some new challenges for regulation, especially liability and accountability in case of adverse events. Current standards of care for negligence likely do not appropriately account for the added layer of complexity AI introduces, complicating matters when it comes to assigning liability.

AI poses multiple challenges in surgical infection management, but it also opens up several avenues for improvement. The capacities of surgical infection experts can be improved by AI in terms of early disease detection and provision of more personalized treatment recommendations. These advantages could be fully realized if all constraints were eliminated, aiming the development and implementation of AI systems at the consideration of the ethics, quality of data, and validation with sufficient robustness. The development and evaluation of AI tools with the participation of doctors may serve as a certain connection between technology and clinical practice for AI, not to replace human experience, but to add some of its own to it.

Conclusion

Artificial intelligence is becoming increasingly important in the field of surgery, including the prevention and treatment of surgical infections. When applied, it enhances patient safety in such a way that its pursuit greatly improves outcomes from surgery.

AI-generated patient data analysis can help doctors make earlier and more precise predictions of infection-onset risks, leading to timely preventive actions. At the same time, AI systems adjust antibiotic prophylaxis based on the patient's individual characteristics and information about microorganism resistance. It improves treatment effectiveness and reduces the possibility of antibiotic resistance.

Monitoring compliance with standards and hygiene protocols in operating rooms by AI guarantees the timely detection of violations of these standards, and this will prevent hospital infections. Algorithms can analyze a patient's postoperative condition, allowing them to respond promptly to the first signs of infection and prevent complications. Robotic surgical systems equipped with AI improve surgical precision and minimize tissue trauma, reducing the risk of infection and promoting faster patient recovery.

The use of artificial intelligence in surgical infection prevention and treatment opens up new opportunities for improving the quality of medical care. AI is becoming a powerful tool that complements doctors' clinical experience and contributes to better outcomes in the fight against postoperative infections, enhancing patient health and quality of life.

Competing interests

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

References

1. Hassan AM, et al. Artificial Intelligence and Machine Learning in Prediction of Surgical Complications: Current State, Applications, and Implications. Am Surg. 2023;89:25-30.
2. Tomé F, et al. Using artificial neural networks for pattern recognition of post-surgical infections. Brazilian Journal of Health Review. 2023;6:3329–3339.
3. Scala A, et al. Risk Factors Analysis of Surgical Infection Using Artificial Intelligence: A Single Center Study. Int J Environ Res Public Health. 2022;19:10021.
4. Chen KA, et al. Improved Prediction of Surgical-Site Infection After Colorectal Surgery Using Machine Learning. Dis Colon Rectum. 2023;66:458-466.
5. Zhang Q, et al. Construct validation of machine learning for accurately predicting the risk of postoperative surgical site infection following spine surgery. J Hosp Infect. 2024;146:232-241.
6. Lu K, et al. Machine learning application for prediction of surgical site infection after posterior cervical surgery. Int Wound J. 2024;21:e14607.
7. Albano D, et al. MRI-based artificial intelligence to predict infection following total hip arthroplasty failure. Radiol Med. 2023;128:340-346.
8. Fitzpatrick F, et al. Using Artificial Intelligence in Infection Prevention. Curr Treat Options Infect Dis. 2020;12:135-144.
9. De Corte, et al. Artificial Intelligence in Infection Management in the ICU. Crit Care. 2022;26:79.
10. Wiemken TL, Carrico RM. Assisting the infection preventionist: Use of artificial intelligence for health care-associated infection surveillance. Am J Infect Control. 2024;52:625-629.
11. Huang T, et al. Effectiveness of an artificial intelligence-based training and monitoring system in prevention of nosocomial infections: A pilot study of hospital-based data. Drug Discov Ther. 2023;17:351-356.
12. M Odat R, et al. Pre- and post-surgery: advancements in artificial intelligence and machine learning models for enhancing patient management in infective endocarditis. Int J Surg. 2024 July 24.
13. Ming Ni, et al. Clinically applicable optimized periprosthetic joint infection diagnosis via AI-based pathology. 16 February 2024, PREPRINT (Version 1) available at Research Square.
14. Wu J-M, et al. A Unified Framework for Automatic Detection of Wound Infection with Artificial Intelligence. Applied Sciences. 2020;10:5353.
15. Viktorsson SA, et al. Sepsis in surgical patients: Personalized medicine in the future treatment of sepsis. Surgery. 2024;176:544-546.

16. Moglia A, et al. A systematic review on artificial intelligence in robot-assisted surgery. Int J Surg. 2021;95:106151.
17. Knudsen JE, et al. Clinical applications of artificial intelligence in robotic surgery. J Robot Surg. 2024;18:102.
18. Takeuchi M, Kitagawa Y. Artificial intelligence and surgery. Ann Gastroenterol Surg. 2024;8:4-5.
19. Li P, et al. Prediction of postoperative infection in elderly using deep learning-based analysis: an observational cohort study. Aging Clin Exp Res. 2023;35:639-647.
20. Rochon M. et al. Post-discharge surgical site infection surveillance using patient smartphones: a single-centre experience in cardiac surgery. Br J Cardiac Nurs. 2024;5:1-11.
21. Tiwari W, et al. Optimizing Antibiotic Prescriptions and Infectious Disease Management in Hospitals using Neural Networks. J Advanced Zoology. 2024;44(S5).
22. Jung J, et al. Using antibiotics wisely. Curr Opin Infect Dis. 2023;36:462-472.
23. Swanson K. et al. Generative AI for designing and validating easily synthesizable and structurally novel antibiotics. Nat Mach Intell. 2024;6:338–353.
24. Bess A, et al. Artificial intelligence for the discovery of novel antimicrobial agents for emerging infectious diseases. Drug Discov Today. 2022;27:1099-1107.
25. Popa SL, et al. Deep Learning and Antibiotic Resistance. Antibiotics (Basel). 2022;11:1674.
26. Talat A, et al. Artificial intelligence as a smart approach to develop antimicrobial drug molecules: A paradigm to combat drug-resistant infections. Drug Discov Today. 2023;28:103491.
27. Samareh A, et al. Artificial Intelligence Methods for Surgical Site Infection: Impacts on Detection, Monitoring, and Decision Making. Surg Infect (Larchmt). 2019;20:546-554.
28. Kovoor JG, et al. Artificial intelligence for surgical services in Australia and New Zealand: opportunities, challenges and recommendations. Med J Aust. 2024;220:234-237.
29. Luz CF, et al. Machine learning in infection management using routine electronic health records: tools, techniques, and reporting of future technologies. Clin Microbiol Infect. 2020;26:1291-1299.
30. Scardoni A, et al. Artificial intelligence-based tools to control healthcare associated infections: A systematic review of the literature. J Infect Public Health. 2020;13:1061-1077.

Chapter 144

Ethical considerations for prescribing antibiotics appropriately across the surgical pathway

Alberto R. Ferreres
School of Medical Sciences University of Buenos Aires. Buenos Aires, Argentina;
Department of Surgery, "Dr Carlos A Bocalandro" Hospital, Buenos Aires, Argentina.

Marina Antelo
School of Medical Sciences University of Buenos Aires. Buenos Aires, Argentina;
Department of Surgery, "Dr Carlos A Bocalandro" Hospital, Buenos Aires, Argentina.

Jenifer Tevez
School of Medical Sciences University of Buenos Aires. Buenos Aires, Argentina;
Department of Surgery, "Dr Carlos A Bocalandro" Hospital, Buenos Aires, Argentina.

Introduction

The overuse, over-prescribing, and misuse of antibiotics in the surgical arena and throughout the surgical pathways have undoubtedly collaborated in the dissemination of antimicrobial resistance, which has become a global public health challenge due to its impact on severe infections, complications, longer hospital stay and increased mortality. Antibiotic effectiveness is by its nature a relatively short-lived phenomenon and antibiotic resistance is a natural reaction of bacteria to exposure to antibiotics.
This situation, which encompasses the appropriateness of antibiotic prescription in the surgical pathway on one side and the protection of future patients from the risk of antimicrobial resistance on the other, should be tackled from an ethical imperative approach. There are ethical implications in the appropriate use of antibiotics during the surgical pathway that are worth considering to support its adequacy, avoiding the risk of antimicrobial resistance.

The why

When Sir Alexander Fleming received the Nobel Prize on December 11, 1945, he stated: "The time may come when penicillin can be bought by anyone in the shops. Then there is the danger that the ignorant man may easily underdose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant. Here is a hypothetical illustration. Mr. X has a sore throat. He buys penicillin and gives himself, not enough to kill the streptococci but enough to educate them to resist penicillin. He then infects his wife, Mrs.

X gets pneumonia and is treated with penicillin. As the streptococci are now resistant to penicillin the treatment fails, so Mrs. X dies. Who is primarily responsible for Mrs. X's death? Mr. X whose negligent use of penicillin changed the nature of the microbe. Moral: If you use penicillin, use enough".

The efficient management and clinical governance preclude the sustainability of the healthcare system from an economic and human perspective, and more importantly the safety not only of patients but of the caregivers as well. And Ethics as well as ethical concerns transverses all the aspects of this activity. The surgical pathway includes the preoperative, intraoperative and postoperative phases, and each of these phases may be the stage for the occurrence of surgical errors. In the preoperative phase, errors are related to issues of knowledge and rules; in the intraoperative phase, errors are linked to aspects of skills or abilities, however errors of the preoperative phase may manifest at this particular moment and in the postoperative phase, errors may be related to the levels of rules, skills and/or knowledge.

Antibiotics have made modern surgery possible, but the greater their use, the less effective they become. The question looks straightforward: simply doctors should not prescribe unnecessary antibiotics, and unnecessary antibiotics prescribing should be forbidden since they contribute to a collective cost without generating any individual or societal good. Appropriateness in their prescription and use is the key to their utmost benefit. However, the unseen effects on the microbial environment make the choice of antibiotics and its use an ethically weighty decision, because the more we use antibiotics the more likely we favor the chance to enhance the development of antibiotic-resistant bacteria which will turn difficult or impossible to treat. Recent evidence even suggests that the alteration of children's microbiome by the use of antibiotics is a risk factor for acquiring autoimmune disorders like Crohn's disease and others. Antimicrobial resistance (AMR), on the other hand, is a health threat with potentially devastating global consequences, and the key contributor to it is the overuse of antibiotics in healthcare and in particular, surgical patients: thus, the huge importance of appropriate antibiotic prescription in the surgical care of both acute and elective patients. One major aspect of concern is the appropriateness of antibiotic prophylaxis, since a high proportion of antibiotic prophylaxis is inappropriate, potentially exposing many patients to avoidable and preventable adverse events. The most common reason for inappropriate procedural surgical antibiotic prophylaxis is incorrect timing of antibiotic administration, while a duration greater than 24 hours is the most common reason for inappropriate postprocedural use.

It is estimated that the average human being hosts about forty trillion bacteria, mostly in the gut. These bacteria may be either: commensal, doing mostly no harm; symbiotic, developing a mutualistic relationship with the host and parasites, and pathogens. Antibiotic resistance occurs when a bacterium acquires the ability to resist the deleterious effects of antibiotics. This resistance may originate either from the mutation of a gene, from the lateral transfer of genes or by the acquisition of genes from other bacteria (conjugation) or viruses (transduction). Resistant infections are not only difficult but also expensive to treat. Besides the added mortality of patients with resistant infections is increasing. AMR is one of the top global public health challenges, estimating that AMR was directly responsible for 1.27 million global deaths in 2019 and contributed to 4.95 million deaths. The present AMR situation may be summarized as follows:

- Drug resistance in bacteria: there are increasing and alarming resistance rates among prevalent bacterial pathogens. Reported rates for third-generation cephalosporin-resistant *E. coli* and methicillin-resistant *Staphylococcus aureus* are a major concern, something similar occurs in urinary tract infections caused by *E. coli*. This data makes it harder to effectively treat common infections. *Klebsiella pneumonia* has also shown increased AMR against critical antibiotics.
- Drug resistance in malaria, tuberculosis and HIV: tuberculosis is a major contributor to antimicrobial resistance with strains that do not respond to isoniazid and rifampicin, the two most effective first-line drugs to treat tuberculosis. The appearance of drug resistance is converting into a major threat to malaria

control. Changes in the HIV genome affecting the ability of antiretroviral agents to block the replication of the virus are causing drug resistance in HIV patients.
- Drug resistance in neglected tropical diseases, affects in particular low-income and less developed countries close to the Equator, such as leprosy, trypanosomiasis and leishmaniasis.

The World Health Organization (WHO) has been proactive in increasing awareness about the situation and defining strategies to address this condition. In 2015, WHO launched the Global Action Plan on Antimicrobial Resistance in more than 100 low- and middle-income countries helping the development of national action plans. Another initiative is the WARNING call to action, setting 10 main rules for achieving optimal antibiotic use in hospital settings. The use of antibiotics in everyday surgical practice is an area characterized by personal views, high financial expenditure and lack of audits and controls. In that sense, there are several factors contributing to the variation in antibiotic prescribing, particularly in the surgical pathway. They may be grouped into:

- Physician-related factors: knowledge, clinical guidelines, experience and training, time pressure, interests
- Patient-related factors: expectation pressure of receiving antibiotics, previous experiences of receiving antibiotics, economic status, education and health literacy levels as well as cultural views
- Health system-related factors: the presence and adherence to evidence-based clinical guidelines and protocols for antibiotic use, pressures of the pharmaceutical industry.

It is important to remark that many developing countries allow antibiotics' availability to patients and consumers without the need of a medical prescription. Besides, a huge proportion of antibiotics worldwide go into animal feed and this is an issue not duly recognized and able to produce a huge impact on overall antibiotic resistance. The high rate of cesarean sections and the overuse of antibiotics in mothers and newborns have contributed to the modification of the microbial species that mothers have always passed on to their newborns.

The inappropriate use of antibiotics will compromise the population-level efficacy and generate direct consequences from several points of view: epidemiologic, medical and surgical, financial and not less important, societal. The development of AMR has a significant impact: the re-emergence of tuberculosis, the increase in the development of sepsis due to methicillin-resistant *Staphylococcus aureus*, and respiratory tract infections due to the spread of resistance in *Streptococcus pneumoniae*. These phenomena show that antibiotic prescription is aimed toward the pathogen rather than the patient and there is always a conflict between what is best for the individual and what is best for the ecological environment. The increase in prevalence and the worldwide dissemination of resistance has led to calls for the restriction of antibiotic prescribing.

Ethical framework

The accountability in the use of antibiotics is probably the only measure to slow down the development of antimicrobial resistance. Before tackling the ethics of adequate prescription of antibiotics in the surgical pathway, some considerations about the appropriateness of its use should be performed. When assessing the appropriateness of an intervention (in this case antibiotics), a balance between the probability of doing good and the probability of causing harm should be considered. In other words, the expected health benefits are placed on one side of the scale, and this includes the prevention of infections, the control of sepsis and/or infections, the reduction of its lethal consequences and an overall improved functional activity. On the other

side, the expected negative consequences include morbidity and mortality, disability and time lost from activity.

Some of the facts that need to be included in the equation regarding the concern for future antibiotic resistance are on one side, the expectations of the patient to the maximum and best treatment, the welfare of the present patient and the shared decision-making process between patient and surgeon. And on the other side, the right of future patients to effective treatments as well as the welfare of future though yet unidentified patients. It is important to highlight the fact that both, current and future patients, have rights regarding the protection of their health, and we, as physicians and surgeons, have the professional duty to observe, protect and respect these rights. The availability of antibiotics in modern medicine, and animal agriculture as well, has created a global, inter-generational and collective action problem. The prescription and/or consumption of antibiotics may have a trivial and insignificant impact on each human being and the microbial environment, but all our choices, taken together, undoubtedly affect the welfare of people, both currently and in the future. The benefit of the adequate use of antibiotics is mostly internalized when they are successful and cure an infection, but several times the costs are socialized among society in the form of antibiotic resistance. Patients and farmers overuse antibiotics and physicians and veterinarians often overprescribe them. Given the current situation and technology, the harm is probabilistic and invisible and it is unclear who bears responsibility for spreading any form of resistance. Since purely individual efforts will be of little if no impact, the ultimate moral goal would be how to explain and convince all stakeholders about the structure of the problem and its solution in order to pursue the greater good of the whole society.

So, when restrictions are imposed on antibiotic use, the immediate consequence is represented by difficult choices for physicians, patients and healthcare organizations. So, the two questions to answer are: Who imposes the restrictions? and Which is the adequate and universal ethical framework? Restrictions may be established from a scientific perspective using clinical pathways, guidelines, recommendations and consensus, but other stakeholders - such as provider organizations and third-party payers - may play a major role, with a special emphasis on the financial aspects. Unlike most other therapies, antibiotic prescription is targeted towards the pathogen rather than the patient. This approach may cause a conflict or imbalance between what is best for the patient and what is best for the ecological situation in terms of maintaining antimicrobial efficacy in the face of increasing resistance. It is important to consider antibiotic resistance as an ethical problem since the use of antibiotics may benefit or harm other people. Although each case may have a trivial impact, the clustered effect of all choices may have important consequences for human welfare. Probably the key to the question from a universal ethical perspective is to identify those patients in need of antibiotic therapy and aim to optimize the therapy to achieve the promptest, safest and most effective bacterial eradication and clinical cure, treating based on knowledge and evidence.

The situation encompasses several controversial aspects, some of which are the following:

- Are we performing prophylactic antibiotic therapy in surgical patients appropriately?
- Patients with moderate to severe infections are given less than maximum empirical antibiotic treatment to reduce the rise in resistance.
- The impact of antibiotic restrictions on present and future patients.
- The ethical implications of antibiotic treatment and resistance, or in other words action *versus* no action.
- Who is/are the one/s accountable?

Some examples of the ethical challenges of antibiotic treatment come from everyday surgical practice. Most antibiotic treatments for moderate to severe postoperative bacterial infections are started empirically, without the precise knowledge of the responsible pathogen or its susceptibility, crucial situation in the first 48/72 hours and without a prospective knowledge of the prognosis or future evolution. The practice of the

restrictive use of broad-spectrum antibiotics to slow down the quick rise in antibiotic resistance involves two ethical conflicts: 1) current identified patients at risk are given less than maximum treatment to benefit future, unidentified patients, 2) the present patient is usually not informed of the possible choices and the patient's consent is not requested although the choice of antibiotics might have serious consequences for the patient's health and the chance of survival. A balance between these two conflicting claims should be sought: the expectation of the patient to maximum treatment and shared decisions, and the right of future patients to effective treatment. Probably, a decision on the collective good or the societal best interest through guidelines and decision support systems may be a convenient solution. Which patient has pre-eminence regarding treatment? Is the present patient undergoing an infection or the future unidentified patient? Probably there is less ground to take into account considerations about future resistance or otherwise, making the ratio of the present *versus* the future patient dependent upon the severity of the disease in the present patient. Appeal to the principle of justice, in the conceptualization of John Rawls, may be particularly useful in determining the greater good.

The ethical principles as collated by Beauchamp and Childress, represent a very useful tool to solve conflicts in antibiotic prescription and resistance in everyday surgical practice. Beneficence means literally "to do good and avoid evil", which, of course, turns on the debate about what is good and what is evil. Beneficence stands for acts of mercy and involves the principle of acting with the best interest of the other in mind. Positive beneficence supports an array of moral rules or duties to protect and defend the acts of others and to prevent harm from occurring to others. Non-maleficence is based on the dictum "*Primum non nocere*" ("above all, do not harm") and imposes refraining from actions that would cause harm to others. This obligation includes not only the duty not to inflict harm but also the duty not to impose a risk of harm. On the other hand, negligence represents the lack of due care and a break from the professional standard that determines due care in any given situation. When addressing negligence, the focus is placed on the behavior or misdemeanor that falls below the standard of care that the law or the moral code has established to protect others from the careless imposition of risks. The following are essential elements in the professional model of negligent care: the surgeon's duty to the patient, the breach of duty from the surgeon, the harm suffered by the patient and the causality link between the breach of duty and the harm achieved. The concept of autonomy precludes individual decision-making in health care and research. There are two conditions considered essential for autonomy: liberty, which is the freedom from external controlling influences and agency, which consists of the capacity and capability for intentional actions. The capacity of self-determination of each patient is achieved through the informed consent process and entails competent judgment. Aristotle considered justice as "the rendering to each individual of what is due to him" and refers to the achievement of fairness and equity. More recent influence in biomedical ethics comes from Rawls' proposal, in which he argues that a social arrangement forming a political state is a community effort to advance the good of all in society. The first aim of Rawls' theory is to achieve a well-ordered and well-administered community by the establishment of a fair distributive system of social goods, based on the social contract discourse. The first subject of justice is the basic structure of society and thus the egalitarian concept of justice.

It is also important to consider the different perspectives of all those involved, the so-called 4-P: the patient, the physician, the policy-maker and the payor/s. The patient usually deserves and requests the best treatment and as such our care should be patient-centered, the physician needs to benefit the current individual patient but also consider prospective situations with future patients, and the policy-maker tends to regulate the activity of both pharmaceutical companies and physicians in different fields as well and finally, payors regulate and tend to save the most of financial resources.

Since Ethics and in particular, Surgical Ethics relies on competence and surgical diligence, the best recommendation to comply with adequate ethical standards should be the dictum "Treat based on knowledge". Medical

knowledge _ in the management of antibiotics in everyday surgical practice_ implies evidence-based information and adequate application on patients. It comprises the following skills: an analytical assessment of clinical problem-solving and knowledge acquirement, its application to clinical situations and an ability to disseminate knowledge by teaching others. The Golden Rule is the principle of treating others as one would want to be treated. It is also known as an ethics of reciprocity, meaning that you should reciprocate to your patients how you would like to be treated in a similar situation. The decision of rational antibiotic prescription should be focused on minimizing different risks. In **Table 1** the decision matrix includes the following risks to be assessed or considered under three possible scenarios (optimal treatment, sub-optimal treatment and no-treatment): efficacy (clinical efficiency), adverse events, resistance and cost-effectiveness equation.

Table1. Decision-matrix for prescribing antibiotics based on minimizing risk.

Risk of			**Worst case**
	Optimal treatment	*No treatment*	*Sub-optimal treatment*
Efficacy	No risk	Risk	Risk
Adverse effect	Risk	No risk	Risk
Resistance	Risk	No risk	Risk
Cost-effectiveness		No risk	

This appraisal of antibiotic treatment and its potential consequences - antimicrobial resistance - mimics the teachings of Jeremy Bentham, the founding father of utilitarianism. The goal is to determine whether antibiotic treatment can demonstrate, in some quantitative way, more benefit than harm in comparison to other alternatives. The level of care deemed adequate should reflect a reasoned judgment not only about the impact of the condition on the welfare of the individual but also about the efficacy and costs of care itself about other conditions and the efficacy and costs of care available to them. This rational effort to evaluate the efficacy and the costs, the burdens and the benefits of antibiotic use an effort essential to just and fair allocation encounters a boundary established by the so-called rule of rescue, as proposed by Jonsen. Our moral behavior to the urgent need for antibiotic administration demands the rescue of the doomed, and this rescue ethics capsizes over medical care and thus on antibiotic prescription. And this rule of rescue is indeed a deontological imperative for physicians.

Another ethical approach to the issue is the following: antimicrobial resistance may be hindered by not incentivizing antibiotic use and by requiring certain consumers of antibiotics to internalize the costs of antimicrobial resistance or to compensate for the costs they are contributing to. The application of the tragedy of the commons fits this approach extensively. Antibiotic effectiveness should be considered a common good or a common supply of resources. The Tragedy of the Commons represents an economic and environmental science problem where individuals have access to a shared resource and act in their own interest, at the expense of other individuals. Garrett Hardin described it through the metaphor of the problem of over-grazing of cattle on shared public land (“the commons” in English villages) available to several herdsmen; these goods are defined by the fact that each individual who enjoys them contributes to their detrition as well. This

can result in overconsumption, underinvestment, and depletion of resources. Generally speaking, the Tragedy of the Commons represents the idea that unrestricted access to a finite resource will lead to its overuse and destruction; and the solution is eminently ethical in its nature: individuals should prioritize the long-term collective interest (the greater good) over their short-term individual interest. Thus, unrestricted, uncontrolled and unnecessary use of antibiotics leads to the phenomenon of antimicrobial resistance, which undoubtedly will affect future patients and represents one of the greatest public health topics of our age. So applied to this issue, the three points to consider are reduction of the unnecessary prescriptions, internalization of the costs or the compensation for the costs imposed or to which one contributes. Following Hardin's proposal of some form of "mutually agreed upon coercion", some authors propose the imposition of penalties or fines or taxation to pursue that that individual may have strong reasons for another course of action: refraining from the use of unnecessary antibiotics. In **Figure 1**, the different stages of the management of prescription and administration of antibiotics are characterized by different ethical approaches, where issues of justice, professional ethics and the Tragedy of the Commons theory are useful for improvement in the decision-making process of antibiotic use and the factors surrounding its use.

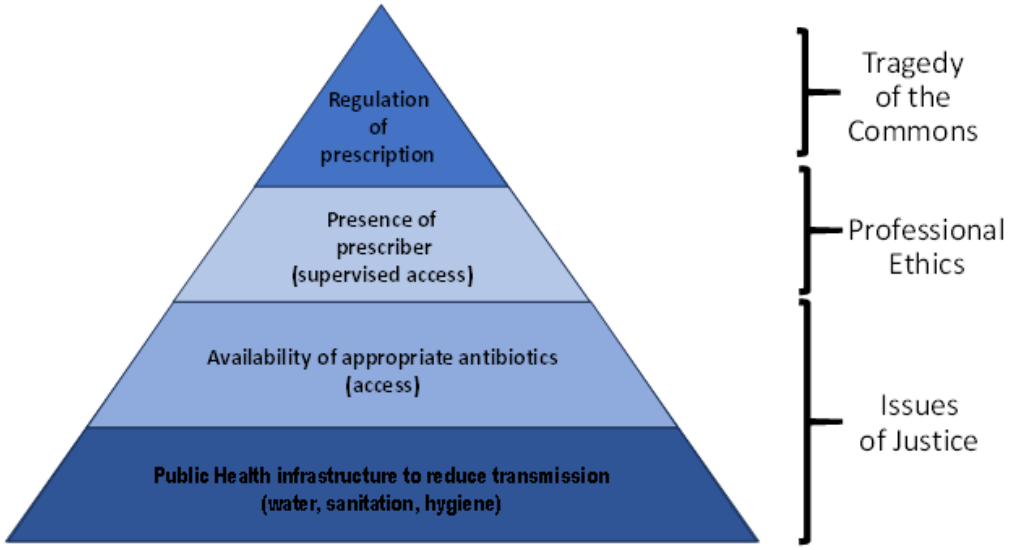

Figure 1. Ethical assessment during the different stages of antibiotic treatment.

The current challenges regarding the adequate and rational prescription of antibiotics and its direct consequences include the following:

- The fair distribution of healthcare resources and the autonomy in treatment features is considered one of the principles of professionalism and the proposed control and audit in antibiotic prescription may be seen as a compromise to this principle.
- On the other side, the commitment to a fair distribution of finite resources and the risk for future patients is considered as the protection of the greater good.
- The accountability in the process of antibiotic prescription is due to its impact and many times to its uselessness.

- A cost-effective approach, trying to pursue the best benefit for the largest number of patients. However, when dealing with a single person, the principle of autonomy may be considered paramount with the right of the individual to make decisions on his or her health, even if these decisions are detrimental. This supremacy is less clear when these decisions affect others, so this freedom should have some limitations, to prevent a compromise of the greater good upon the rest of society and future patients.
- The welfare of future patients is assured by the application of the principles of non-maleficence and justice, and professional associations and healthcare organizations should be active in designing clinical practice guidelines or assembling a detailed support system to aid in antibiotic usage.
- Besides, the government and all the healthcare stakeholders should make public the considerations of antibiotic policies, creating awareness about its benefits when well prescribed and its disadvantages, when inappropriately.

Take-home messages

- Surgery is a moral practice and every surgeon is a moral agent and an advocate for the patient's welfare and the welfare of society. Within this domain falls the prescription and administration of antibiotics across the surgical pathway.
- Surgical Ethics lies at the core of professionalism and the surgeons' conducts are guided by altruism.
- The correct and appropriate prescription and use of antibiotics in the surgical pathways have an ethical imperative and all surgeons should abide by these goals, inherent to the professionalism embedded in the surgical practice.
- The prescription of the right antibiotic/s and the prevention of antimicrobial resistance lies within this domain.
- Surgeons have a collective responsibility to seek the benefit of humanity.
- Aiming for the greater good should be the *leit-motiv* of the surgeon's demeanour.

Competing interests

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

References

1. Fleming A. Penicilin. Nobel Lecture, December 11, 1945 (page 93). Available at: https://www.nobelprize.org/uploads/2018/06/fleming-lecture.pdf. Last accessed: 14 August 2024.
2. Mak JWY, et al. Childhood antibiotics as a risk factor for Crohn's disease: The ENIGMA International Cohort Study. JGH Open. 2022; 6: 369–377.
3. Sandora TJ, et al. National Variability and Appropriateness of Surgical Antibiotic Prophylaxis in US Children's Hospitals. JAMA Pediatr. 2016;170:570-576.
4. Ierano C, et al. Appropriateness of Surgical Antimicrobial Prophylaxis Practices in Australia. JAMA Netw Open. 2019;2:e1915003.
5. Sender R, et al. Revised estimates for the number of human and bacterial cells in the body. PLoS Biol. 2016;14:e1002533.

6. Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. Lancet. 2022;399:629-655.
7. Global antimicrobial resistance and use surveillance system (GLASS) report: 2022. Available at: https://www.who.int/publications/i/item/9789240062702. Last accessed: 18 August 2024.
8. World Health Organization. Antimicrobial resistance. Available at: https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance. Last accessed: 6 August 2024.
9. Worldwide Antimicrobial Resistance National/International Network Group (WARNING) Collaborators. Ten golden rules for optimal antibiotic use in hospital settings: the WARNING call to action. World J Emerg Surg. 2023;18:50.
10. Kasse GE, et al. Factors contributing to the variation in antibiotic prescribing among primary health care physicians: a systematic review. BMC Primary Care. 2024;25:8.
11. Neu J. Rushing J. Cesarean versus vaginal delivery: long-term infant outcomes and the hygiene hypothesis. Clin Perinatol. 2011;38:321-331.
12. Garau J. Impact of antibiotic restrictions: the ethical perspective. Clin Microbiol Infect. 2006;12:16-24.
13. Gerding DN, et al. SHEA conference on antimicrobial resistance. Society for Healthcare Epidemiology of America. Infect Control Hospital Epidemiol. 2000;21:347-351.
14. Park RE, et al. Physician ratings of appropriate indications for six medical and surgical procedures. Am J Public Health. 1986;76:766-772.
15. Liittman J, et al. Antibiotic resistance: an ethical challenge. Int J Antimicrob Agents. 2015;46:359-361.
16. Jamrozik E, et al. Ethics and anbibiotic resistance. Br Med Bull. 2022;141:4-14.
17. Anomaly J. Ethics, antibiotics and public policy. The Georgetown Journal of Law and Public Policy. 2017;15:999-1015. Available at: https://philarchive.org/archive/ANOEAA. Last accessed: 6 August 2024.
18. Leibovici L, et al. Ethical dilemmas in antibiotic treatment. J Antimicrob Chemother. 2012;67:12-16.
19. Rawls J. A theory of justice (revised edition). Harvard University Press. Cambridge MA, 1999.
20. Beauchamp TL. Childress JF. Principles of biomedical ethics. 4th edition. Oxford University Press. New York NY, 1994.
21. Jonsen AR. Bentham in a box: technology assessment and health care allocation. Law Med Health Care. 1986;14:172-174.
22. Giubilini A. Antibiotic resistance as a tragedy of the commons: an ethical argument for a tax on antibiotic use in humans. Bioethics. 2019; 33:776-784.
23. Hardin G. The tragedy of the commons. Science. 1968;162:1243-1248.

Chapter 145

Research on surgical infection in low-resource settings: reality and the way forward

Fikri M. Abu-Zidan
The Research Office, College of Medicine and Health Sciences, United Arab Emirates University, Al Ain, UAE;
World Society of Emergency Surgery, Bologna, Italy.

Mohamud Sheek-Hussein
Institute of Public Health, College of Medicine and Health Sciences, United Arab Emirates University, Al Ain, UAE;
Loma Linda University, School of Public Health, Loma Linda, California, USA.

Introduction

The burden of surgical infections in low-income countries remains poorly defined compared with high-income countries. The need for basic surgical services in low-income countries will continue to rise. Morbidity and mortality of common surgical conditions have grown in the world's poorest countries; 5 billion people do not have access to necessary safe and affordable surgical care. Effective prevention and control of surgical infection is of high importance and priority.

Patients in countries with a low human development index are disproportionately affected by higher rates of surgical infection and antibiotic resistance compared with middle and high-income countries. Despite that, there are limited publications related to surgical infection in developing countries and a lack of high-quality interventional randomised trials aiming at preventing and reducing surgical infection in these low-income countries.

Despite challenges present in low-income countries, good quality scientific research may impact global health. These challenges include weak infrastructure of health care systems, limited resources, ethical considerations, difficulty in recruitment of participants, and sociocultural barriers. Researchers in low-resource countries need a deep understanding of their local circumstances, such as legislation, the composition of their populations, socio-cultural perceptions, and access to research participants, families, and organisations.

It is important to identify the weakness in the research infrastructure in low-resource settings that limit the ability to improve surgical care and address them, hoping to increase opportunities for performing proper research with a high impact on the community. In 2008, the WHO developed a surgical safety checklist to improve patient safety in healthcare settings and operating rooms so as to reduce surgical infection. The checklist outlines essential standards of surgical care applicable in low-resource settings which were designed to be simple, widely applicable, address common surgical procedures, and can be modified and adapted to low-resource settings. This includes recognising the specific bacteriology of developing countries which can help in developing useful guidelines for using antibiotics in the prevention and treatment of surgical infection, aiming at improving surgical outcomes and reducing antimicrobial resistance. The aim of this book chapter is

to highlight the obstacles encountered when performing research on surgical infection in low-resource settings and to suggest solutions to overcome these obstacles hoping to promote international global collaboration in this important area.

The reality

Differences between developed and developing countries

The World Society of Emergency Surgery (WSES) has been running multiple global studies including both developed and developing countries. The Management of Appendicitis Globally Based on Income of Countries (The MAGIC) study is one of them. We have learned many lessons from this study when comparing developed with developing countries. There was great variation in the demographics of patients, disease severity, radiological diagnosis, and surgical procedures depending on the national income. Lower–middle-income countries rarely used CT scan, while high-income countries commonly used laparoscopy instead of open surgery. Intensive Care Units were more used in developed countries compared with developing countries. Despite that, the complication or death rates were not statistically different between these countries.

We have to appreciate that definitions of the research setting have to be well described in the methods section when performing research on infectious diseases because this may affect the clinical outcome. For example, the ICU in Africa can be only a unit used for close observation, non-invasive monitoring and oxygen delivery. This may cost a few dollars daily. There may be also significant variations in the number of ICU beds in the hospitals.

Furthermore, we have noticed in both The MAGIC study and The Physiological parameters for Prognosis in Abdominal Sepsis (PIPAS) study that there was a major imbalance between the number of patients recruited from the studied countries. No patients were enrolled from low-income countries, and much fewer patients participated from lower-middle-income countries compared with higher-income countries. This will have a major impact on the global generalizability of the results as it carries a risk of selection bias and jeopardizes the relevance of the results to low-income countries. This global research imbalance was also noted by others.

Ethical considerations

The basic ethical principles of performing research in developing countries are the same as those all over the world. These include: 1) Do not do harm (nonmaleficence), 2) Do good (beneficence), 3) Respect patient's will (autonomy), and finally 4) Fairness between patients. The imbalance of economic resources and differences in technological development between developing and developed countries usually makes the developed countries in control of the process of performing any combined research projects because they are usually supported by major enterprise companies.

Performing research in developing countries poses numerous ethical questions which are raised by differences in economic, cultural, and socio-political differences. Although volunteers of developing countries who participate in international research projects, may receive optimal health care during the trial "universal standard of care", the improvements obtained in medical care which stemmed from these studies may not be translated into improvements in health care in the developing countries after the trial.

Study participants may not understand the risks of an intervention nor completely have individual autonomy in making their decisions to sign an "informed consent". Access to medical facilities by enrolment into a clinical trial may itself be an incentive. Participants may not have access to the best available treatment for a disease and accordingly may accept a less effective one, or take more risk if there was a financial incentive.

Interventional studies require the approval of a Human Research Ethics Committee, which is a committee at an institution that guards research ethics and protects participants by reviewing the methods proposed for research involving human subjects to ensure that the research projects are ethically following internationally accepted standards. This may put up further barriers, particularly if the research is controversial or sensitive, which presents an additional challenge. It is pivotal that proper ethical research rules be implemented in developing countries under the control of properly established committees that protect participants while at the same time considering the research benefits to the communities. Research Ethics Committees should have the local legal authority, the minimum required number of members, the diversity of the members to represent the community, and the required ethical standards, rules, and processes to perform such an important role.

Academic researchers in University Hospitals in developed countries usually limit their clinical services to their areas of research interest. This will enable them to develop scholarship expertise in a narrow clinical area. The borders between the experts' areas and service provision are not well-demarcated in developing countries. Clinical service and teaching responsibilities will usually have priority over research. This burdens clinical researchers, who have fine clinical skills but are heavily involved in research projects, with a heavy ethical burden. They have an ethical responsibility to their communities, which may have sponsored their education and training overseas, to provide medical service and to improve the quality of life in their settings. They may find it extremely difficult, psychologically and morally, to refuse requests to participate in daily clinical activities which may not be related to their research interest. This may even affect the work environment, and negatively impact their research collaboration with those health care providers of the hospitals. Furthermore, financial support for researchers is very limited in developing countries and researchers may find themselves obliged to do clinical services, or other part-time jobs to support their families.

It is so essential to develop clear policies to define exactly the professional responsibilities of clinical researchers in developing countries and to follow them. What is their primary role? What percentage of their time should be spent in teaching and clinical services? What type of support should be given to them to protect their time and prevent them from being "burned out" in routine medical services? Only those who experience these difficulties in real life will appreciate the stressful professional and ethical conflict of academic researchers being stretched between their own patients' needs and the extensive time needed for their research activities. Sometimes, there are written policies that try to address the above concerns. Nevertheless, they may not be followed in real practice. Written policies will have minor effects if not followed properly.

The way forward

Research training

Training on research methodology to study preventive interventions for surgical infection will improve clinical outcomes. In general, research education and training are suboptimal in low-income countries due to lack of experience and limited budget allocation. This is reflected by the presence of few publications on surgical infection from low-income countries. Therefore, there is a need to design and run research training courses for researchers interested in the prevention and management of surgical infection in low-income countries which are tailored depending on the needs of these researchers taking into account the limited available funding. Developed countries have an ethical obligation to support such efforts. Furthermore, surgical infections and antibiotic resistance in low-income countries may cross borders and impact those in developed countries. Participants should be selected to be of multi-disciplinary nature including surgeons, anesthesiologists, obstetricians and gynecologists, medical doctors, and registered nurses. This is important to build up

bridges closing the gaps between different specialties so as to build up the needed teamwork. This may enhance the transfer of research knowledge into practice in low-income countries. Training should include methods of defining proper relevant research questions covering important research areas like the safety of the surgical environment, control of contamination, and appropriate antibiotics administration that is tailored towards the local setting. Furthermore, there should be stress on ethical and cultural appropriateness when undertaking local research with a high level of research ethics and credibility.

Training researchers in developed countries

Developed countries may participate in training researchers from developing countries in their own institutions for a limited time. Understandably, it is an ethical obligation for those trained to come back to their own countries to promote research in their own setting. Nevertheless, they will swiftly realize the huge difference between the two settings and may decide to continue their own research career in a more comfortable environment if chances rise, or alternatively completely change their career. Obstacles that hinder medical research in developing countries are numerous and challenging which may discourage researchers from coming back to their own countries. These include a lack of support for researchers including research training and grants, difficulties in establishing research labs, and a lack of teamwork. Collaborative projects with research-intense international institutions that include short-term visits and training may support these young researchers, raise their moral, and encourage them to pursue research in their own setting.

Research training in developing countries

Building the infrastructure of biomedical research needs continuous training and education on research methodology and data analysis which should be implemented on both undergraduate and postgraduate levels. Our own experience shows that this is a difficult task because of the lack of expert trainers, lack of interest, and scarce funding to support these educational activities. Despite that, skilled researchers have an ethical obligation to train other researchers, which increases the burden on them. Critical thinking is important for both clinical practice and research. Critical appraisal of the literature became an essential part of clinical practice as clinicians are requested to follow the most relevant updated evidence. Researchers should grasp this chance. Teaching critical appraisal of the literature can be routinely done in hospitals using journal clubs and case presentations which are commonly used educational tools in university hospitals of developing countries.

Formulating a research question

Generating the research question is the most important part of any research project. It is actually defining the aim of the study and what it is going to answer. This will define the road map (protocol) on how to answer the research question including the study design, methodology, whether going in a quantitative or qualitative direction, the needed sample size, manpower, and budget.

Research funding

There is a major discrepancy between developed and developing countries in the budget allocated for research. Ninety per cent of the global health problems are located in low-income countries where less than 10% of the global funds for research are spent. This is clearly demonstrated in **Figure 1** which shows the global maps for Gross National Income (GNI) of year 2018 (A), global science publications of year 2016 (B), and global infectious disease deaths during the years 2001- 2017. There is a clear discrepancy of GNI between the north and south (A) which is much higher in the north. This is highly correlated with science publications (B) where most publications came from the north. In contrast, the infectious disease deaths during the period of 2001-

2017 occurred mainly in the south. The low quantity and weak quality of research in developed countries can be partially attributed to a shortage of funds although other factors including sub-optimal training, and weak research systems are contributing factors. It is our experience that funding can be raised from local communities even in low-resource settings if the importance of the research and its impact on the health of the local population is clearly understood by the community. Furthermore, there are specific research designs that require low budgets like case series, retrospective studies, and secondary and tertiary data including death certificates and medical registries.

As a response to the pronounced disproportionate scarce resources in low-income countries compared with the tremendous disease burden, one of the most important challenges is to set up priorities for medical research. This will maximize the impact of investments, which is very relevant to countries with limited resources. Nasser and Crowe developed a Research Priority Setting for research groups. This was designed and implemented in specific contexts, settings, and populations using defined principles, values and preferences.

Research collaboration

Local research in low- and middle-income countries is important for overcoming global health problems. Yet, remains insufficient and fragmented. Clinical quality outcomes are linked to the research methods used and their most recent results. Collaborative research is essential for achieving an optimal healthcare outcome. This includes establishing local, regional and international research networks for collaboration among all healthcare professionals having shared knowledge. This will lead to the dissemination of the best research practices on surgical infection in developing countries, will enable shared learning and development of new research opportunities, and will be very useful and supportive for low-resource countries.

The WSES has been performing global studies, inviting all its members to participate, which encourages those from low- and middle-income countries to be part of them. Recognising the limited success of these efforts, the society has recently established “The Developing Country Surgery Group” in an attempt to overcome obstacles preventing members of the Society from low- and middle-income countries to be part of these global efforts.

Lack of research interest in the majority of practicing physicians in developing countries makes it more difficult for academic researchers to perform prospective clinical trials. Even if they become part of external studies run by developed countries, research questions are usually defined by those who fund the studies, and most probably would serve the funding agent agenda. Researchers in developing countries, should thrive to solve their own local problems by devotion to their cause and collaborating with each other.

Publications

Medical research is completed only when the results become public as a scientific publication following proper peer review. We have repeatedly encountered difficulties in publishing our own research findings in prestigious journals because these findings have been considered to be more of local than global interest. Nevertheless, we have learned over time that the real value of research depends on its impact on the community by changing medical practice towards improving healthcare. Accordingly, we have now no hesitancy to publish our findings in properly peer-reviewed regional journals when needed. This will also improve the scientific standard of these journals. Open-access journals, which are an excellent tool to quickly disseminate medical knowledge in developing countries, can be sometimes expensive. Some journals may take this into consideration and exempt the authors from developing countries from the publication’s fees which cannot be covered by their institutions. We think that the discrepancy of income between countries will not only affect running research projects but also their publication.

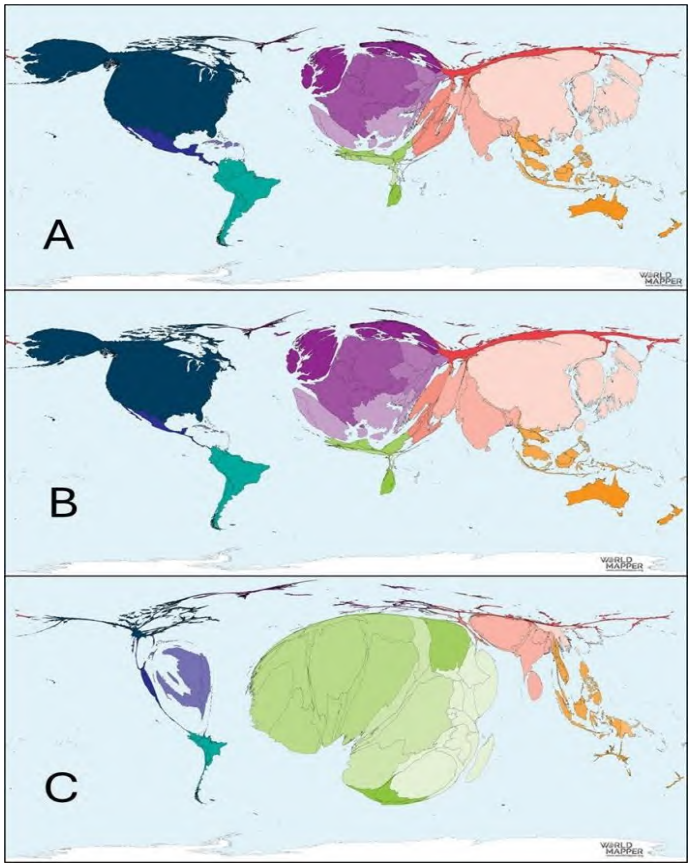

Figure 1. Global maps of Gross National Income (GNI), Year 2018 (A), global science publications, Year 2016 (B), and global infectious disease deaths (Years 2001- 2017). Note the discrepancy of GNI between the north and south (A) which is correlated to science publications (B). Most publications came from the north. In contrast, observe that the infectious disease deaths during the period 2001-2017 (C) occurred mainly in the south (Adapted from World Mapper (https://worldmapper.org/maps/).

The need to improve health research systems

Medical research is important to improve public health which in turn improves both the social and economic status of a community. This should be well understood both by researchers and their societies. Developing countries should have their own policies and models to achieve this goal and part of their health care system, and not simply follow those of developed countries. These policies should stem from a deep understanding of their own problems and how to solve them.

Community support

Community understanding, appreciation and support for change in common medical practices are important for the implementation of research findings related to surgical infections. Community engagement in research is defined as “a process of inclusive participation that supports mutual respect of values, strategies, and actions for authentic partnership." This will overcome mistrust in research, inadequate enrollment, and poor uptake of findings. This was evident during the COVID-19 Pandemic when members of the community adopted the conspiracy theory and used media to antagonise vaccination against the virus. Researchers should demonstrate ethical integrity, transparency, proper communication, and respect for their communities in practical ways so as to gain their trust.

One Health, One World approach

The One Health, One World approach is an integrative, systemic approach that promotes and emphasizes inter- and multi-sectorial understanding by fostering the exchange of research results at a global level. This stems from the understanding that humans and animals live in the same world and each affects the other. This was very evident during the COVID-19 and monkeypox Pandemics when animal infections affected humans causing a pandemics disaster. Similarly, antibiotic resistance in birds can affect those in humans. The One Health, One World approach aims to link a variety of researchers in different specialties. This multidisciplinary strategy is essential to perform high-quality useful research. In 2024, The United Nations formed The One Health High-Level Expert Panel to support and improve cooperation among governments to address global health challenges including obstacles, governance, and funding.

Conclusion

Low-income countries are disproportionately affected by higher rates of surgical infection and antibiotic resistance compared with middle and high-income countries. Despite that, there are limited publications related to surgical infection stemming from these countries. This is attributed to multiple barriers including weak infrastructure of health care systems, limited resources, ethical considerations, the difficulty of recruitment of participants, and sociocultural barriers. The real strength of research on surgical infection in low-income countries stems from the ability to find possible solutions for the numerous local surgical infectious problems. To achieve that goal there is a need to improve the health research systems, promote research collaboration, encourage research training, define research priorities, get the support of local communities, target high ethical standards when performing research, and adopt the One Health, One World approach. Researchers in developing countries should establish their own policies and models that are tailored to fit their circumstances and needs, and not simply copy those of other countries.

Competing interests

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

References

1. Rickard J, et al. Surgical Infections in Low- and Middle-Income Countries: A Global Assessment of the Burden and Management Needs. Surg Infect (Larchmt). 2020; 21:478-494.
2. Meara JG, et al. Global Surgery 2030: evidence and solutions for achieving health, welfare, and economic development. Lancet. 2015;386:569-624.
3. GlobalSurg Collaborative. Surgical site infection after gastrointestinal surgery in high-income, middle-income, and low-income countries: a prospective, international, multicentre cohort study. Lancet Infect Dis. 2018;18:516-525.
4. Aw TC, et al. Challenges and strategies for quantitative and qualitative field research in the United Arab Emirates. Asian Pac J Cancer Prev. 2011; 12:1641-5.

5. World Health Organization & WHO Patient Safety. (2008). The second global patient safety challenge: safe surgery saves lives. World Health Organization. Available at: https://iris.who.int/handle/10665/70080. Last accessed: 26 August 2024.
6. Ombelet S, et al. Clinical bacteriology in low-resource settings: today's solutions. Lancet Infect Dis. 2018;18:e248-e258.
7. Gomes CA, et al. Management of Appendicitis Globally Based on Income of Countries (MAGIC) Study. World J Surg. 2018;42:3903-3910.
8. Baker T. Critical care in low-income countries. Trop Med Int Health. 2009;14:143-148.
9. Marshall JC, et al. What is an intensive care unit? A report of the task force of the World Federation of Societies of Intensive and Critical Care Medicine. J Crit Care. 2017;37:270-276.
10. Adhikari NK, et al. Critical care and the global burden of critical illness in adults. Lancet. 2010;376:1339-1346.
11. Sartelli M, et al. Physiological parameters for Prognosis in Abdominal Sepsis (PIPAS) Study: a WSES observational study. World J Emerg Surg. 2019;14:34.
12. GlobalSurg Collaborative. Laparoscopy in management of appendicitis in high-, middle-, and low-income countries: a multicenter, prospective, cohort study. Surg Endosc. 2018;32:3450-3466.
13. Belsky L, et al. Medical researchers' ancillary clinical care responsibilities. BMJ. 2004;328:1494-1496.
14. Kent DM, et al. Clinical trials in sub-Saharan Africa and established standards of care: a systematic review of HIV, tuberculosis, and malaria trials. JAMA. 2004;292:237-242.
15. U.S. Department of Health and Human Services. Serve On Boards To Review And Monitor Clinical Trials. Available at: https://toolkit.ncats.nih.gov/module/clinical-trials-and-fda-review/serving-on-boards-to-review-and-monitor-clinical-trials/institutional-review-board/ Last accessed: 24 July 2024.
16. Rahman MM, et al. Biomedical research in developing countries: Opportunities, methods, and challenges. Indian J Gastroenterol. 2020;39:292-302.
17. Ayub Khan MN, et al. Task-based training to prevent surgical site infection: A formative evaluation. Infect Prev Pract. 2022;4:100235.
18. Amerson RM, et al. Addressing the Challenges of Conducting Research in Developing Countries. J Nurs Scholarsh. 2015;47:584-591.
19. Bhutta ZA. Ethics in international health research: a perspective from the developing world. Bull World Health Organ. 2002;80:114-120.
20. Selman M, et al. Problems encountered in high-level research in developing countries. Chest. 1998;114:610-613.
21. Edejer TT. North-South research partnerships: the ethics of carrying out research in developing countries. BMJ. 1999;319:438-441.
22. Abu-Zidan FM, et al. Research in developing countries: problems and solutions. Int Urogynecol J Pelvic Floor Dysfunct. 2005;16:174-175.
23. Global Forum for Health Research. The10/90 Report on Health Research 2003-2004. Global Forum for Health Research, Geneva 2004. Available at: https://www.files.ethz.ch/isn/17141/1090.04.pdf. Last accessed: 28 July 2024.
24. Lansang MA, et al. Building capacity in health research in the developing world. Bull World Health Organ. 2004;82:764-770.
25. Anonymous. Priority setting for health research: lessons from developing countries. The Working Group on Priority Setting. Health Policy Plan. 2000;15:130-136.
26. Nasser M, et al. An introduction to research priority setting (RPS) for research groups in the Cochrane collaboration. Cochrane Methods. Available at: https://methods.cochrane.org/prioritysetting/sites/methods.cochrane.org.prioritysetting/files/uploads/Introduction%20to%20Research%20Priority%20Setting.docx. Last accessed: 20 August 2024.
27. Franzen SR, et al. Health research capacity development in low and middle income countries: reality or rhetoric? A systematic meta-narrative review of the qualitative literature. BMJ Open. 2017;7:e012332.
28. Sartelli M, et al. A proposal for a comprehensive approach to infections across the surgical pathway. World J Emerg Surg. 2020;15:13.

29. World Health Organization. (2010). Framework for action on interprofessional education and collaborative practice. World Health Organization. Available at: https://iris.who.int/handle/10665/70185. Last accessed 15 August 2024.
30. Abu-Zidan F. Quantity and quality of research from the Gulf Corporation Council countries. Saudi Med J. 2001;22:1040-1041.
31. Goldemberg J. What is the role of science in developing countries? Science 1998; 279: 1140-1141
32. Holzer JK, Ellis L, Merritt MW. Why we need community engagement in medical research. J Investig Med. 2014;62:851-855.
33. Mettenleiter TC, et al. The One Health High-Level Expert Panel (OHHLEP). One Health Outlook. 2023;5:18.

Chapter 146

A global strategy for surgical infections

Jennifer Rickard
Department of Surgery, University of Minnesota, Minneapolis, MN, USA.

Introduction

Infections in surgical patients constitute a significant challenge encompassing such diverse conditions as intraabdominal infections, skin and soft tissue infections, and surgical site infections. The causes and contributing factors for surgical infections are diverse; therefore, the solutions need to be similarly cross-cutting and varied. As surgical infections represent a global problem, strategies to address them should be on a global level. When addressing the term global, this is not meant to merely denote to a physical reference. Rather, a global approach to the management of surgical infections is meant to address issues which are universally present, surpassing any national or international boundaries. This global strategy should utilize tactics which take into account a population-based approach to the management of surgical infections which is both interdisciplinary and cross-sectoral. Components of a global strategy for surgical infections will need to focus on the burden of disease, interventions to address this burden, goals and targets, and an implementation plan. Through such an approach, we envision a reduction in surgical infections as well as improved outcomes for those who encounter these conditions.

Definition

Surgical infections include any infection in a surgical patient. This includes any infectious process requiring surgical intervention or any infection that occurs as a result of a surgical intervention. Cornerstones of management for surgical infections include source control (through surgical, interventional, or endoscopic means) and antimicrobial therapy. Common examples of surgical infections include intraabdominal infections, skin and soft tissue infections, and healthcare-associated infections. Surgical infections are most commonly due to bacterial pathogens, but can also be due to fungal or other pathogens. However, the definition of surgical infection is not well articulated, leading to discrepancies in collecting and reporting data.

Some disease processes, once considered infectious in nature, are now considered more inflammatory in nature. Some disease processes are multifactorial in nature, with infectious pathogens only accounting for a portion of the disease. Cholecystitis, appendicitis and diverticulitis have traditionally been thought to be an infectious process. However, there has also been debate about whether these processes are infectious *versus* inflammatory in nature. Peptic ulcer disease has multiple factors which contribute to the disease process. Peptic ulcer disease may be due to *Helicobacter pylori*, but non-steroidal anti-inflammatory medications use may also cause peptic ulcer disease. To date, they remain under the domain of surgical infections given that their treatment involves both source control and antibiotics. As knowledge of disease processes evolves, our understanding and qualification of surgical infections will evolve as well.

Similarly, the timeframe can complicate the definition of surgical infections. For example, intestinal obstruction is not normally considered a surgical infection given that the disease is due to a mechanical process. However, delays in presentation can result in patients presenting with gangrenous and perforated bowel, which then fits within the definition of surgical infection as these patients require both source control and antibiotics for management. In addition, the trauma patient, the diabetic foot, or the vascular patient can all present with wounds. In each of these instances, with timely presentation and management, these conditions would not be considered infections. However, in situations where there is delayed presentation or management, each of these conditions could present as a surgical infection.

An accurate definition of surgical infection is important. Much like challenges faced with defining the field of global health, surgical infections face similar challenges. Surgical infections are not a discrete disease entity and do not target a specific demographic. Surgical infections address a diverse set of cross-cutting health problems within the healthcare system. A clear and accurate definition of surgical infections allows for better organization and communication. It also helps delineate critical stakeholders.

A definition allows for a common language. First and foremost, a clear, concise, consistent definition of surgical infection is essential for research purposes. With a clear definition of surgical infection, we can capture data on the incidence and outcomes of surgical infections. The information can then be used to determine the burden of disease, outcomes, economic impact, and morbidity and mortality associated with surgical infections. We can further estimate the burden of disease that is potentially preventable through scaling up surgical care.

It is also critical for advocacy efforts and championing funding priorities for hospitals, governments, and the international community. A well-delineated definition of surgical infections is imperative to communicate goals, marshal resources, and define priorities. Failure to accurately and adequately define surgical infections leads to fractured groups and competing priorities, compromising the surgical community's ability to tackle this disorder.

Burden of disease

Once the definition of surgical infection is clearly stated, our next step should focus on estimating of the global burden of surgical infections. This should include the epidemiology of the disease as well as the outcomes associated with the disorder.

To date, there is no study providing an overall quantification of the global burden of surgical infections. The African Surgical Outcomes Study found that 13% of operations were performed for acute infectious conditions. Other studies have attempted to break down an estimate of individual disease processes. Most of the reporting on the global burden of disease looks at defined diagnosis categories and does not discriminate on which patients require surgery or not. In 2017 there were 19 million people with appendicitis, 30.6 million people with biliary disease and 17.2 million with peptic ulcer disease. In 2000, there were an estimated 21 million cases of typhoid fever, but only a percentage of these progressed to typhoid intestinal perforation. While these numbers give a good estimate of the burden of disease, they do not capture how many individuals needed (or had) surgery.

Surgical site infections are the most common healthcare-associated infection globally. In an international, prospective, multicenter cohort study of patients undergoing gastrointestinal surgery, 12.3% of patients have a surgical site infection within 30 days of surgery. Rates of surgical site infections have been found to be highest after dirty/infected surgery and in low-human development index countries.

Overall, the global burden of surgical infections is large, but precise numbers are lacking due to inconsistencies in definitions and challenges with data capture. An estimate of the burden of disease is valuable as a baseline metric for tracking changes and the effectiveness of interventions. Furthermore, it can be used in advocacy efforts to alert stakeholders to the extent of the problem.

Prevention

Many surgical infections can be effectively addressed through prevention efforts. Hand hygiene is a simple yet effective means of reducing infections. Typhoid fever is mitigated through safe water and sanitation practices. *H. pylori* infection and peptic ulcer disease can be prevented through *H. pylori* eradication programs. Early surgical intervention for intestinal obstruction and open fractures can prevent complicated intraabdominal infections and skin and soft tissue infections resulting from delays in management. By introducing safe and timely surgical care, we can prevent or reduce the burden of surgical infections.

There is strong evidence to show that surgical site infections can be reduced through prevention efforts. Prevention of surgical site infections through surgical antibiotic prophylaxis occurs through a bundle of interventions focused on administering the appropriate antibiotic at the appropriate dose and time. A multicenter, randomized cluster trial found that routine changing of gloves and instruments prior to wound closure compared with a control group resulted in a 13% reduced rate of surgical site infections at 30 days after abdominal surgery.

Infection prevention and control is an evidence-based approach to prevent infections. National surgical site infection screening programs have been shown to decrease surgical site infections and these programs are often housed within national IPC programs. However, there are few national surgical site infection screening programs in low- and middle-income countries. Effective surgical site infection surveillance programs require high-quality data which can be used to emphasize the priority and economic impact of surgical site infections. Focused efforts to introduce and strengthen IPC and surgical site infection surveillance can help prevent infections globally.

Source control

Source control refers to interventions used to control the source of infection. This is commonly accomplished through surgical or procedural (interventional or endoscopic) means. However, techniques for source control vary depending on the locale and resources available.

Surgical care as an essential component of the healthcare system has been neglected in many parts of the world and therefore the resources for performing surgery may be underdeveloped or non-existent. The Lancet Commission on Global Surgery found that approximately 5 billion people do not have access to safe, affordable surgical and anesthesia care when needed and an additional 143 million surgical procedures are needed each year to save lives and prevent disability. Investing in surgical services in low- and middle-income countries is affordable, saves lives, and promotes economic growth. Universal health coverage and sustainable development goals will be impossible to achieve without ensuring that surgical and anesthesia care is available, accessible, safe, timely, and affordable. Previously, surgical care was considered too complex and too costly for low-resource settings. However, this notion has been challenged. In recent years, there has been increased focus and attention on scaling up and supporting surgical care globally.

Access to surgical care differs widely around the globe. Effective source control requires far more than an operating room. Rather, it requires a functioning surgical ecosystem with a multidisciplinary team of surgeons, anesthesiologists, pharmacists, nursing staff, biomedical engineers, cleaning staff, and more. This also includes an efficient operating theater, a trained healthcare workforce, a materials and supply chain to ensure reliable supplies, and biomedical engineering to ensure infrastructure maintenance. Investment in health system strengthening and building surgical capacity is essential to address surgical infections on a global scale.

Beyond the operating room, a wide range of techniques for source control have been developed and are increasingly used. This can include minimally invasive (laparoscopic or robotic) surgery, interventional radiology, or endoscopy. However, these less invasive options tend to be more accessible in high-resource settings. Less invasive interventions result in faster healing times and fewer complications and are usually cost-effective. Unfortunately, these resources are not always available in all settings. When we develop guidelines or best practices for the management of surgical infections, we need to take into consideration the range of resources available for source control.

Few guidelines address optimal surgical or interventional means of source control and most guidelines are developed in high-resource settings. There are inherent challenges in designing studies on surgical techniques (ex: control populations, standard of care, blinding, etc.) and these studies are often costly and difficult to implement. However, efforts are underway to address this limitation in the current medical literature. For example, a pragmatic, multicenter, randomized controlled trial found that there was no benefit of 2% alcoholic chlorhexidine compared with povidone-iodine or with triclosan-coated sutures compared with non-coated sutures in the prevention of surgical site infections in clean-contaminated, contaminated, or dirty surgical wounds. Guidelines should include data-driven, evidence-based medicine with global, multi-institutional studies. Whenever possible, guidelines should integrate stratification or options based on resource availability. Cost-benefit data can help to develop tools which allow prioritization of responses, particularly in contexts where resources are limited. Where guidelines are based on expert opinion, this should include global experts from a wide range of regions and settings to get the best representation.

Antimicrobial therapy

Antimicrobial therapy plays an important role in the management of surgical infections, but this requires more than simply the availability of antibiotics. Management of surgical infections requires available and accessible antibiotics, laboratory resources to determine common pathogens and resistance patterns, and multidisciplinary support for infection prevention and control and antibiotic stewardship programs.

Many infections will initially be treated with empiric antibiotics. This entails an understanding of common pathogens, local antibiotic resistance patterns, and the available antibiotics. Access and availability of antibiotics vary widely around the globe. Many low-resource settings have a limited number of antibiotics, but these antibiotics can often be purchased over the counter through local pharmacies. This aids in improved access to antibiotics with the downside of overuse and/or misuse of antibiotics. Regulations on the control of antibiotics vary between countries.

Tailoring of antibiotics is dependent on routine culture and sensitivity testing. Unfortunately, many low-resource settings do not have the resources or capacity for surveillance cultures. The data which is currently available is primarily from referral hospitals with little data from smaller health centers, which skews the data. One option is the sharing of data, with locoregional patterns of antimicrobial resistance used to guide antibiotic choice.

One of the biggest challenges facing the management of infections is the growing threat of antimicrobial resistance with fewer antimicrobial agents to treat these infections. Pathogens know no borders. Therefore, a resistant pathogen in one country is a threat or risk to individuals in any and all countries. In an international, prospective, multicenter cohort study of patients undergoing gastrointestinal surgery, 21.6% of patients with microbiology results had a surgical site infection that was resistant to the prophylactic antibiotic used. In a single-institution study from Rwanda, 59% of isolates had resistance to a third-generation cephalosporin and 53% of isolates were extended-spectrum beta-lactamase-producing pathogens. Overuse of antibiotics, easy accessibility of antibiotics, livestock treatment, and other factors have all contributed to the rise of multi-drug-resistant pathogens. Antimicrobial resistance has widespread consequences including an impact on economics, human development, health equity, security and food production.

Antimicrobial stewardship programs are one method to optimize antibiotic use. These programs provide locally relevant guidelines on antibiotic use, limiting misuse of antibiotics while ensuring good patient care. Traditional models of antibiotic stewardship have been developed based on models developed in high-resource settings, which may be challenging to implement in low-resource settings. Novel techniques should be trialed to support antimicrobial stewardship in low-resource settings in a manner which is feasible and effective.

Global strategies

As surgical infections are a global disease, strategies to address them should be on a global level. This can be at the international, national, facility, or community level with coordination across partners including government, private sector, and civil service. To implement and achieve a global strategy, there must be advocacy and support at all levels. Surgical care is cross-cutting and does not fit into one nice disease or demographic category. This can make it more challenging to align with sustainable development goals, funding priorities, and other interests. Currently, surgical care and infections are seen as two separate entities. While we can benefit from the support from both advocacy groups, we need to ensure that surgical infections are covered under both agendas. Defining the scope of the problem is critical to advance a global agenda.

To date, the World Health Organization, through the World Health Assembly, has supported several measures relevant to surgical infections. These include resolutions on antimicrobial resistance, infection prevention and control, and emergency and essential surgical care as a component of universal health coverage. The World Health Assembly resolutions give the World Health Organization a mandate to develop action plans. These resolutions and resultant action plans have a significant impact on donor funding decisions.

Several countries have developed National Surgical Anesthetic, and Obstetric Plans (NSOAPs) which provide an outline and strategy for building surgical capacity. Surgical infections should be specifically addressed and targeted in these NSOAPs by ensuring that infection prevention and control programs and surgical site infection surveillance systems are integrated into these plans. As the quantity of surgical care increases globally, it is essential to ensure that the quality of care is maintained or increased through monitoring of surgical site infections.

As antimicrobial resistance is due to a multitude of factors, solutions must also be addressed at multiple levels. In 2015, the World Health Assembly adopted the global action plan on antimicrobial resistance which lays out five strategic objectives --- improve awareness and understanding of antimicrobial resistance; strengthen knowledge through surveillance and research; reduce the incidence of infection; optimize the use of antimicrobial agents; and develop the economic case for sustainable investment. In response to this,

multiple regions and countries have developed national action plans for antimicrobial resistance. These action plans for antimicrobial resistance factors in the management and prevention of surgical infections.
Financial challenges remain a barrier to the implementation of these plans. NSOAPs have been challenged with the funding necessary for implementation. Similarly, while many countries have developed national action plans for antimicrobial resistance, many of these have been hamstrung by the lack of financial resources to implement such programs. As funding is one of the main limitations of successful implementation of any advocacy or action plan, it is critical that data is obtained to support the economic argument for surgical infection prevention and management. The basis of this economic argument will rely on collecting accurate and reliable data on the burden of surgical infections and their associated outcomes.

Conclusion

In conclusion, surgical infections are of global concern and can be addressed in a coordinated effort, building on current efforts to strengthen surgical care globally as well as ongoing efforts to approach and mitigate antimicrobial resistance. These efforts need to recognize the global nature of the disease, addressing solutions at the population level and recognizing the multidisciplinary nature of the disease. A clear definition for surgical infections and easy-to-use data platforms are needed to track infections and antibiotic resistance patterns. These tools can be used to optimize data capture, quantify disease burden, and characterize the global impact of surgical infections. Guidelines and recommendations that are developed need to be universally applicable and ideally triaged based on resource availability and costs. Through these measures, we can better reduce the burden of disease caused by surgical infections and improve patient outcomes.

Competing interests

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

References

1. Dare AJ, et al. Global surgery: defining an emerging global health field. Lancet. 2014;384:2245-2247.
2. Rickard J, et al. Surgical Infections in Low- and Middle-Income Countries: A Global Assessment of the Burden and Management Needs. Surg Infect (Larchmt). 2020;21:478-494.
3. Barie PS, et al. Infection or Inflammation: Are Uncomplicated Acute Appendicitis, Acute Cholecystitis, and Acute Diverticulitis Infectious Diseases? Surg Infect (Larchmt). 2023;24:99-111.
4. Biccard BM, et al. Perioperative patient outcomes in the African Surgical Outcomes Study: a 7-day prospective observational cohort study. Lancet. 2018;391:1589-1598.
5. Collaborative G. Surgical site infection after gastrointestinal surgery in high-income, middle-income, and low-income countries: a prospective, international, multicentre cohort study. Lancet Infect Dis. 2018;18:516-525.
6. Mvukiyehe JP, et al. Improving hand hygiene measures in low-resourced intensive care units: experience at the Kigali University Teaching Hospital in Rwanda. Int J Infect Control. 2021;17:20585.
7. Sartelli M, et al. Six Long-Standing Questions about Antibiotic Prophylaxis in Surgery. Antibiotics (Basel). 2023;12:908.

8. Sartelli M, et al. Surgical Antibiotic Prophylaxis: A Proposal for a Global Evidence-Based Bundle. Antibiotics (Basel). 2024;13:100.
9. Surgery NGRHUoG. Routine sterile glove and instrument change at the time of abdominal wound closure to prevent surgical site infection (ChEETAh): a pragmatic, cluster-randomised trial in seven low-income and middle-income countries. Lancet. 2022;400:1767-1776.
10. Forrester JD, et al. Survey of National Surgical Site Infection Surveillance Programs in Low- and Middle-Income Countries. Surg Infect (Larchmt). 2020;21:621-625.
11. Mehtar S, et al. Implementation of surgical site infection surveillance in low- and middle-income countries: A position statement for the International Society for Infectious Diseases. Int J Infect Dis. 2020;100:123-131.
12. Forrester JD, et al. Components of Existing National Surgical Site Infection Surveillance Programs Based on a Case Series of Low- and Middle-Income Countries: Building Blocks for Success and Opportunities for Improvement. Surg Infect (Larchmt). 2023;24:112-118.
13. Meara JG, et al. The Lancet Commission on Global Surgery Global surgery 2030: Evidence and solutions for achieving health, welfare and economic development. Surgery. 2015;157:834-835.
14. Surgery NGRHUoG. Reducing surgical site infections in low-income and middle-income countries (FALCON): a pragmatic, multicentre, stratified, randomised controlled trial. Lancet. 2021;398:1687-1699.
15. Muvunyi V, et al. Community- and Hospital-Acquired Infections in Surgical patients at a Tertiary Referral Hospital in Rwanda. World J Surg. 2020;44:3290-3298.
16. Sutherland T, et al. Widespread antimicrobial resistance among bacterial infections in a Rwandan referral hospital. PLoS One. 2019;14:e0221121.
17. Rickard J. Bacterial Resistance in Surgical Infections in Low-Resource Settings. Surg Infect (Larchmt). 2020;21:509-515.
18. Cohn J, et al. Accelerating antibiotic access and stewardship: a new model to safeguard public health. Lancet Infect Dis. 2024;24:e584-e90.
19. WHA. Strengthening emergency and essential surgical care and anaesthesia as a component of universal health coverage. World Health Assembly; 2015. Contract No.: WHA68.15.
20. WHA. Global action plan on antimicrobial resistance. World Health Assembly; 2015. Contract No.: WHA68.7.
21. WHA. Global Strategy on Infection Prevention and Control. World Health Assembly; 2022. Contract No.: A75/A/CONF./5