Chapter

Management of *E. coli* Sepsis

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Abstract

E. coli is the most common cause of urinary tract infections (UTIs) in humans and is a leading cause of enteric infections and systemic infections. The systemic infections include bacteremia, nosocomial pneumonia, cholecystitis, cholangitis, peritonitis, cellulitis, osteomyelitis, and infectious arthritis. *E. coli* is also the leading cause of neonatal meningitis.

Keywords: bacteremia, septicemia, septic shock, antimicrobial therapy

1. Introduction

Escherichia coli strains compose, physiologically part of the microflora of the gastrointestinal tract [1–4]. Belonging to the Enterobacteriaceae family, fermentative, non-sporulated and facultative anaerobic commensals, they are mainly from the large intestine [5, 6].

Despite being commensal microorganisms, they are the Gram-negatives which are most often a cause of human infections, having pathogenic strains that cause a wide variety of intestinal or extra-intestinal infections, such as urinary tract, intra-abdominal and soft tissue, sepsis, neonatal meningitis, gastrointestinal infection, and pneumonia, often leading to bacteremia [3, 7]. Although Gram-positive microorganisms have been increasing as a cause of sepsis due to the instrumentation of medical care—understood as the use of invasive devices or tools for the treatment or diagnosis of patients, and to infections associated with health care—*E. coli* continues to be an important and perhaps the most frequent cause of threatening infections in our environment [8, 9].

They are classified as Gram-negative bacteria and divided into 3 main groups: commensal lines, intestinal pathogenic lines (enteric or diarrhea) and extra-intestinal pathogenic lines [10].

Furthermore, Gram-negative bacteria produce large molecules consisting of a lipid and a polysaccharide, known as lipopolysaccharides (LPS), lipoglycans and endotoxin, which increases their pathogenicity in relation to Gram-positive bacteria [11].

2. Epidemiology

E. coli is one of the most commonly isolated bacteria in the bloodstream (responsible for approximately 20% of all clinically significant isolates) and is the

Gram-negative organism most frequently isolated in adult patients with bacteremia [12]. In the United States of America, *E. coli* sepsis was associated with approximately 40,000 deaths in 2001, a number that corresponds to 17% of all cases of sepsis [13].

Studies have shown an increasing incidence of *E. coli* early-onset sepsis in all age groups, overruling group B *Streptoccocus* for the last 10 years. Beyond that, *E. coli* resistant strains also increased equally in all age groups, with high resistance rates to first line antibiotics available (ampicillin and gentamicin).

Very low birth weight newborns remained the group with higher incidence (10.4 cases per 1000 live births) and mortality (35.3%). Systematic use of PCR increased *E. coli* early-onset sepsis diagnosis, mainly in the term newborn group. There was also an increase in resistant *E. coli* strains causing early-onset sepsis, with especially high resistance to ampicillin and gentamicin (92.8 and 28.6%, respectively) [14].

3. Risk factors

Several hospital-based studies have suggested that a number of comorbid illnesses, including diabetes, malignancy, chronic lung disease, cirrhosis and heart disease, may increase the risk of *E. coli* bacteremia. Previous researches have also identified age (very young and very elder), hospital acquisition, comorbid illnesses, presence of shock, non-urinary focus, and antimicrobial resistance in conjunction with inadequate treatment as being associated with higher rates of death [15–17].

Dialysis, solid organ transplantation and neoplastic disease were important risk factors for acquiring *E. coli* bacteraemia. Ciprofloxacin resistance and non-urinary focus were independently associated with an increased risk of death [18]. For males, urinary catheterization and incontinence were associated as risk factors to *Escherichia coli* bloodstream, and for females, cancer, renal failure, heart disease and urinary incontinence were risk factors reported [19]. Several risk factors which have significantly mortality due to *E. coli* bacteremia are age, severe sepsis or shock, non-urinary origin, Charlson index, inadequate empirical treatment (**Table 1**).

Mortality risk factor	*P*	**OR (95% CI)**
Age	0.03	1.04 (1–1.08)
Severe sepsis or shock	<0.0001	14.64 (6.14–30.86)
Non-urinary origin	0.013	2.78 (1.24–6.2)
Charlson index	0.006	1.31 (1.08–1.59)
Inadequate empirical treatment	0.006	2.98 (1.25–7.11)

Table 1.
Results of multivariate analyses examining risk factors for mortality associated with bacteraemia due to E. coli [15].

4. Pathogenesis

The human gastrointestinal tract is normally inhabited by *Escherichia coli*, which is why they are the bacterial species most commonly found in the isolation

of fecal culture [20, 21]. By the time the strains acquire additional genetic material, they can become pathogenic and circulate widely throughout the body. Pathological clones are divided into two major groups: intestinal (among the most virulent enteric pathogens) and extraintestinal (less present, but not less dangerous) [22, 23].

4.1 Intestinal

4.1.1 EPEC

Typical enteropathogenic *Escherichia coli* (tEPEC) contains a virulence plasmid (pEAF) that encodes the bundle-forming pilus (BFP), the primary factor for colonization [24, 25]. In addition, EPEC carries the crossomic island of locus for enterocyte effacement, which features the eae gene, which is the encoder of a colonization factor in the outer membrane protein called intimin [26, 27]. Only the *E. coli* strain that has pEAF and the eae gene can be considered tEPEC, one that has only the eae gene and is called atypical EPEC (aETEC) [28].

The small intestine is the most likely place for EPEC infection to occur. For the onset of diseases, tEPEC obeys the following steps:

- Initial localized adhesion of organisms to enterocyte via BFP.
- Induction of signal transduction in the enterocyte by secretion of protein toxins.
- Development of intimin-mediated intimate adhesion to the enterocyte.

Around 20 protein toxins are injected directly into the target epithelial cell, made, together with the intimin, by the chromosomal island LEE and expressed by both tEPEC and aEPEC [29]. The complex nanomachine called type III secretion injector is the one that injects protein toxins. It is assumed that some modifications happen to the epithelial stem cells, which is physiologically absorbent, and through a pathological process, it becomes a secretory dynamo [30].

What is believed is that type III ejection toxins are responsible for binding to protein elements of the cell's signal transduction apparatus. This event is accompanied by the mobilization of calcium from the intracellular compartment, activation of protein kinase C, kinase light chain myosin and induction of protein phosphorylation by tyrosine. The rearrangement of cytoskeletal proteins is induced by effectors, which results in the classic lesion "attaching and erasing," changes in the secretion of water and electrolytes and increased permeability of the tight intestinal junctions [31].

4.1.2 ETEC

Enterotoxigenic *Escherichia coli* (ETEC) consists of ingestion of bacteria, intestinal colonization and production of virulence factors. Colonizing fimbriae (CFs) must be expressed by ETEC to allow the consolidation of the bacteria in the intestine [32].

After colonization, ETEC produces two classes of secretory toxins encoded by plasmids: heat-labile toxin (LT) and heat-stable toxin (ST). To be classified as ETEC, *E. coli* must contain one or both classes of toxins [33, 34].

LT toxin is related to Vibrio cholera toxins in terms of structure, function and mechanism. It works by stimulating adenylate cyclase and increasing adenosine

intracellular cyclic monophosphate (AMP), a fact that stimulates chloride secretion from intestinal crypt cells and inhibits the absorption of sodium chloride at the ends of the villi. After that, the water secretion is free in the intestinal lumen, clinically developing watery diarrhea [35].

STa toxin, the only ST variant that causes disease in humans, activates cyclic GMP of enterocytes, leading to increased chloride secretion and decreased sodium chloride absorption. As a final result, the secretion of free water in the intestinal lumen clinically appears as watery diarrhea [36].

4.1.3 EHEC

Among the pathotypes that cause the most severe conditions, the strains classified as enterohemorrhagic (EHEC) stand out, which are the most common to cause disease in developed countries [29].

They are bacteria responsible for food infections and represent a risk to the health of the population, so they must be monitored frequently. Thus, good hygiene practices, as well as the use of quality tools, are extremely important to help reduce the risk of cross-contamination and human infection.

EHEC has the ability to attach itself to the host and to produce shiga-toxins, which gives the strain pathogenicity. The toxins produced by EHEC cause damage to the mucosa of the large intestine, where they are absorbed by reaching the bloodstream, which makes it possible to affect other organs, such as the kidneys [37]. An average of 5–10% of patients confirmed with EHEC infection develop potentially fatal complications, such as hemolytic uremic syndrome (HUS), which leads to sudden renal failure and hemolytic anemia [38].

Outbreaks are related to the ingestion of contaminated food and water, causing watery diarrhea and hemorrhagic colitis to those infected. The disease has a sudden onset with severe abdominal cramps and watery diarrhea that progresses to bloody, on average after 24 hours, lasting between 1 to 8 days.

The treatment consists of supportive therapy for fluid replacement, since the use of antibiotics is not indicated, as there is no proven efficacy. In fact, it could increase the risk of developing HUS, since the death of the bacteria would increase the release of toxins, predisposing to the syndrome [39].

4.1.4 EIEC

Enteroinvasive *E. coli* (EIEC) is very close to Shigella and develops a colitis similar to shigellosis. The intestinal cell is invaded by the EIEC which multiplies intracellularly and reaches the adjacent intestinal cells [40].

To differentiate Shigella from EIEC it is necessary to analyze the strains, those from EIEC ferment glucose and xylose, this differentiates them. Nucleic acid tests, including multiplexed panels, are used to detect organisms [41].

4.1.5 DAEC

Diffusely adherent *E. coli* is associated with diarrhea, which is characterized as watery and can become persistent in children between 1 and 5 years of age, occurring more frequently in developing and developed countries. In addition, this bacterium is also related to urinary tract infections and complications during the pregnancy period.

The pattern of diffuse adhesion in HEp-2 or HeLa cells is a characteristic that differentiates this pathotype from the others, although DAEC strains are quite

heterogeneous. This adhesion is mediated by fimbrial and afimbrial adhesins, which can cause damage to microvilli due to the disorganization of the cytoskeleton. However, some strains produce an adhesin involved in diffuse adhesion (AIDA-I), instead of encoding the diffuse adhesion pattern, which is why they are called atypical DAEC [42].

In addition, DAEC can also provide a pro-inflammatory effect [43].

4.2 Extraintestinal

The type of *E. coli* responsible for the invasion, colonization and induction of diseases in body sites outside the gastrointestinal tract is the extraintestinal pathogenic *Escherichia coli* (ExPEC). It is noteworthy that diseases caused by ExPEC range from urinary tract infections, neonatal meningitis, sepsis, pneumonia, surgical site infections to infections in other extraintestinal sites, representing a burden in terms of medical costs and lost productivity [44].

Thereto, the ExPEC strains were isolated from food products, in particular raw meat and poultry, indicating that these organisms potentially represent a new class of foodborne pathogens [45].

4.2.1 Urosepsis

Almost 25% of sepsis cases originate from the urogenital tract. [46–48]. Considering this percentage, the most common pathogen that causes urinary tract infection (and, consequently, urosepsis) is *Escherichia coli* (50%) [49]. It is known that this condition is better managed with an interprofessional team of health professionals—a nephrologist, infectious disease expert, urologist, intensivist, a nurse and a pharmacist [50, 51]. The outcomes after urosepsis depend on the cause and severity of the infection, and if the patient has a complicating factor in the urinary tract that is identified and warrants treatment, it should be performed as soon as possible. As an example, the literature reveals Foley catheter placement to relieve urinary retention or stent placement to bypass an obstructing ureteral calculus causing urosepsis. Moreover, the prognosis also depends on the type of bacteria, antimicrobial resistance, and patient comorbidity.

In addition to early antibiotics, there are some important parts of the management of sepsis. Initial fluid resuscitation with crystalloid is still recommended at a minimum of 30 mL/kg. Consider early administration of vasopressor support to maintain a mean arterial pressure greater than 65 mm Hg. The first choice for vasopressor support in sepsis is norepinephrine (with epinephrine and vasopressin 2 and 3). Tight glucose control is also recommended, with corticosteroids and blood products being more controversial in the literature [52].

5. Antimicrobial resistance

Although *Escherichia coli* is one of the most-studied microorganisms worldwide, its characteristics are constantly changing. Elseways, one important global problem is the increase of antimicrobial resistance shown by bacteria, being considered as "threatens the achievements of modern medicine" [53, 54].

E. coli resistant strains increased equally in all age groups, with high resistance rates to our first line antibiotics (ampicillin and gentamicin), with relevant highlight in neonatal *E. coli* isolates from invasive infection [55]. **Table 2** shows the temporal trends for antibiotic resistance to *E. coli*.

Agent or phenotype [n (%)]	**1997** *n* = **58**	**1998** *n* = **49**	**1999** *n* = **52**	**2000** *n* = **83**	**2001** *n* = **86**	**2002** *n* = **70**	**2003** *n* = **87**	**2004** *n* = **122**	**2005 (January–June)** *n* = **56**	**Total** *n* = **663**	*P*
Ampicillin	27 (46.6)	24 (49)	24 (46.2)	50 (60.2)	54 (62.8)	46 (65.7)	55 (63.2)	70 (57.9)	35 (62.5)	385 (58.2)	0.02
Trimethoprim/ sulfamethoxazole	14 (24.1)	11 (22.4)	13 (25.0)	28 (33.7)	21 (24.4)	28 (40)	32 (36.8)	41 (33.6)	20 (35.7)	208 (31.4)	0.02
Ciprofloxacin	9 (15.5)	7 (14.3)	10 (19.2)	7 (8.4)	14 (16.3)	16 (22.9)	22 (25.3)	27 (22.1)	13 (23.2)	125 (18.9)	0.02
Amoxicillin/ clavulanate	9 (15.5)	4 (8.2)	9 (17.3)	16 (19.3)	8 (9.3)	7 (10)	11 (12.6)	15 (12.3)	20 (35.7)	99 (14.9)	0.1
Gentamicin	4 (6.9)	6 (12.2)	5 (9.6)	5 (6.0)	8 (9.3)	6 (8.6)	7 (8.0)	8 (6.6)	8 (14.3)	57 (8.6)	0.8
Piperacillin/ tazobactam	1 (1.7)	4 (8.2)	1 (1.9)	8 (9.6)	6 (7.0)	4 (5.7)	5 (5.7)	2 (1.6)	2 (3.6)	33 (5)	0.4
Cefotaxime	11	2 (4.1)	0	2 (2.4)	3 (3.5)	5 (7.1)	3 (3.4)	12 (9.8)	4 (7.1)	31 (4.7)	0.001
ESBL production	0	0	0	2 (2.4)	3 (3.5)	3 (4.3)	2 (2.3)	9 (7.4)	3 (5.4)	22 (3.3)	0.002
MDR	4 (6.9)	4 (8.2)	5 (9.6)	9 (10.8)	9 (10.5)	12 (17.1)	15 (17.2)	17 (13.9)	12 (21.4)	87 (13.1)	0.006

Table 2.
Number, yearly percentages, and P values for temporal trend of non-susceptible cases of E. coli bacteraemia.

6. Evaluation

The sepsis' diagnosis confirmation is done from the evaluation of the clinical status of the patient, analyzing some criteria. For adult patients, it is confirmed or a diagnosis of sepsis is made when two criteria are present: hyperthermia>38.3 °C or hypothermia <36°C, tachycardia>90 bpm, leukocytosis (>12,000 μL-1) or leukopenia (<4000 μL-1) or >10% bands, acutely altered mental status, tachypnea > 20 bpm, hyperglycemia (>120 mg/dl) in the absence of diabetes [56].

7. Clinical assessment and patient presentations

7.1 History and physical examination

Collect a careful history from patient, addressing information such as previous illnesses, surgeries, how long ago the symptoms started, if there are comorbidities, if it have traveled to a place recently and other details, added to a complete physical examination, which provides very relevant information and leads to a line of rationality, it is extremely important to start the development of a preliminary differential diagnosis of the patient's complaints.

All this information collected is recorded and saved in medical records, more recently, electronics, which are more organized, more readable and allows a better comparison, in relation to written records [57].

Some of the most frequent reasons that lead patients to go to a medical consultation are dyspnea, cough with or without hemoptysis and chest pain, as these symptoms can be indications of serious illnesses, it shows the importance of asking questions and exams in a way attentive and careful [58].

7.2 Presentations

7.2.1 Pneumonia

Ventilator-associated pneumonia (VAP) is the most common fatal hospital infection [59]. One of the bacteria most involved in the clinical picture in question is Enterobacteriaceae *Escherichia coli* [60, 61] and there is little awareness when it comes to the pathophysiology of *E. coli* pneumonia.

Studies show that these *E. coli* pathogenic islands (PAIs) are involved differently in the pathogenicity of the lung compared to those present in urinary tract and bloodstream infections [62]. In addition, research on mice has also shown that these isolated strains are highly virulent extra-intestinal pathogens that express virulence factors, representing potential targets for new therapy. A French national study also demonstrated that, despite the genomic and phylogenetic characteristics of *E. coli* pneumonia isolates from critically ill patients, they belong to the same extra-intestinal pathogen as *E. coli*, they have specific distinct characteristics when lungs [63].

7.2.2 Acute-bacterial meningitis

E. coli meningitis is rare in adult forms of the disease [64–66], but it is a frequent pathogen in the pediatric field [67]. Despite its rarity, it has a serious clinical course [64–66]. It is usually diagnosed based on clinical signs and cerebrospinal fluid (CSF) analysis.

Due to the severity of the disease, early diagnosis, adequate antibiotic treatment and hemodynamic control are essential [68].

E. coli meningitis follows a high degree of bacteraemia and invasion of the blood–brain barrier. With mortality rates ranging from 15 to 40%, Meningitis due to this bacterium leaves approximately 50% of survivors with some type of neurological sequelae [69–78].

Although the process is unknown, it is known that, for the onset of the disease, it is necessary to have an invasion of the blood–brain barrier by *E. coli*, which requires specific microbial and host factors such as specific signaling molecules for microbes and hosts. Thus, blocking these microbial and host factors that contribute to the invasion of the blood–brain barrier by *E. coli* is effective in preventing the penetration of *E. coli* into the brain.

With the complete discovery of this mechanism, it is likely that new targets for the prevention and therapy of *Escherichia coli* meningitis will be achieved [79].

Regarding treatment, it is currently known only that antimicrobial chemotherapy has limited efficacy [79–81].

7.2.3 Intra-abdominal infections

Intra-abdominal infections (IAI) are invasive and bacterial multiplications in the hollow organ walls and beyond. Usually, it is located in the abdominal cavity, in the retroperitoneum and in the abdominal organs, being a common complication in the post-surgical period [82]. In addition, they have a wide variety of pathological conditions, from appendicitis to fecal peritonitis, which makes IAI generally have a poor prognosis (especially in high-risk patients) and is an important cause of morbidity [83]. Mostly, the most common source of this infection is the appendix, followed by gastroduodenal perforations. The Gram-negative bacteria *E. coli* is the most common causative agent of IAI. Therefore, it is important to know that they have great sensitivity to imipenem, meropenem, mainly, and to amoxi-clavulanate, amikacin and piperacillin-tazobactam, next [84, 85]. However, amici-clavulanate is prescribed as a first-line drug in developing countries, due to cost factors [86].

7.2.4 Enteric infections

Although *E. coli* strains have been isolated as part of the normal beneficial flora of the intestine, some strains have developed pathogenic mechanisms to cause disease in humans and animals. One of these strains capable of causing diseases is enteric *Escherichia coli* (*E. coli*), comprising important pathogens, since they cause significant morbidity and mortality worldwide. Traditionally enteric *E. coli* was divided into 6 pathotypes, however two other divisions were proposed by several studies (as mentioned individually in topic 4) [87].

Although there are many etiological agents responsible for diarrhea, pathogenic *E. coli* is a major contributor. On the other hand, the onset and complications of enteric *E. coli* vary significantly, despite there are many common features in the pathogenic process of colonizing the intestinal mucosa and the onset of disease [88].

Outbreaks are common all over the world, with fatal consequences mainly in children under 5 years of age living in underdeveloped countries, where diarrheal diseases can lead to death more frequently [89].

The transmission of enteric *E. coli* is also a public health concern, related to the development of countries, since its transmission is through contaminated water and food. Thus, the seriousness in relation to the microorganism can be exemplified by national and international surveillance programs, created by developed countries that aim to constantly monitor outbreaks [90]. In developing countries ETEC,

EPEC and EAEC are considered to be the main causes of childhood diarrhea, and when left untreated, they have potentially fatal consequences. However. in developed countries, these infections are mild and self-limiting, with EHEC and, more recently, EAEC and STEAEC being the main *E. coli* pathotypes associated with food poisoning outbreaks [91, 92].

7.2.5 UTI

Among the most common types of bacterial infections that occur both in the community and in hospitals, urinary tract infections (UTI) stand out. Urinary tract infections can be associated with the hospital (HAUTIs) and the community (CAUTIs). In the case of CAUTIs, it is known whether women are the predominant group of patients.

Although the UTI is multifactorial, the main bacteria related to the diagnosis is *E. coli*, predominant in both community and nosocomial UTIs [93].

Co-trimoxazole (trimethoprim/sulfamethoxazole), nitrofurantoin, ciprofloxacin and ampicillin are the antibiotics commonly recommended for the treatment of UTIs. However, there is an overall increase in antibiotic resistance among pathogens in the urinary tract, which is a limitation on treatment options [94, 95].

Since the evidence suggests a significant relationship between the extensive use of antibiotics and antimicrobial resistance, it is necessary to prescribe and use antibiotics in order to reduce their complications and costs [96].

For this reason, in order to guide the selection of empirical therapy, surveillance of antibiotic resistance is crucial for determining the pattern of antimicrobial resistance [97].

8. Workup

8.1 Urine culture

It aims to check the presence of fungi and bacteria in the urine, being carried out from a urine sample, which was placed in Petri dishes. The urine culture is placed in an incubator (1–2 days) and if there is any microorganism in the tested material, colonies grow and are visible on the plate. When the result is positive for some bacteria, a test antibiogram is performed, which determines the type of antibiotic needed to act against the pathogen [98].

The culture of urine is important precisely because it allows the precise recognition of the bacteria and, consequently, the best antibiotic to be used [99].

As urine culture is most frequently requested when UTI is suspected, the most common bacteria found are *Escherichia coli* (between 47.5% and 56.4% of all urine culture) [100, 101].

8.2 Blood culture

Blood culture is part of the routine assessment of patients with suspected bloodstream infection, and is crucial to guide therapeutic intervention. The ideal method for collecting blood culture is venepuncture, since it increases diagnostic yield, and has lower rates of contamination, according to some studies [102].

Since the timing of blood culture collection does not influence the detection of clinically relevant microorganisms, most authorities recommend collecting several sets simultaneously or for a short period of time, with the exception of patients with endovascular infection who need documented continuous bacteremia [103, 104].

Two to four sets of blood samples should be collected, whenever possible, at independent locations [103–106]. For adults, the volume required for the examination varies between 40 and 160 mL of blood, and for babies and children, the volume is age-based and does not exceed 1% of the patient's total blood volume [103, 107].

The importance of blood culture, as well as urine, is related to the determination of the bacteria and the antibiogram, which directs the treatment to the best antibiotic to be used [108].

8.3 Localization of underlying abnormality

In some cases, it is possible to suspect a complicated urinary tract infection/urosepsis without being serious urological abnormalities. In such cases, there are some screening options that can be performed to assist in the management of the patient. Thus, simple abdominal radiography, intravenous urography, ultrasound, computed tomography and magnetic resonance imaging are cited [109].

8.4 Imaging exams

The anatomical identification of most areas of infection has become common with the development of high resolution cross-sectional images, which allow visualization of bacterial and viral metabolism, early diagnosis and treatment. Thus, the cross-sectional image was included as part of the routine investigation of unidentified infection sites and sources of sepsis. The trend is that the use of these images will become increasingly widespread and become part of standard clinical care in the near future [110].

8.4.1 Ultrasonography

When abdominal sepsis is suspected, ultrasound is a valuable tool. As it is a portable scanning technique, it is ideal for clinically unstable patients who cannot be transported to an examination room [110].

Ideal for the diagnosis of liver sepsis and gallbladder, ultrasound identifies and indicates the presence and location of intra-abdominal fluids (subphrenic space, in pericological calculations or pelvis) [110–113]. Intrahepatic fluids are also well visualized, and can even be drained percutaneously with ultrasound guidance [110].

The main obstacle for ultrasound responses is air interference, highlighted in loop regions of the intestine with intraluminal gas, since the USG image is darkened and makes it difficult to visualize interloop abscesses or peri-pancreatic collections. The intestine in patients with disease due to sepsis or recent intra-abdominal surgery is also capable of compromising the quality of the ultrasound [114].

8.4.2 CT scanning

The availability of CT scanners with multiple detectors allows rapid acquisition of images, making this method the most common in the diagnosis and detection of intra-abdominal abscesses [114, 115]. It is an interesting option especially for sick patients who have difficulty holding their breath, obese or with abdominal or chest bandages.

In addition, CT is essential in the diagnosis of interloop and retroperitoneal pathologies (including retroperitoneal abscesses or pancreatitis or intra-biliary

stones), in addition to being highly sensitive in the detection of chest pathologies (pneumonia, pleural effusion and localized collections) [113, 115–117]. For intra-abdominal fluids and abscesses, CT showed a sensitivity of 90–100%, while ultrasound showed sensitivity between 80% and 85% [115, 118, 119].

Due to the contemporary contrast protocols available, it is possible to identify by CT even small infected collections [110].

8.4.3 Hybrid PET/MRI systems

With the development of hybrid cameras, the combination of PET and magnetic resonance imaging was introduced, which despite having interesting advantages and clinical applications, is still such an expensive tool.

The simultaneous acquisition of PET and magnetic resonance imaging can provide quantitative molecular functional information about the inflammatory lesion and precise location, in addition to anatomical changes with movement correction, improving the differential diagnosis and guiding anti-inflammatory treatment strategies.

Since MRI cannot visualize all parts of the body at once, the new hybrid technique may require collaboration between radiologists and nuclear medicine doctors to interpret the image and can be more expensive than PET/CT (capital and operational costs).

The functional image of inflammation and infection was mainly restricted to the flat image and SPECT, however, with the increasing development of PET radiopharmaceuticals, the detection and quantification of specific aspects of inflammatory processes became more sensitive. Precisely for this reason, there is an interesting potential in the application of hybrid whole body PET/MRI in the context of the investigation of infectious and inflammatory diseases [120].

8.5 Biologic scanning

Imaging technique that uses biological radionuclides to track hidden infections and improve the specificity of the infection diagnosis that allows the detection of early pathophysiological changes even when there are no apparent anatomical changes. When compared to ex vivo techniques (blood culture), in vivo biological screening is preferred since it is accurate, does not require a sterile environment and does not expose the health team to the risk of contamination by blood-borne pathogens.

This type of tool is used mainly in patients suspected of infection or abscess, but who have had negative results for the cross-sectional image. Thus, the use of marked leukocyte traffic allows a response to hidden sites, based on the recognition of white blood cells marked with radionuclides. The marked leukocytes travel to the infection sites and allow noninvasive images in areas of hidden infection, such as osteomyelitis, orthopedic prosthesis, endocarditis or inflammation and intestinal disease [110].

9. General management of sepsis and septic shock

9.1 Hemodynamic support

Adequate organ perfusion must be ensured. Hypotension should be managed initially with intravenous fluid administration and the goal should be maintenance

of pulmonary capillary wedge pressure at 12–16 mm Hg or central venous pressure at 8–12 cm H2O. Urine output rate should be kept at greater than 0.5 mL/kg/hr. A mean arterial blood pressure of greater than 65 mmHg (systolic blood pressure greater than 90 mmHg) and a cardiac index of greater than or equal to 4 L/min/m^2 should be maintained. Vasopressor therapy should be initiated in the event of failure to achieve these goals with iv fluids alone. These include dopamine, dobutamine and norepinephrine [109].

9.2 Respiratory support

Ventilatory support should be provided for patients with progressive hypoxemia, hypercapnia, altered sensorium or respiratory muscle fatigue. A study of "early goal directed therapy" (EGDT) found that prompt resuscitation to maintain SvO_2 > 70% was associated with improved survival in patients of severe sepsis [121]. In this study, failure to maintain saturation after fluids and vasopressors was followed by erythrocyte infusion to raise hematocrit to 30%. Patients requiring mechanical ventilation should be adequately sedated and stress ulcer prophylaxis should be administered.

9.3 Metabolic support

Blood glucose levels should be maintained at less than 150 mg/dL during initial few days of severe sepsis and normoglycemic range could be targeted later. Frequent blood glucose monitoring should be done to avoid hypoglycemia in patients on intensive insulin therapy. Multi-organ dysfunction, if any should be managed. Disseminated intravascular coagulation, if accompanied by major bleeding, should be treated with fresh-frozen plasma and platelet transfusion. Hypercatabolic individuals with acute renal failure benefit substantially from hemodialysis or hemofiltration. Prophylaxis for deep vein thrombosis and nutritional supplementation should be undertaken [109].

10. Treatment of carbapenem-resistant Enterobacteriaceae

10.1 Monotherapy vs. combination therapy for treatment

Considering the limited knowledge about the combination of antibiotics, the susceptibility of these pathogens to drugs and the lack of evidence to support the routine use of combined antimicrobial therapy, the decision regarding the ideal therapy is the responsibility of medical professionals [122]. Regarding the most appropriate approach, it is prioritized in the literature that the optimization of antimicrobial therapy includes adaptation of the appropriate antibiotics in terms of class, dose, frequency, route and duration [123].

The combination of different antibiotics has been widely used by large centers when it comes to invasive infections by multi-resistant Gram-negative bacteria [122].

10.1.1 Positive and negative aspects of combination therapy for treatment

The various positive and negative aspects of combination therapy are depicted in **Table 3**.

Positive aspects of combination therapy for treatment	Negative aspects of combination therapy for treatment
1. Greater probability of choosing an effective agent and well-founded theoretical reasons to support its use 2. Considering the increase in mortality related to the delay in the establishment of treatment and delays in appropriate and effective antimicrobial treatment, it is prudent to initiate empirical broad-spectrum antimicrobial treatment in the first suspected infection in critically ill patients 3. Indicated for patients with compromised immune systems, previous ICU admissions or who have recently received broad-spectrum antibiotics [124]	1. Increased toxicity in treatment by combining antibiotics (nephrotoxicity and ototoxicity). In such cases, it is suggested to discontinue the old therapy and introduce a new one, based on the clinical evolution of the patient and the results of the culture and susceptibility profile 2. This type of therapy has not been shown to be effective by clinical data (meta-analyses performed with the evaluation of randomized clinical trials demonstrate that there was no difference in clinical results between the two strategies for definitive treatment of Gram-negative bacteria infections) [124]

Table 3.
Comparison of positive and negative aspects of combination therapy.

10.2 Colistin

Antibiotics such as colistin are the last resort to deal with infections by carbapenem-resistant Enterobacteriaceae (CREB), and when the pathogen does not respond to colistin, therapeutic options are severely restricted. Thus, it becomes necessary to restore the sensitivity of the pathogen to the drug [125].

The combination of colistin + salicylate + potent efflux pump inhibitor (BC1) has been documented with highly positive results, providing a connection between colistin and the efflux pump inhibitor (BC1), which prevents extrusion of colistin [126].

The reduction in affinity between the drug and Gram-negative bacteria is due to the modification of lipid A, linked to the appearance of the gene that confers resistance to bacteria, which is present in animals that receive colistin and are part of human food. Despite this, there is still no complete explanation of the mutation and resistance of Gram-negative bacteria (especially Enterobacteriaceae) in patients who received administered colistin [127].

10.3 Carbapenems

Due to the increased resistance of bacteria to cephalosporin (and aminopenicillins), the use of narrow-spectrum β-lactamases, especially carbapenems, has increased considerably, being the only β-lactamase antibiotics with proven effectiveness in serious infections due to ESBL-producing bacteria [128–130].

With the discovery of *E. coli* isolates capable of producing new b-lactamases, a new strain of *E. coli* was found capable of resisting the action of carbapenems, mediated by plasmids.

These enzymes are able to confer resistance to drugs of the class b-lactamases, and in relation to *E. coli* specifically, the main types of enzymes are CMY, CTX-M and NDM of b-lactamase [131].

10.4 Tigecycline and other tetracyclines

Tigecycline is a new expanded-spectrum antimicrobial agent in the glycylcycline class. Developed with the objective of overcoming the most common processes of bacterial resistance, the drug has emerged as a great therapeutic option in the

treatment of serious infections, which endanger the patient's life, and which no longer respond to traditional antibiotics. The use of tigecycline is mainly interesting for the initial therapy of major infections, and is largely effective in the action against multi-resistant Gram-negative bacteria [132].

10.5 Aminoglycosides

Aminoglycosides are natural or semi-synthetic drugs obtained from actinomycetes, used as an antibiotic since the beginning of bacterial treatment. As it was replaced in the 1980s by cephalosporins, carbapenems and fluoroquinolones, aminoglycosides had little use.

With the increase in the number of cases of multidrug-resistant bacteria, aminoglycosides were again considered for their ability to synergize with a variety of other classes of antibacterials, improving the safety and effectiveness of the class through optimized dosing regimens, being broad-spectrum and quickly bactericidal.

Enzymatic modification by acetylation of an amino group, impaired uptake and phosphorylation of aminoglycosides are the most commonly reported processes that confer resistance to bacteria in relation to aminoglycosides [133].

10.6 Fosfomycin

Fosfomycin is an antibiotic from the 1969s, prescribed mainly in its oral form for the treatment of uncomplicated urinary tract infections (UTI), and considered as an option in the treatment of bacteria with advanced resistance, causing serious infections [134].

For *E. coli* NDM-producing strains, fosfomycin, colistin and tigecycline are more effective than other antibiotics [135].

The best pharmacological approach to *E. coli* infections resistant to carbapenems is still an obstacle to be overcome, since patients infected with this type of bacteria have more limited clinical results and when compared to patients infected with bacteria susceptible to drugs [136].

10.7 Duration of therapy

The duration of treatment for infection caused by *Escherichia coli* varies in the literature, but most patients require treatment for about 14–21 days [109]. For *E. coli* perinephric abscesses or prostatitis, it is recommended that the minimum antibiotic use time should be 6 weeks, intra-abdominal infections 14–21 days, and pneumonia 14 days (**Table 4**) [137].

Condition	General	Perinephric abscesses	Prostatitis	Intra-abdominal infections	Pneumonia
Duration	14–21 days	42 days	42 days	14–21 days	14 days

Table 4.
Recommended duration of antibiotic therapy depending upon the type of infection.

11. Special considerations

11.1 Urinary infections in diabetes mellitus

In general, infectious diseases occur more frequently and cause greater concern when dealing with diabetic patients. This occurs because the environment offered

by the organism is rich in glucose, which favors immune dysfunction, including decreasing the antibacterial activity of the urine and its motility [138].

Moreover, when comparing *E. coli* isolated in the urine of diabetics and non-diabetics, the same virulence factors and the same resistance to antimicrobials are found, inferring that there is no difference in the causative bacteria. This way, what makes the prevalence of urinary infections to be higher in diabetic patients is the greater adhesion of *E. coli* bacteria to diabetic uroepithelial cells, the reduction of urinary cytokine secretion and the number of leukocytes [139].

Hence, to treat the disease, the most commonly prescribed antimicrobials are used—amoxicillin, nitrofurantoin, trimethoprim/sulfamethoxazole (TMP/SMX) and ciprofloxacin. It is understood that the same treatment choice used by non-diabetic patients can be made, depending only on the local resistance patterns of the commonly found uropathogens [140, 141].

Generally, most uropathogens have a high resistance to TMP/SMX, in addition, this antimicrobial can cause hypoglycemia, which makes it not a good first choice of treatment for this portion of patients [142].

As for the treatment, it is recommended to consider the urinary tract infection complicated, it is advisable to keep the treatment for a period of 7 to 14 days [143].

11.2 Acute pyelonephritis

Acute pyelonephritis is an infection located in the upper urinary tract, which accommodates either parenchyma and renal pelvis, with *Escherichia coli* being the most common etiological agent [144, 145].

Approximately 250,000 cases of this disease are reported each year, with more than 100,000 eventually requiring hospitalization [146].

In order to confirm the diagnosis of the disease, the patient's urine culture is performed before the start of antibiotic therapy [147]. In addition, it is recommended to perform a microbial susceptibility test in order to select the most appropriate antimicrobial regimen [148, 149].

If the diagnosis is uncertain or the patient is immunocompromised and suspected of having a hematogenic infection, blood culture analysis is requested [150, 151].

In the last few decades, there has been an increasing rate of resistance of *E. coli* bacteria to beta-lactam antibiotics of extended spectrum [152]. Thus, for patients with mild and uncomplicated acute pyelonephritis, fluoroquinolone is a good choice for initial outpatient antibiotic therapy, if the drug resistance rate is 10% or less in the community [153].

On the other hand, in cases of complicated infections, sepsis or failed outpatient treatment, hospital treatment is best indicated [154]. After antibiotic therapy, urine culture should be performed again after 1–2 weeks to conclude whether the treatment was successful or not [155].

11.3 Emphysematous pyelonephritis

Emphysematous pyelonephritis (EPN) is a severe necrotizing infection of the renal parenchyma and its surrounding tissues—resulting in the presence of gas in the renal parenchyma, collecting system or perinephric tissue—and is caused in 70% of cases by *Escherichia coli* (isolated in cultures of urine or pus from patients with the condition) [156].

The clinical evolution of EPN when not recognized and treated immediately can be serious and pose a risk to the patient's life. Another fact that should be mentioned is that up to 95% of the cases of EPN are underlyingly associated with uncontrolled diabetes mellitus [157, 158].

In addition to the risk of developing EPN primarily, the risk of developing secondary to an obstruction of the urinary tract is considerably relevant, about 25–40% can be considered as positive findings in EPN [159, 160].

The combination of percutaneous drainage (PCD) and medical management (MM) revealed a significant reduction in mortality rates [161, 162]. Thus, it is recommended that PCD be performed in patients with localized areas of gas and the presence of functional renal tissue. Another approach that can be used in association with treatment is emergency nephrectomy, classified as simple, radical or laparoscopic [163].

11.4 Renal abscess

Being caused by kidney stones, structural abnormality, history of urological surgery, trauma or any other cause of obstruction, renal abscess can also be related to pathogens [164]. The predominant organisms causing renal abscesses are Gram-negative organisms, and the most common is *Escherichia coli* [165–167].

Among the various intra-abdominal abscesses, renal abscess is a rare entity, especially in children and accounts for a number of cases of "missed diagnoses" [166, 168].

With regard to the symptoms of pediatric patients, the presentation of fever, flank pain, with or without a palpable mass, has been established in the literature; increased leukocyte count and increased erythrocyte sedimentation rate [169].

Early diagnosis is a key factor in the management of these patients, which can be aided by Ultrasound (USG). Drainage of pus and appropriate antibiotic therapy is the gold standard for treatment, being able to treat a great amount of cases. Thereby, the most successful combination of antibiotics was ceftriaxone, being associated with amikacin. Cases that cannot be resolved by the conventional approach can be treated with surgery, such as nephrectomy. Thus, complications such as extension of the peritoneal cavity, skin or chest can be avoided [166, 167].

11.5 Perinephric abscess

Perinephric abscess results from perirenal fatty necrosis, usually a complication of urological infection (more than 75%) [170]. Most of these abscesses have *Escherichia coli* as the main responsible, about 51.4% [171]. Perinephric abscess, when more diffuse, is capable of affecting the renal capsule and also Gerota's fascia [170]. Since the condition has an insidious onset of nonspecific protein symptoms, it is necessary for a clinical physician to maintain a high level of attention to avoid possible delay in diagnosis, since perinephric abscesses are associated with significant morbidity and mortality [172].

11.6 Renal papillary necrosis

Renal papillary necrosis (NPN) is a condition defined as ischemic necrobiosis of the papilla in the kidney medulla. Among several etiological factors important for the involvement of papillary necrosis, pyelonephritis due to bacterial uropathogens such as *E. coli* is one of those mentioned in the literature [173].

In order to improve the prognosis of the disease and reduce morbidity, the ideal is that the diagnosis of the disease is as early as possible. In this sense, it is clear that the radiological image is able to offer an early diagnosis and guidance in relation to the immediate treatment of papillary necrosis, thus minimizing the decline in renal function [174].

11.7 Prostatic abscess

Failure to respond to standard therapy for acute bacterial prostatitis can lead to complications, such as prostate abscess or fistula [175].

Acute bacterial prostatitis is a common and clinically important genitourinary disorder that has a higher incidence in patients with diabetes, cirrhosis and suppressed immune system. Usually caused by an ascending infection, it can also be triggered by organisms that cause other common genitourinary infections that may also be responsible for acute bacterial prostatitis. Being introduced during transrectal prostate biopsy, the clinical presentation ranges from mild symptoms of the lower urinary tract to total sepsis, and *Escherichia coli* is one of the main bacteria related to the clinical picture.

Regarding the therapeutic approach, oral or intravenous antibiotics are most effective in curing the infection. In this sense, the progression to chronic bacterial prostatitis is uncommon. It should be noted that special attention is needed in relation to immunosuppressed patients, whereas bacterial prostatitis in these patients may be caused by atypical infecting organisms and, therefore, may require additional therapies [176].

12. Prevention

It is already known that iron is an essential micronutrient for most bacteria and hosts, in this thought line, it is also known that there are relatively rare classical siderophilic pathogens that cause an increase in hepcidin in the body, responsible for the sequestration of iron for macrophages and enterocytes and, consequently hypoferremia [177–180]. So, current studies investigate if this mechanism used by the body against rare siderophilic bacteria, it also works for a wider set of bacteria. Results of these studies are shown to be positive, by demonstrating that excess iron allows rapid bacterial replication and spread, which means a susceptibility to infection caused by *E. coli* and that hepcidin is essential to protect against infections caused by *Escherichia coli*. [181, 182]. Thus, the use of hepcidin agonists promises to be an effective early intervention in patients with infections and dysregulated iron metabolism to avoid complications.

With regard to urinary tract infection, an effective preventive measure is the characterization and correction of the underlying genitourinary abnormalities that promote the infection. Another alternative mentioned in the literature is the future development of catheters whose material limits the growth of biofilm [109].

13. Conclusion

Early symptom recognition, followed by appropriate investigations, accurate diagnosis and early goal-directed therapy, is essential to improve results. Patient management includes an interprofessional team approach, with microbiologists, radiologists, surgeons and intensive care physicians [109].

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