CAROL DAVILA UNIVERSITY OF MEDICINE AND PHARMACY BUCHAREST
DOCTORAL SCHOOL
FIELD OF MEDICINE

Analysis of the epidemiological profile of intra-abdominal infections in surgical patients

SUMMARY OF THE DOCTORAL THESIS

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GENERAL PART

Intra-abdominal infections (IAIs) represent significant clinical conditions that substantially impact morbidity and mortality in surgical patient populations. Effective management of IAIs requires prompt and accurate diagnosis, appropriate resuscitation measures, timely initiation of antimicrobial therapy, early and definitive source control, as well as regular assessment of the patient's clinical progress to inform adjustments to the treatment strategy [1]. A rigorous classification of intra-abdominal infections should include the primary source of infection, anatomical extent, suspected pathogens, risk factors for major resistance patterns, and the patient's clinical status. The development of a universally accepted classification that allows patients to be stratified according to their risk of an unfavorable prognosis is essential for optimizing therapeutic approaches. Understanding the microbiology of IIA requires a fundamental knowledge of the pathophysiology governing microbial translocation, proliferation, and the host immune response in the peritoneal cavity.

Community-acquired intra-abdominal infections (CA-IIA) occur in patients who have not been hospitalized or have been hospitalized for less than 48 hours. Historically, they involve predictable flora susceptible to standard narrow-spectrum antibiotics.

Healthcare-associated intra-abdominal infections (HA-IIA) encompass all infections acquired within healthcare settings. HA-IIA encompasses infections acquired within hospitals (nosocomial), nursing homes for institutionalized patients, or developed in individuals receiving long-term care or those engaged in outpatient services such as dialysis or chemotherapy. It also includes infections resulting from invasive outpatient procedures (for example, transesophageal echocardiography, upper and lower gastrointestinal endoscopies) and, additionally, infections associated with home care settings, including intravenous therapy. In the context of IIA, there is relatively little data on the concept of infections associated with extra-hospital healthcare. Infections that develop more than 48 hours after admission are also considered healthcare-associated infections. These are associated with a shift in the microbiological landscape towards MDR pathogens and higher mortality.

Acquiring results from bacterial and fungal cultures obtained at the site of infection provides two primary advantages [2]:

- the possibility of extending the antimicrobial regimen if the initial option was insufficient;
- reducing the spectrum of antimicrobial therapy if the empirical regimen was too broad.

Intraperitoneal sampling for microbiological evaluation is always recommended in

patients with HA-IIA or CA-IIA at risk of resistant pathogens (e.g., previous antimicrobial therapy), as well as in critically ill patients [2-5].

Although identification from culture media is the gold standard, complete characterization of anaerobic microorganisms is often limited by technical difficulties present in many clinical laboratories [3]. The integration of rapid molecular diagnosis with conventional methods can contribute significantly to the prompt detection of factors determining antimicrobial resistance [6]. Continental surveillance networks, such as *the European Antimicrobial Resistance Surveillance Network* (EARS-NET) and *the European Surveillance of Antimicrobial Consumption Network* (ESAC-NET), aggregate resistance data from all regions, but may not capture all IIA-specific trends as they focus on strains isolated from invasive infections (e.g. through blood cultures) [7].

Inappropriate initial antimicrobial therapy is associated with increased mortality, prolonged hospitalization and higher healthcare costs [8]. The use of empiric therapy based on local bacterial resistance data, followed by immediate reassessment upon microbiological susceptibility results, lead to optimized patient prognosis. Accurate identification of the pathogens involved and their resistance profiles is a fundamental step in optimizing the therapeutic strategy [9].

Antimicrobial resistance has reached alarming levels globally, threatening the very essence of modern medicine. In the European Union and the European Economic Area (EU/EEA), more than 35,000 people die each year as a direct result of infections caused by antibiotic-resistant bacteria – a health impact comparable to that of influenza, tuberculosis and HIV/AIDS combined [10]. According to both the referenced report and the EU/EEA analysis on antibiotic consumption, there has been an increase in overall annual antibiotic usage over the past five years. Additionally, the proportion of antibiotics prescribed from the AWaRe classification's 'Access' group—which consists of first-line treatments suitable for most community-acquired infections—has remained steady at approximately 60% since 2019 [10-13]. The economic ramifications are substantial, as antibiotic-resistant infections impose significant financial burdens on healthcare systems, resulting in annual losses exceeding €1.5 billion across the continent [14]. The interconnected nature of antimicrobial resistance, covering human medicine, veterinary practice, agricultural use and environmental reservoirs, has required coordinated international responses based on *the 'One* Health' principle [15].

Romania faces significant challenges in terms of antimicrobial resistance, reflecting broader regional trends while also presenting country-specific characteristics that require tailored responses. The country has been characterized as being in the 'red zone' in terms of

both excessive antibiotic consumption and the prevalence of antibiotic-resistant bacteria [16]. This designation reflects several worrying indicators: high rates of ESBL-producing Enterobacterales in the clinical setting, among the highest rates of carbapenem resistance in Europe for *Acinetobacter baumannii*, increased carbapenem resistance for *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*, and antibiotic consumption rates substantially above European averages, particularly in the outpatient setting [17]. Molecular epidemiology studies have revealed various types of carbapenemase circulating in Romanian healthcare facilities, including KPC, NDM, OXA-48 and VIM variants, indicating multiple chains of transmission and independent patterns of resistance [18].

Infection prevention and control, alongside antimicrobial stewardship, constitute complementary approaches in addressing antimicrobial resistance. Their combined application has been progressively highlighted within the guidelines and recommendations issued by international societies and organizations [19, 20].

Blood cultures, although essential for detecting secondary bacteremia, demonstrate sensitivity rates of only 30-40% in sepsis associated with IIA [21]. Biomarkers such as procalcitonin and C-reactive protein provide indirect evidence of infection, but are not specific to certain pathogens, nor can they indicate even an increased likelihood of polymicrobial infections. These diagnostic gaps create an urgent clinical need for rapid, sensitive, and comprehensive molecular approaches in the context of the AMR threat. The emergence of molecular diagnostic technologies, particularly multiplex polymerase chain reaction (mPCR) panels and next-generation sequencing (NGS), have fundamentally transformed the paradigm of infectious disease diagnosis [22]. These platforms offer the possibility of same-day or next-day pathogen identification, direct sample testing, simultaneous detection of multiple organisms, and identification of antimicrobial resistance determinants [23-25]. Next-generation sequencing (NGS) comprises a series of massive parallel sequencing technologies capable of simultaneously interrogating millions of DNA or RNA fragments. In the diagnosis of infectious diseases, two main NGS strategies are used: targeted amplicon sequencing (e.g., 16S rRNA gene sequencing for bacteria, ITS sequencing for fungi) and unbiased metagenomic NGS (mNGS), which sequences all nucleic acids in a clinical sample without a priori assumptions about the pathogens present [24, 26].

The swift emergence of resistance to advanced-generation antibiotics, combined with the limited progress in discovering new antibiotic classes, underscores the necessity for developing novel therapeutic strategies. To reduce the risk of bacterial resistance, various additions to antimicrobial treatments are being explored, such as nanoparticles (NPs),

antimicrobial peptides (AMPs), bacteriophages, the CRISPR/Cas system, and probiotics. To this end, over the last 25 years, more than 25 new antibiotics or compounds with antibacterial activity have been launched worldwide [27-29].

ORIGINAL PART

Fundamental hypothesis and objectives

This doctoral research is based on the following working hypothesis: the epidemiological profile of complicated intra-abdominal infections in surgical patients is characterized by a high prevalence of multidrug-resistant organisms, with resistance patterns significantly influenced by the environment in which the infection is acquired, the anatomical source of the infection, and the adequacy of source control; in addition, the presence of resistant pathogens is associated with higher rates of treatment failure, prolonged hospitalization, and higher overall mortality, which requires a reassessment of current empirical antimicrobial protocols in light of locally obtained microbiological and epidemiological data.

To test the above working hypothesis, the following general and specific objectives were formulated:

- To determine the demographic, clinical, and surgical characteristics of patients with complicated intra-abdominal infections, including age, sex, comorbidities, and severity;
- Identification of the microbiological spectrum and frequency of mono- versus polymicrobial cultures, as well as the prevalence of aerobic, anaerobic, Gram-negative, Gram-positive and fungal agents;
- Comparison of microbiological profiles and resistance between community-acquired and hospital-associated infections, highlighting risk factors for multidrug-resistant organisms;
- Analysis of the effects of antimicrobial resistance and inappropriate therapy on clinical outcome (treatment failure, length of stay, mortality);
- Supplying local epidemiological data to inform the creation of institutional algorithms for empirical therapy and to support recommendations for antimicrobial stewardship.

Research methodology

To achieve the above-mentioned aims and objectives, an observational, prospective, cohort study on patients over 18 years of age was conducted, on patients admitted to the Surgery Clinic of the Elias University Emergency Hospital, diagnosed at admission or postoperatively (up to 30 days) with intra-abdominal infections, who required emergency (immediate or delayed) surgery.

Inclusion criteria: age over 18 years, intra-abdominal infection complicated by peritonitis (localized/generalized) and surgical control of the source, readmissions within 30 days or reoperations for healthcare-associated infections complicated by peritonitis, positive intraoperative cultures (peritoneal fluid/abscess) for bacteria or fungi.

Exclusion criteria: spontaneous bacterial peritonitis, conservative management of infection, interventional drainage of abscesses, negative samples for bacteria/fungi, SARS-CoV-2 co-infection.

Individual data, biological parameters, and microbiological data were included in the statistical analysis. The significance level threshold for all statistical tests performed was $\alpha = 0.05$.

Study 1 - The Evolving Microbiology and Antimicrobial Resistance in Peritonitis of Biliary Origin

Extensive analysis of resistance patterns for microorganisms involved in intra- and extrahepatic biliary tract infections, as well as those responsible for peritonitis secondary to gastrointestinal perforations, has allowed the outline of complex resistance patterns, risk factors for MDR, ineffective treatment, and mortality.

The microbiology of biliary peritonitis directly reflects the primary biliary tract infection and varies depending on the patient's history. The pathogenic flora is becoming increasingly complex and resistant, with *Pseudomonas aeruginosa*, *Enterococcus* spp. and MDR bacteria being predominant, especially in healthcare-associated infections. Resistance to common antibiotics is increasing, including third-generation cephalosporins, fluoroquinolones, and piperacillin-tazobactam. The emergence of ESBL-, CRE-, and VRE-producing Enterobacterales complicates treatment and requires a personalized clinical strategy that includes assessment of the risk of resistant organisms, not just the severity of the disease.

Despite the wealth of data on biliary tract infections (BTI), there are still significant gaps in our knowledge of biliary peritonitis. Prospective, multicenter studies are needed to specifically analyze the microbiology, antimicrobial resistance patterns and clinical outcomes of biliary peritonitis as a distinct clinical entity. The clinical impact and optimal management of fungal biliary infections, particularly those caused by *Candida* species, are not well defined. Furthermore, although newer antibiotics with activity against MDR organisms are available, their efficacy, safety, and optimal place in the treatment of severe and resistant biliary infections require evaluation in dedicated clinical trials.

Table 1 summarizes this analysis into an applicable clinical tool, providing empirical recommendations on antibiotics, stratified according to risk.

Table 1. Empirical antibiotic regimens for biliary infections according to severity and risk of resistance

	Mild to moderate severity (Tokyo grade I/II)	Severe/septic shock (Tokyo grade III)
Low risk of resistance (community-acquired, no recent interventions/antibiotics, no recent hospitalization)	First line: Ceftriaxone OR Ampicillin/Sulbactam. Rationale: Covers common community pathogens (*E. coli*, *Klebsiella pneumoniae*). Considerations: Add Metronidazole if biliary-enteric anastomosis is present. Check local resistance rates to Ceftriaxone.	First line: Cefmetazole OR Piperacillin/Tazobactam. Rationale: Broader spectrum covering common pathogens plus some *Pseudomonas* and anaerobes. May also cover ESBL-producing pathogens in areas with high community resistance rates. Considerations: Provides more reliable coverage than cephalosporins in sicker patients or in areas with higher prevalence of ESBL producers.
High risk of resistance (associated with healthcare, previous biliary intervention, recent antibiotics, known MDR colonization)	First line: Cefmetazole OR Piperacillin/Tazobactam OR Meropenem. Justification: Broad coverage needed for potentially resistant *Pseudomonas*, *Enterococcus,* and Enterobacterales. Considerations: Even with "mild" signs, the risk of a resistant pathogen is high. A carbapenem (Meropenem) may be considered if local resistance to piperacillin-tazobactam is high (>15-20%) or if the patient is a known ESBL carrier.	First line: Meropenem OR Imipenem/Cilastatin. Rationale: Provides the broadest empirical coverage for ESBL producers and most other resistant pathogens. Considerations: Add Linezolid OR Daptomycin if the patient is a known VRE carrier or is in a high VRE prevalence setting. Consult an infectious disease specialist for potential use of novel agents if CRE is strongly suspected.

Study 2 - Invasive liver abscess syndrome caused by Klebsiella pneumoniae

The KLAS study is the first case series describing patients with this pathology in Romania and highlights the emerging threat of hypervirulent strains of *K. pneumoniae* in the European context, beyond the traditional epicenter of the syndrome in Southeast Asia, underscoring the need for prompt diagnosis, aggressive sepsis management, and antimicrobial stewardship guided by local resistance profiles.

Fifty-seven patients were included in the study, of whom 20 required surgery for abscess drainage and had microbiological confirmation of the diagnosis. Mortality in this cohort was considerable, at 25%. The need for open drainage and the occurrence of in-hospital complications proved to be significant predictors of death, while other independent risk factors, such as diabetes mellitus, high blood glucose levels at admission, septic shock at admission, and ESBL-positive strains, indicated a trend toward unfavorable outcomes. A critical finding of our study was the significant association between ESBL positivity and mortality ($p = 0.026$), with ESBL-positive patients having an unfavorable outcome, resulting in death. Although only two cases were identified, this finding is consistent with the growing global concern about antimicrobial resistance in pathogens causing KLAS [30]. In the only case in our study where samples were analysed phenotypically, the K1 serotype was identified. We have not found any articles to date reporting the more aggressive K2 serotype at a national level.

These findings underscore the importance of aggressive management of sepsis and addressing antimicrobial resistance. The conflicting results regarding the statistical significance of independent risk factors, due to the limited sample size, highlight the need for larger studies to confirm these results.

Study 3 - Pathogens involved in complicated acute diverticulitis

The study on complicated acute diverticulitis is one of the few prospective observational studies published so far that has analysed the bacterial strains involved in this pathology. Sixty-nine patients were included in the study, and the results revealed alarmingly high rates of antimicrobial resistance among community-acquired intra-abdominal pathogens. *Escherichia coli*, the most commonly isolated organism, was multidrug-resistant in nearly half of the cases and ESBL-producing in approximately 24% of cases, while *Klebsiella pneumoniae* presented even more worrying profiles, with 80% of strains being both ESBL-positive and MDR. More than half of the *Enterococcus* spp. isolates were resistant to vancomycin (Table 2).

Table 2. Distribution of patients with identified pathogens according to bacterial resistance

Resistance profile	Value (No., % of total)
Gram negative	
Escherichia coli – resistance to 1 class of ATB	5 (12.2%)
Escherichia coli – ESBL+ve	10 (24.4%)
Escherichia coli – MDR (including ESBL+ve)	18 (43.9%)
Klebsiella pneumoniae ESBL+ve/MDR	8 (80%)
Gram positive	
Enterococcus VRE	4 (57.14%)

Furthermore, the data showed that Hinchey III/IV diverticulitis increases the chances of having ESBL/VRE pathogens by 8.339 times, and the presence of polymicrobial infections in peritoneal fluid or abscesses increases the probability of having ESBL/VRE strains by 7.459 times (Table 3).

Table 3. Univariate and multivariate binomial logistic regression models used in predicting ESBL/VRE resistance using the analysed parameters.

Parameter	Univariate analysis		Multivariate analysis	
	OR (95% C.I.)	*p*	OR (95% C.I.)	*p*
Age ≥ 50.5 years	14.25 (1.667–121.8)	**0**	6.659 (0.676–65.58)	0.104
Hinchey class III/IV	8.556 (2.297–31.871)	**0**	8.339 (1.72–40.43)	**0.008**
Multiple pathogens	6.818 (1.542–30.152)	**0.011**	7.459 (1.19–46.76)	**0.032**
Inadequate AB therapy	13 (2.413–70.051)	**0.003**	-	-

Prospective studies are needed in regions with varying antimicrobial resistance profiles to develop region-specific empirical guidelines for antibiotic use in complicated acute diverticulitis. In addition, studies should explore the role of emerging pathogens, such as *Fusobacterium nucleatum*, in intra-abdominal infections secondary to diverticulitis, given its increasingly recognized pathogenic potential beyond the oral cavity. Furthermore, the impact of variables not captured in this study, such as obesity, smoking, and prior SARS-CoV-2 infection, warrants further investigation, as these factors may independently influence both antimicrobial resistance patterns and surgical outcomes in this patient population.

Study 4 – Secondary generalized peritonitis: community-acquired versus healthcare-associated pathogens

The study on secondary peritonitis and the pathogens involved in these potentially fatal

emergencies makes a relevant contribution by confirming, in a contemporary cohort of 150 patients (100 with CAI and 50 with HAI), the central role of age and procalcitonin as independent predictors of mortality, results that are consistent with the conclusions of recent multicenter reference studies [31-33]. At the same time, a novel element of the present study is the individual analysis of mortality predictors according to the origin of the infection, community-acquired versus healthcare-associated, a distinction that has not yet been sufficiently explored in the literature, but with major therapeutic implications, given the significant differences in microbiological spectrum, resistance profiles, and pathophysiological mechanisms, between the two categories.

The significant survival discrepancy between patients with and without bacterial resistance confirms that antimicrobial resistance is not just an abstract microbiological challenge, but a factor with a direct and measurable impact on the mortality and morbidity of surgical patients, justifying sustained investment in research into new therapeutic strategies, the development of rapid microbiological diagnostic tests, and the systematic implementation of antimicrobial resistance surveillance and control programs at an institutional and national level. Patients aged 70.5 years or older had an approximately four times higher risk of death compared to younger patients, thus confirming the decisive role of advanced age as an independent risk factor for unfavorable outcomes in patients with peritonitis. Procalcitonin proved to be an independent predictor of comparable importance, with patients with PCT values greater than or equal to 3.49 ng/mL having a 3.63 times higher risk of death than those with values below this threshold (Figure 1 and Table 4).

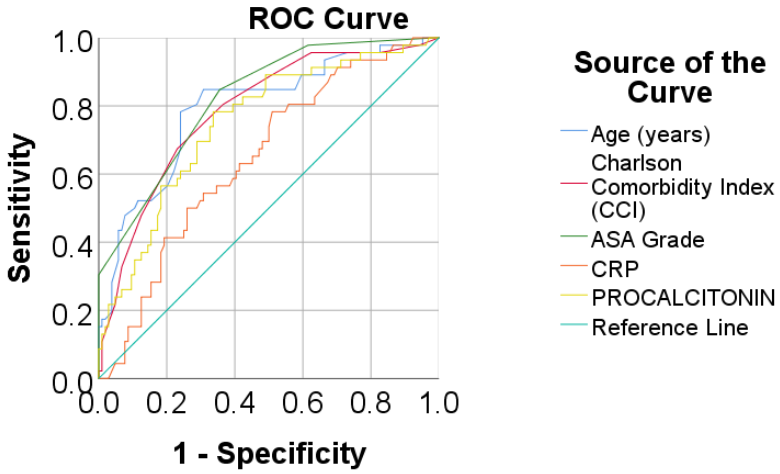

Figure 1. ROC curve analysis for mortality prediction

Table 4. Univariate and multivariate Cox proportional hazards regression models used for mortality prediction

Parameter	Univariate		Multivariate	
	HR (95% C.I.)	***p***	**HR (95% C.I.)**	***p***
Age ≥ 70.5	6.97 (3.33-14.60)	**<0.001**	4.12 (1.81-9.41)	**0.001**
CCI ≥ 6.5	4.03 (2.13-7.60)	**<0.001**	1.23 (0.57-2.64)	0.598
ASA ≥ 3.5	4.41 (1.96-9.92)	**<0.001**	2.16 (0.88-5.33)	0.093
PCT ≥ 3.49	3.88 (1.92-7.85)	**<0.001**	3.63 (1.74-7.57)	**0.001**
Multiple pathogens	1.81 (0.99-3.32)	0.05	-	**-**
RAM	3.06 (1.09-8.56)	**0.033**	2.65 (0.91-7.69)	0.073

The identification of ASA score and polymicrobial infection as independent predictors of bacterial resistance makes an original contribution to the literature, in which risk factors for antimicrobial resistance in secondary peritonitis have been insufficiently explored using rigorous multivariate models (Table 5). The role of the ASA score as a predictor of antimicrobial resistance is a relatively new observation, which opens interesting perspectives for future research on the interaction between patient frailty, exposure to the healthcare system and microbial ecology.

Table 5. Univariate and multivariate binomial regression models used in predicting bacterial resistance

Parameter	Univariate		Multivariate*	
	OR (95% C.I.)	***p***	**OR (95% C.I.)**	***p***
CCI	1.15 (1.01-1.32)	**0.03**	**-**	**-**
ASA grade	1.67 (1.13-2.49)	**0.010**	1.57 (1.04-2.36)	**0.030**
Multiple pathogens	4.53 (1.63-12.55)	**0.00**	4.14 (1.47-11.60)	**0.007**

*Multivariate Wald stepwise ascending binomial logistic regression model

Furthermore, the observation regarding the spread of ESBL mechanisms in the community aligns with a well-documented global trend, which has highlighted the gradual blurring of the traditional boundary between nosocomial and community-acquired antimicrobial resistance (Table 6). The results of this study suggest that this therapeutic dichotomy is becoming increasingly inadequate in the current epidemiological context and that a more nuanced approach is needed, based on the individualized assessment of risk factors for resistance, including those identified in this study.

Table 6. Distribution of patients according to the type of infection and the type of antimicrobial resistance mechanisms

Parameter	Total	CAI	HAI	*p*
Special RAM mechanisms	38 (25.3%)	21	17	0.111
Type of RAM mechanism				
***E. coli* ESBL**	17 (44.7%)	10 (47.6%)	7 (41.2%)	**0.002**
***K. pneumoniae* ESBL**	7 (18.4%)	6 (28.6%)	1 (5.9%)	
***E. coli* ESBL and *K. pn.* ESBL**	5	**5 (23.8%)**	**0**	
KPC	3 (7.9%)	**0**	**3 (17.6%)**	
OXA48	2 (5.3%)	0	2 (11.8%)	
OXA-48+NDM	2 (5.3%)	0	2 (11.8%)	
VRE	1 (2.6%)	0	1 (5.9%)	
VRE and OXA48+NDM	1 (2.6%)	0	1 (5.9%)	
Antifungal susceptibility testing				
Sensitive	22 (81.5%)	5 (83.3%)	17 (81%)	1,000
Resistant to fluconazole	5 (18.5%)	1 (16.7%)	4	

Finally, the high prevalence of fungal infections in patients with healthcare-associated intra-abdominal infections and the alarmingly low rate of appropriate empirical antibiotic therapy in nosocomial infections are findings that indicate the need to integrate antifungal therapy into empirical protocols for severe intra-abdominal infections and to optimize antimicrobial *stewardship* programs.

Antimicrobial resistance in secondary peritonitis, especially in nosocomial infections, where it affects over 90% of cases and reduces overall survival by more than three times, can no longer be considered a clinical exception, but a dominant epidemiological reality that requires abandoning conventional empirical therapeutic regimens in favor of individualized strategies, guided by accessible predictive factors such as the ASA score and the polymicrobial nature of the infection, capable of anticipating resistance and guiding therapeutic decisions before microbiological confirmation.

Conclusions and personal contributions

The findings of this study are part of a growing body of scientific evidence documenting the global escalation of antimicrobial resistance in intra-abdominal infections, a phenomenon recognized by the World Health Organisation as one of the most pressing threats to global public health [11, 34-36]. In a medical research landscape where large-scale international studies have mapped the epidemiological and microbiological coordinates of intra-abdominal

infections globally, this study makes a valuable contribution by detailing local realities, providing population-specific data that complements and nuances the picture provided by multinational studies [31, 37-40]. The epidemiology of antimicrobial resistance shows considerable geographical variations, determined by differences in antibiotic use policies, health system structures, infection control practices and the local prevalence of resistant bacterial clones, which is why local data are indispensable for informing therapeutic decisions and public health policies at regional level.

The data from these four studies confirm the working hypothesis on which this doctoral research was based. The epidemiological profile of complicated intra-abdominal infections is characterized by increased rates of antimicrobial resistance, both for community-acquired and healthcare-associated infections, which requires empirical treatment to be adapted to the local ecology, and not just to current international guidelines.

Based on original research and published evidence, **personal contributions** include:

- **Innovation in clinical guidelines (TG18 update):** Development of a proposal for a paradigm shift for the Tokyo Guidelines (TG18), replacing models based solely on severity with a dual risk stratification approach for biliary peritonitis;
- **KLAS evidence-based management:** Definition of significant predictors of mortality in invasive *Klebsiella pneumoniae* liver abscess syndrome, highlighting the critical role of ESBL-positive strains and the need for surgical drainage in complicated cases;
- **Assessment of mortality risk in acute diverticulitis:** Age, leukocytosis, procalcitonin, and length of hospitalisation in the ICU are excellent predictors of mortality in these patients. The threshold levels identified to calculate the risk of death in the study cohort showed that an increase of 1000 leukocytes/μL and one day of hospitalisation in intensive care, respectively, increase the risk of death by 1.2 and 2.1 times, which highlights the importance of rapid assessment upon admission, but also the implementation of supportive measures for rapid postoperative recovery;
- **Risk modelling for RAM in complicated diverticulitis:** Hinchey III/IV diverticulitis is an independent risk factor for MDR and correlates with inappropriate empirical antibiotic therapy. The identification of specific clinical predictors for the presence of ESBL/VRE pathogens in diverticulitis (age > 50.5 years, Hinchey stage III/IV, polymicrobial cultures) allows surgeons to adapt

antibiotic administration in surgical emergencies;

- **Mortality risk stratification in secondary peritonitis:** Age and procalcitonin are the most robust independent predictors of mortality in secondary peritonitis. The role of peritonitis aetiology as an exclusive predictor of mortality in nosocomial infections and the superior discriminatory capacity of biomarkers in community-acquired infections argue for a differentiated prognostic and therapeutic approach, adapted to the context of infection acquisition. The identified thresholds (age ≥70.5 years, PCT ≥3.49 ng/mL) provide simple and accessible tools for early risk stratification, with the potential for integration into clinical protocols for the management of secondary peritonitis;
- **Early assessment of MDR bacteria in secondary peritonitis:** The ASA score and polymicrobial infection are independent predictors of bacterial resistance - polymicrobial infection increases the risk of multidrug resistance fourfold, for both CAI and HAI. Antimicrobial resistance in HA-IIA affects over 90% of cases and reduces overall survival by more than three times, requiring individualised strategies and the implementation of new microbiological tools capable of anticipating resistance and guiding therapeutic decisions more quickly than microbiological confirmation through cultures;
- **Prospective characterization of local AMR rates:** a robust local database was created, identifying a critical threshold of 39% MDR in the community, which calls into question the use of standard first-line therapies.

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Chapter 6 - The evolution of microbiology and antimicrobial resistance in peritonitis of biliary origin (pp. 43-54)

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Chapter 7 - Pathogens involved in acute complicated diverticulitis **(**pp. 66-81)