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Antimicrobial treatment among critically ill patients:

Prospective observational single centre study

Mémoire réalisé par
Liliana Cristina Teixeira Lopes

Promoteur
Annie Robert

Année académique 2017-2018
Master en sciences de la santé publique
Finalité spécialisée

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"A dream doesn't become reality through magic; it takes sweat, determination and hard work."

Colin Powell

Le plagiat

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Abbreviations and acronyms

A. baumannii	*Acinetobacter baumannii*
AMR	Antimicrobial resistance
APACHE	Acute Physiology and Chronic Health Evaluation
ATC	Anatomical Therapeutic Chemical
BAPCOC	Belgian Antibiotic Policy Coordination Committee
CAI	Community-acquired infection
CDC	Centre for Disease Control and Prevention
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CPE	Carbapenemase-producing *Enterobacteriaceae*
CRP	C-reactive protein
CRRT	Continuous renal replacement therapy
DDD	Defined Daily Dose
DF	Degrees of freedom
EARS-Net	European Antimicrobial Resistance Surveillance Network
ECDC	European Centre for Disease Prevention and Control
ECMO	Extracorporeal membrane oxygenation
ECCO$_2$R	Extracorporeal carbon dioxide removal
E. coli	*Escherichia coli*
EEA	European Environment Agency
EMEA	European Medicines Agency
EPIC	Extended prevalence of infection in intensive care
ESBL	Extended-spectrum β-lactamase
EU	European Union
GNB	Gram-negative bacteria
GPB	Gram-positive bacteria
GCS	Glasgow Coma Scale
HCAI	Healthcare-associated infection
ICUs	Intensive Care Units
JIACRA	Joint Interagency Antimicrobial Consumption and Resistance Analysis
K. pneumoniae	*Klebsiella pneumoniae*
MDR	Multidrug-resistant
MIC	Minimum inhibitory concentration
MSSA	Methicillin-sensitive *Staphylococcus aureus*
MRSA	Methicillin-resistant *Staphylococcus aureus*
OR	Odds ratio
P. aeruginosa	*Pseudomonas aeruginosa*
PCT	Procalcitonin
PD	Pharmacodynamics
PDR	Pandrug-resistant
PK	Pharmacokinetics
PPS	Point prevalence survey
PACU	Post-anesthesia care unit
RCT	Randomised controlled trial
SOFA	Sequential organ failure assessment
spp.	Species
S. aureus	*Staphylococcus aureus*
VAP	Ventilator-associated pneumonia
VISA	Vancomycin Intermediate and resistant *Staphylococcus aureus*
VRE	Vancomycin-resistant *Enterococcus faecium*
vs.	Versus
WHO	World Health Organisation
XDR	Extensively-drug resistant bacteria

1. Introduction

Some decades ago, infectious diseases were the leading cause of mortality in the world. With the discovery of penicillin by Sir Alexander Fleming in 1928, antimicrobials transformed modern medicine and saved millions of lives [1]. However, the wide use of antimicrobials consequently induced the appearance of bacterial resistance. In the past twenty years, the emergence of extremely resistant strains occurred with a disturbing regularity, leading some to claim that a post-antibiotic era is not far [2].

Antimicrobials are commonly prescribed drugs in medicine. Its use is the main factor leading to bacteria resistance around the world. Around 50% of all antimicrobials prescribed to treat humans are not needed or are not optimally effective as prescribed [3].

Antimicrobial resistance (AMR), especially to Gram-negative bacteria, represents one of the greatest threat to public health and patient safety worldwide, so the optimal antimicrobial use is fundamental [4]. Analyses from the ECDC (European Centre for Disease Prevention and Control) estimated that infections caused by resistant bacteria are responsible for about 25.000 deaths per year in European Union (EU) alone [5]. Globally, AMR is also a serious social and economic burden: statistical modelisation suggests that the 700.000 annual deaths currently attributed to antimicrobial resistant infections will increase to 10 million by 2050 (meaning one person dying every 3 seconds) [6].

AMR proliferation increases not only the incidence of treatment failures and deaths, but also healthcare costs. The annual impact of resistant infections is estimated to be 1.6€ billion in excess health care costs and 2.5 million additional hospital days in the EU alone [2].

In 2017, the second European JIACRA[a] report confirmed the link between antimicrobial consumption and AMR both in humans and in food-producing animals [7]. There were substantial variations across the EU regarding antimicrobial consumption in animals and in humans, but in 18 of 28 countries, antimicrobial consumption was lower in animals (median antimicrobial consumption of 67 mg/kg in animals versus 118 mg/kg in humans) [7]. Aside the inherent difficulties in comparing data from animal and human consumption, this wide variation suggests that there is potential in both sectors to improve antimicrobial use and consequently reduce AMR.

[a] Joint Interagency Antimicrobial Consumption and Resistance Analysis

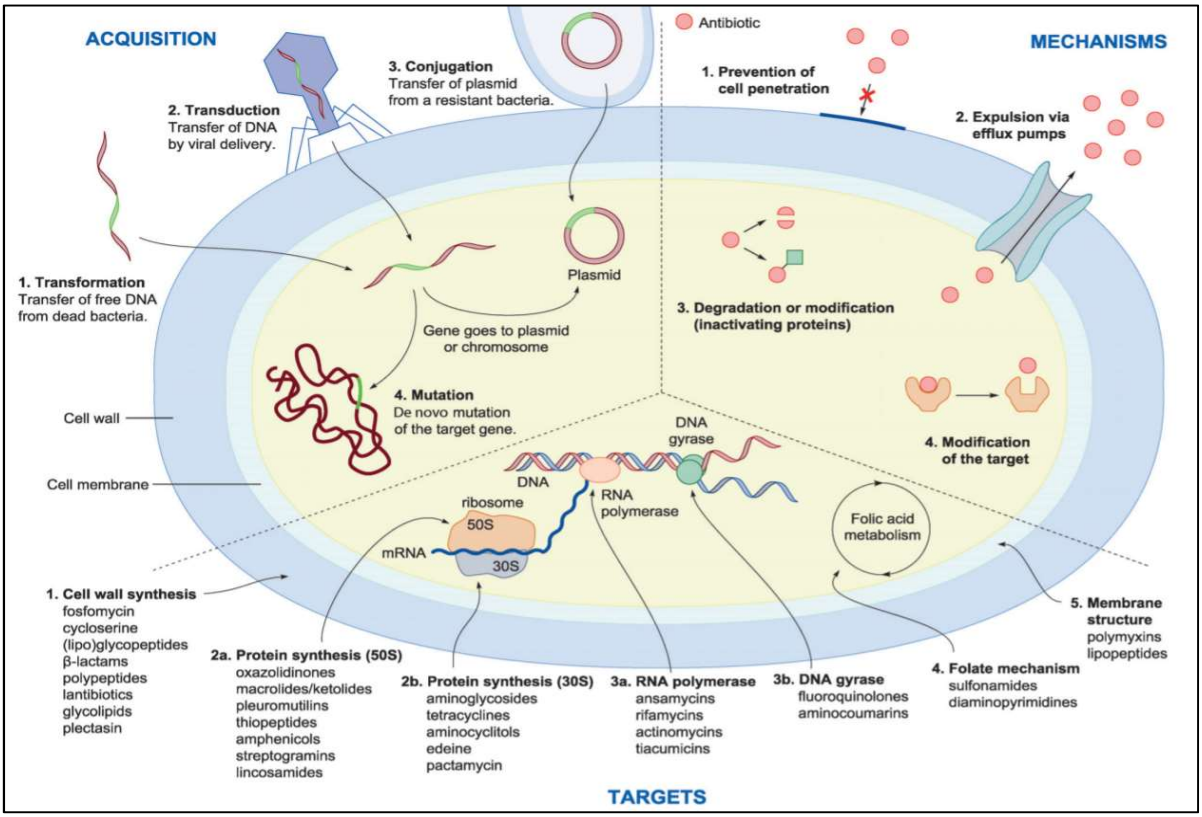
2. Antimicrobials characteristics

Antimicrobials agents are active against a variety of infections, such as those caused by bacteria (antibiotics), viruses (antivirals), fungi (antifungals) and parasites (i.e. anthelmintics or antimalarials). Regardless of the antimicrobial type, the name "antibiotic" usually prevails in clinical practice because they are the most common used.

The development of antimicrobials was one of the greatest scientific achievements of the last century. Since 1940s, the widespread use of these drugs to treat infectious diseases has contributed significantly to the reduction of morbidity and mortality. Effective antimicrobial agents ensuring the prevention of infection complications are also crucial for many medical interventions such as major surgery, solid organ and stem cell transplantations, implantation of devices, chemotherapy treatments and intensive care medicine [5].

After the discovery of penicillin, other antimicrobials have been discovered and developed by elucidation of the targets. There are currently five main targets for antimicrobials, while resistance can essentially be acquired through four different pathways and expressed by four different mechanisms [8] (***Figure 1***). Most current antimicrobials inhibit cell wall synthesis or protein synthesis.

Figure 1 *- The five main targets for antimicrobials, the four resistance acquisition pathways and the four main mechanisms of resistance.*



Source: [8]

2.1. Antimicrobial resistance

With the discovery of penicillin, it was believed that infectious diseases would no longer be a problem in medical practice. Shortly after its widespread use in the 1940s, penicillin resistance became a substantial clinical problem, so that by the 1950s, many of the advances of the prior decade were threatened [1]. Other antibiotics were discovered and used, but inevitably some bacteria strains always managed a way of becoming resistant to the new drugs (see ***Figure 2***).

Figure 2 – *Developing Resistance: timeline of key antibiotic resistance events.*

PDR= pan-drug-resistant;
R=resistant;
XDR=extensively drug-resistant.

Dates are based upon early reports of resistance in the literature. In the case of pan drug-resistant - Acinetobacter and Pseudomonas, the date is based upon reports of healthcare transmission or outbreaks.

Note: penicillin was in limited use before 1943.

Source: [3]

AMR is the ability of a microorganism to resist the action of one or more antimicrobial agents. The consequences can be severe, as prompt administration of adequate antimicrobial therapy is the most effective intervention to reduce the risk of poor outcome among serious infected patients [5].

The majority of the antimicrobial-resistant infections happen in the general community, but most deaths related to AMR happen in healthcare settings (hospitals and nursing homes) [3]. In order to promote the collection of reliable and comparable data across different settings around the world, Magiorakos *et al.* [9] propose a standardised international terminology to

describe acquired resistance profiles in bacteria often responsible for healthcare-associated infections (HCAI) which are prone to multi-drug resistance (e.g., *Staphylococcus aureus*, *Enterococcus* spp., *Enterobacteriaceae*, *Pseudomonas aeruginosa* and *Acinetobacter* spp.). The authors suggest the following definitions:

- Multidrug-resistant (MDR) bacteria - non-susceptible to at least one agent in three or more antimicrobial categories;
- Extensively-drug resistant bacteria (XDR) - non-susceptible to at least one agent in all but two or fewer antimicrobial categories;
- Pandrug-resistant (PDR) bacteria were defined as non-susceptible to all agents in all antimicrobial categories.

Through genetic exchange mechanisms (see ***Figure 1***), many microorganisms become MDR. The first cases of methicillin-resistant *Staphylococcus aureus* (MRSA) were identified in the 1960s (in the United Kingdom in 1962 and in the United States in 1968) [1].

2.2. Factors linked to antimicrobial resistance

The main factors leading to AMR are the following: overuse by humans, inappropriate prescription and misuse by the food industry.

2.2.1. Overuse/Misuse by humans

One of the most important causes accelerating the evolution of AMR around the world is the public misconceptions about antimicrobials which leads to their overuse and misuse (e.g., premature cessation of therapy) [3]. Legislation tries to prevent the sale of antimicrobials "over-the-counter", but these regulations may be weakly enforced or non-existent in some countries. In some parts of Southern and Eastern Europe, 20% to 30% of antimicrobials are consumed without prescription, while in some parts of Africa this may reach higher proportions [6].

In Europe, epidemiological studies have demonstrated a significant association between antimicrobial consumption and resistance of *Klebsiella pneumoniae* (*K. pneumoniae*) to "last-resort" antimicrobials (i.e. carbapenems and polymyxins) in humans [7]. Also in humans, multivariate analyses demonstrated that *Escherichia coli (E. coli)* resistance to fluoroquinolones and 3rd and 4th-generation cephalosporins was associated with antimicrobial consumption [7].

In many bacteria, genetic material can be transferred between species via horizontal gene transfer [10], which makes the process of AMR quite transferable. So, suboptimum doses facilitate the outgrowth of resistant pathogens, as a result of natural selection [10]. The same is

true for plasmid-borne resistance, since low antimicrobial concentrations often only prevent bacterial replication and dormant cells can still receive plasmids.

Many organizations, including the Belgian Antibiotic Policy Coordination Committee (BAPCOC), recommend a surveillance of antimicrobials consumption in order to better understand the relationship between antimicrobials use and the emergence of bacterial resistance. Gathering information regarding antimicrobials prescription and consumption trends is crucial in order to assess the public health consequences of antimicrobial misuse and to evaluate the impact of interventions to reduce AMR.

There is a marked variation in antimicrobial consumption both in the community and in the hospital sector across Europe [11]. In 2015, Belgium antimicrobial consumption was slightly lower than the EU average: 1.66 versus 2.05 DDD[b]/1000 inhabitants/day [11] (see ***Table 1***). Malta had the highest rates of antimicrobial consumption (2.86 DDD/1000 inhabitants/day) with the Netherlands reporting the lowest rates (0.98 DDD/1000 inhabitants/day) [11]. This wide variation suggests that there is a possibility to safely reduce antimicrobial use, both in Belgium and in Europe.

2.2.2. Inappropriate prescription

Inappropriate antimicrobial prescription (incorrect drug, dose or duration therapy) can also induce the bacteria resistance [3]. Often antibiotics are prescribed for the common cold, against which there is no evidence of benefit from these drugs [12].

Antimicrobials are one of the most frequently prescribed treatments among hospitalized patients, especially in the intensive care units (ICU). An internet-based global point prevalence survey conducted in 2015 showed that approximately 35% of hospitalized patients was receiving at least one antimicrobial as treatment or prophylaxis of infections [13]. In Europe, almost 32% of the patients were being treated with an antimicrobial, but if we only consider the ICU patients, the prevalence almost doubled (60%) [13].

Appropriate empirical antimicrobial treatment is associated with a significant reduction in all-cause mortality [14]. But the altered pathophysiology in critically ill patients represents a challenge in the diagnosis of infection and in the identification of causative microorganisms and their antibiotic susceptibilities [15].

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[b] In 1996, World Health Organization recognized the need to use the Anatomical Therapeutic Chemical (ATC) classification system and the Defined Daily Dose (DDD) as a measuring unit for international drug utilization research (https://www.whocc.no/). The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults, but it does not necessarily reflect the recommended or prescribed daily dose. The ATC/DDD system allows to evaluate trends of consumption over time and to make comparisons between groups of population. It is used to obtain a rate, such as "DDD/1000 inhabitants/day" and it makes possible the verification of real consumption oscillations, regardless of the population growth or the number of patients.

Table 1 *– Trends in consumption of antibiotics for systemic use in the hospital sector in European countries, 2011-2015 (expressed as DDD/1000 inhabitants/day).*

Country	2011	2012	2013	2014	2015	Trends in antimicrobial consumption, 2011–2015	Average annual change 2011–2015	Statistically singificant trend
Netherlands	0.97	0.96	0.95	0.95	0.98		<0.01	
Hungary	1.20	1.23	1.20	1.25	1.23		0.01	
Norway	1.47	1.44	1.39	1.41	1.40		-0.02	
Bulgaria	1.45	1.40	1.41	1.45	1.40		<0.01	
Poland (a)				1.43	1.43			N/A
Portugal (c)	1.45	1.46	1.64	1.55	1.57		0.03	
Belgium	2.02	1.71	1.67	1.60	1.66		-0.08	
Sweden	1.60	1.65	1.67	1.57	1.67		0.01	
Slovenia	1.66	1.56	1.55	1.61	1.68		0.01	
Luxembourg	2.02	2.02	2.00	1.81	1.78		-0.07	<
Estonia	1.86	2.11	1.91	1.94	1.82		-0.03	
Croatia	1.88	1.98	1.80	1.86	1.91		-0.01	
Ireland	1.79	1.76	1.79	1.66	1.91		0.01	
EU/EEA	**1.96**	**1.98**	**2.05**	**2.01**	**2.05**		**0.02**	
Greece	2.18	2.08	2.00	2.11	2.14		-0.01	
France	2.12	2.12	2.17	2.20	2.18		0.02	
Latvia	2.39	2.27	2.30	2.25	2.24		-0.03	
Denmark	1.74	1.78	2.02	2.13	2.34		0.16	>
Slovakia (a)		2.02	2.30	2.47	2.40			N/A
Italy	2.32	2.46	2.23	2.22	2.43		<0.01	
Finland (b)	3.09	2.79	2.77	2.64	2.50		-0.13	<
Lithuania (a)		2.39	2.38	2.35	2.54			N/A
United Kingdom (a)			2.45	2.59	2.55			N/A
Malta	1.67	1.44	1.75	2.18	2.86		0.31	>

EU = European Union; EEA = European Environment Agency

The numbers for the European countries refer to the corresponding population-weighted mean consumption.

(a) These countries did not report data for all years during the period 2011–2015.

(b) Finland: data include consumption in remote primary healthcare centres and nursing homes.

(c) Portugal: data relate to public hospitals only.

< Significantly decreasing trend. > Significantly increasing trend

N/A.= not applicable; linear regression was not applied due to missing data, changes in the type of data or changes of sector for which data were reported (community versus total care data) between 2011 and 2015.

Source: [11]

A recent systematic review showed that inappropriate usage of antibiotics ranged from 14% to 79% in patients with severe infection [16]. The main causes of inadequate antimicrobial treatment of severe infections seems to be discordance with local guidelines, discordance with susceptibility pattern of isolated microorganisms, incorrect treatment duration and absence of treatment de-escalation [14, 16]. Inadequate antimicrobial use seems to increase 30-day hospital mortality in patients with severe bacterial infection [16]. So, it is important to tailor antimicrobial therapy in order to prevent the significant harms associated with suboptimal antimicrobial treatment and decrease the healthcare costs.

During antimicrobial therapy, inhibitory concentrations of drugs are followed by sub-inhibitory concentrations which can generate phenotypic changes in microorganisms and, thus, contribute to the selection of resistant microorganisms [17]. Therefore, incorrectly prescribing expose patients to sub-inhibitory and sub-therapeutic antimicrobials concentrations that can promote the development of AMR by supporting genetic alterations, such as changes in gene expression, horizontal gene transfer and mutagenesis [1]. For instance, sub-inhibitory concentrations of piperacillin/tazobactam have been shown to induce changes in the proteome of *Bacteroides fragilis* [17].

2.2.3. Misuse by the food industry

There are circumstances where antimicrobials are required in food animals and aquaculture. However, much of their global use is not for treating sick animals, but instead either to prevent infections or to promote growth by using continuous sub-therapeutic application of antimicrobials usually to compensate for poor farming practices [6].

The use of antimicrobials in food-producing animals kills or suppresses susceptible microorganisms, allowing antibiotic-resistant microorganisms to thrive [3]. Then resistant microorganisms can be transmitted to humans through the food supply, causing adverse results regarding the antimicrobial effectiveness in human medicine.

Therefore, antimicrobials use in agriculture boosts the development of AMR that can spread and affect humans and animals alike. Recent data from the EU showed that consumption of macrolides in animals was significantly associated with macrolide resistance in *Campylobacter coli* in animals and humans [7]. Also, resistance to fluoroquinolones in *Salmonella spp.* and *Campylobacter spp.* from humans was related to consumption of fluoroquinolones in animals [7].

Antimicrobials use in agriculture also affects the environmental microbiome because near 90% of the antibiotics given to livestock are excreted in urine and stool, then widely dispersed through fertilizer, groundwater, and surface runoff [1]. Environmental sub-inhibitory concentrations of antimicrobials have been shown to contribute to the arising of new highly multi-resistant organisms such as *Pseudomonas aeruginosa* (*P. aeruginosa*) [18].

2.3. Development of new antimicrobials

Although the current pipeline of antimicrobials could lead to around 10 new approvals over the next 5 years, these new treatments will add little to the already existing arsenal and will not be sufficient to tackle the impending AMR threat [19]. Moreover, most of the new antimicrobials target Gram-positive bacteria, while the major challenge is to find new

antibiotics against Gram-negative bacteria, which are identified as critical by World Health Organisation (WHO) on its priority pathogens list (see ***Table 2***) [20].

Table 2 – World Health Organisation priority list of drug-resistant bacteria to guide research and development of new antimicrobials.

Priority 1: CRITICAL
-Acinetobacter baumannii - Gram-negative carbapenem-resistant
-Pseudomonas aeruginosa - Gram-negative carbapenem-resistant
-Enterobacteriaceae* - Gram-negative carbapenem-resistant and 3rd generation cephalosporin-resistant
*Include: ***Klebsiella pneumonia*, *Escherichia coli*, *Enterobacter spp.*, *Serratia spp.*, *Proteus spp.*, *Providencia spp*, *Morganella spp.***
Priority 2: HIGH
-Enterococcus faecium – Gram-positive vancomycin-resistant (**VRE)**
-Staphylococcus aureus – Gram-positive methicillin-resistant (**MRSA**), vancomycin intermediate and resistant (**VISA)**
-Helicobacter pylori – Gram-negative clarithromycin-resistant
-Campylobacter – Gram-negative fluoroquinolone-resistant
-Salmonella *spp.* – Gram-negative fluoroquinolone-resistant
-Neisseria gonorrhoeae – Gram-negative 3rd generation cephalosporin-resistant and fluoroquinolone-resistant
Priority 3: MEDIUM
-Streptococcus pneumoniae – Gram-positive penicillin-non-susceptible
-Haemophilus influenzae – Gram-negative ampicillin-resistant
-Shigella spp. – Gram-negative fluoroquinolone-resistant

Source: [20]

The availability of few new antimicrobials is linked to the fact that these drugs are typically prescribed for short periods making them far less profitable than other drugs to treat chronic conditions. Besides, in order to delay the emergence of resistance, newly approved antimicrobials are considered "last-line" and only prescribed for infections that more established antimicrobials are unable to treat [2]. So, initial return to pharmaceutical industry investment is usually limited.

Also, the development of new antimicrobials by the pharmaceutical industry is delayed by some of the regulatory obstacles [2]. Using placebo is unethical, so trials are designed to demonstrate non-inferiority of new antimicrobials compared to existing drugs, which requires a large sample population and consequently high costs, making the development of antimicrobials uneconomical and unattractive [1].

3. Infection in the intensive care units

Infection is a common problem in the critical care setting and it is associated with considerable morbidity, mortality and costs [21]. The presence of infection is an important outcome determinant in critically ill patients: on one hand, infection may be the reason for admission; on the other hand, infection can be a consequence related to immunosuppression usually associated with critical illness and the high use of invasive procedures [15]. A study in several ICUs from 75 countries found that infection was present in 51% of patients [21].

Sepsis, a life-threatening organ dysfunction caused by a dysregulated host response to infection, is associated with hospital mortality greater than 10% [22]. Septic choc, a subset of sepsis, is clinically identified by elevated lactate levels (>18 mg/dl) in the absence of hypovolemia and vasopressor requirement to maintain a mean arterial pressure ≥ 65 mmHg; it is associated with a greater risk of mortality when compared with sepsis alone (mortality rates superior to 40%) [22].

Sequential Organ Failure Assessment (SOFA) score is a simple and objective score that evaluates the degree and severity of organ failure and it is generally used to monitor the patient's condition during ICU stay. SOFA score cut-off point for outcome prediction of critically ill patients ranges from 7 (30-day mortality) to 10 (hospital mortality) [23, 24]. A higher SOFA score is associated with an increased probability of mortality [22]. So an increase in this score may be a warning sign for infection acquisition or re-infection.

ICUs are the hospital wards with the highest prevalence of HCAI [25]. Critically ill patients are vulnerable to infections because they are exposed to numerous invasive procedures, including mechanical ventilation, vascular and urinary catheters. Also, some medications (sedatives, analgesics, muscle relaxants) commonly used in critical care increase the risk for ICU-acquired infection [26]. In 2014, 8% of critically ill patients presented at least one ICU-acquired infection under surveillance[c]. Since critical care patients are at high-risk for HCAI, the critical care setting is the ideal place to study the patterns of antimicrobials use and AMR.

3.1. Main bacterial threats

Almost all the pathogens present in the hospital settings may cause HCAI, but the microorganisms presented in the WHO priority list (see ***Table 2***) are the most threatening ones.

In the critical care setting, around 68% of isolates found in hospital-acquired bloodstream infections are caused by multidrug-resistant or extensively drug-resistant bacteria

[c] The minimal required was to include data regarding bloodstream infections and pneumonia; data collection on urinary tract infections and central venous catheter-related infections was optional.

[27]. The presence of a multidrug-resistant organism was associated with a longer time before receiving adequate antimicrobial therapy and with an increase in 28-day mortality [27].

3.1.1. Methicillin-resistant *Staphylococcus aureus* (MRSA)

Among Gram-positive bacteria, MRSA is one of the most problematic in terms of their occurrence and impact on the clinical outcome of hospitalized patients. MRSA causes different illnesses, from skin and wound infections to pneumonia and bloodstream infections that can cause sepsis and death [3]. It is one of the most common causes of HCAI [3]. Fortunately, a number of antimicrobials still retain activity against MRSA, including glycopeptides (e.g., vancomycin), linezolid, tigecycline and some new beta-lactams [1]. In Europe, the population-weighted mean percentage decreased from 18.8 % in 2012 to 16.8 % in 2015, yet it remains a public health priority, as MRSA percentages remain high in several countries [5]. This reduction in the European incidence of HCAI caused by MRSA is mainly linked to the aggressive hospital preventive hygiene measures implemented in countries like the United Kingdom or the Netherlands [28]. Regarding ICU-acquired infections, in 2016, MRSA was present in 25.3% of *S. aureus* isolates [25].

3.1.2. Vancomycin-resistant *Enterococcus faecium* (VRE)

Enterococci are Gram-positive bacteria that become pathogenic when they colonize niches where they are not normally found. They belong to the normal microbiota of the gastrointestinal tract of humans and animals, but when the commensal relationship with the host is disrupted they can cause a variety of infections (endocarditis, bloodstream infections, urinary tract infections, peritonitis and intra-abdominal abscesses) [5]. Although the increase at the European level (from 8.1% in 2012 to 8.3% in 2015) was not statistically significant, 12 of 26 European countries have reported a significant increase in VRE [5]. Few antimicrobial options are available to treat VRE, including linezolid, quinupristin/dalfopristin and tigecycline.

3.1.3. ESBL-Producing *Enterobacteriaceae* (ESBL)

ESBL-Producing *Enterobacteriaceae* are Gram-negative bacteria that produce an enzyme called “Extended-spectrum β-lactamase”. This enzyme enables bacteria to become resistant to a wide variety of penicillins and cephalosporins [3]. ESBL-producing bacteria (especially *K. pneumoniae* and *E. coli*) predominantly colonise hospitalised individuals and are mainly found in the gastrointestinal tract, skin, oropharynx and upper airways.

In Europe, more than one third of the *K. pneumoniae* isolates reported in 2015 were resistant to at least one antimicrobial group under surveillance (fluoroquinolones, 3rd-generation cephalosporins, aminoglycosides and carbapenems) [5]. The majority of infections caused by *K. pneumoniae* are HCAI and they can spread rapidly between colonised or infected patients via the hands of hospital personnel, leading to nosocomial outbreaks [5].

Regarding ICU-acquired infections, resistance to 3rd-generation cephalosporins was found in 17.3% of *E. coli* isolates, in 43.7% of *Klebsiella spp.* isolates and in 43.5% of *Enterobacter spp.* isolates [25].

The percentage of ESBL-producing isolates resistant to 3rd-generation cephalosporins was high within European countries and combined resistance to more than one antimicrobial group was common [5]. The increase in combined resistance to more antimicrobial groups and the high frequency of ESBL bacteria is increasing the use of carbapenems, thus favouring the further dissemination of carbapenemase-producing bacteria [5].

3.1.4. Carbapenemase-producing *Enterobacteriaceae* (CPE)

The global dissemination of CPE showing extensively-drug resistant phenotypes is one of the most worrying aspects of the ongoing AMR crisis. Carbapenemases are a group of enzymes that can hydrolyze most β-lactams, including carbapenems, leaving quite a few options to treat CPE infections (such as colistin, tigecycline, fosfomycin or new drugs like ceftazidime/avibactam) [5]. Almost 50% of all bloodstream infections caused by CPE result in death [3].

In Europe, there is an increasing trend for carbapenem resistance. In 2015, carbapenem resistance percentages ranged from zero to 61.9 %, with a majority of the countries reporting percentages lower than 1% (including Belgium) [5]. Carbapenem-resistant bacteria (e.g., *K. pneumoniae* and *E. coli)* pose a significant threat to public health worldwide and are associated with higher healthcare costs, prolonged hospital stays, treatment failure and mortality [5].

In ICUs, the high prevalence of carbapenem resistance reflect the challenges of treatment in critically ill patients, a highly vulnerable patient population. In 2016, carbapenem resistance (regarding ICU-acquired infections) was reported in 7.7% of *Klebsiella spp.* isolates, 0.9% of *E. coli* isolates, 1.5% of *Enterobacter spp.* isolates, 27.7% of *P. aeruginosa* isolates and 63.5% of *Acinetobacter baumannii* isolates [25].

3.1.5. *Pseudomonas aeruginosa* (multidrug-resistant)

P. aeruginosa is a common cause of hospital-acquired pneumonia (including ventilator-associated pneumonia), bloodstream and urinary tract infections [5]. Because of its ubiquity,

enormous versatility and intrinsic tolerance to most detergents, disinfectants and antimicrobial compounds, it is difficult to control *P. aeruginosa* in hospital settings [5].

P. aeruginosa is frequently resistant to many classes of antimicrobials. In 2015, multi-drug resistance was common in Europe, with 14.9% of the isolates being resistant to at least three antimicrobial groups and 5.5 % being resistant to all five groups under regular EARS-Net[d] surveillance [5]. High percentages of resistance in *P. aeruginosa* were reported, especially from eastern and south-eastern parts of Europe [5]. Regarding ICU-acquired infections, in 2016, ceftazidime resistance was found in 24.2% of *P. aeruginosa* isolates [25].

3.1.6. *Acinetobacter* spp. (multidrug-resistant)

The most common resistant *Acinetobacter* species is *A. baumannii*, an opportunistic Gram-negative, facultative anaerobic pathogen [2]. The *A. baumannii* group has a limited number of virulence factors, which is why infections due to this bacteria are more likely to occur in critically ill or otherwise debilitated individuals [5]. Therefore, the risks for acquiring a MDR strain of the *A. baumannii* group include prolonged mechanical ventilation, prolonged ICU/hospital stay, exposure to infected or colonised patients, increased invasive procedures, increased disease severity and receipt of broad-spectrum agents, especially 3rd generation cephalosporins, fluoroquinolones and carbapenems.

In 2015, the percentage of MDR *Acinetobacter* isolates in Europe ranged from zero (Belgium and United Kingdom) to 87.0 % (Croatia) [5].

3.2. Strategies to optimize antimicrobial use

Antimicrobial stewardship programs are becoming commonplace in hospitals and they have been correlated to significant reductions in some strains of resistant bacteria and cost savings [2, 3]. Antimicrobial stewardship has two aims: to ensure effective treatment of patients with infection and to minimize collateral damage from antimicrobial use [29]. Effective stewardship ensures that every patient gets the maximum benefit from the antimicrobials, avoids unnecessary harm from side effects and helps preserve the life-saving potential of these drugs for the future [3].

However, improving antimicrobial use in the ICU can be a challenge. First, infection severity often delays withdrawing the antimicrobial treatment; second, the complex decision-making process frequently involves doctors with limited expertise; third, it is difficult to ensure continuity of care by the same medical team 24 hours a day, 7 days a week [30].

[d] European Antimicrobial Resistance Surveillance Network

According to one of the Cochrane reviews [29], the use of an antimicrobial policy leads to improved prescribing practices and reduces the duration of antimicrobial treatment. Also, interventions that are directed to physicians (to improve their antimicrobial prescribing practices) have decreased hospitals length of stay by 1.12 days and have not increased the risk of mortality [29].

To promote antimicrobial stewardship, it is crucial to ensure that all orders have dose, duration and indications; that cultures are collected before starting antimicrobials and that antimicrobial treatment "timeout" is taken to reassess therapy after 48-72h [3]. By 2019, the quality indicators of the BAPCOC strategic plan target the following values: antimicrobials prescription in accordance with local guidelines in at least 90% of cases and antimicrobials indication therapy mentioned in the medical file in at least 90% of cases [31].

Other essential elements of an antimicrobial policy include a stable and restrictive list of antimicrobials in use, treatment guidelines, audit and feedback of prescriptions, surveillance of antimicrobial use, surveillance of bacterial resistance and education at all levels [4].

3.2.1. Rapid identification of patients with infection

The diagnosis of infection in ICU patients and the identification of causative microorganisms and their antibiotic susceptibilities is not easy and yet early, adequate antimicrobial therapy is associated with improved outcomes [15].

There are some factors associated with sepsis. For instance, older patients (> 60 years) have higher predisposition to infections because of the effects of ageing on their immune responses [32]. Estrogens seem to have protective effects on women immune response and cardiovascular functions, while male sex hormones impair cell-mediated immune response, which could explain the greater risk of sepsis in male gender [32]. Also, the risk of sepsis is increased by the presence of at least one of the following comorbidities: renal failure, malignancy, diabetes mellitus, chronic pulmonary disease, congestive heart failure and immunosuppression [32].

In the absence of a gold-standard test for infection, many routine laboratory test results are indicative of inflammation or organ dysfunction. For instance, biomarkers such as C-reactive protein (CRP) or procalcitonin (PCT) may help with the identification of bacterial infections and facilitate therapeutic decisions. One observational study suggested that the CRP cut-off level for infection diagnosis in critically ill patients was 87 mg/L [33]. While a recent meta-analysis showed that CRP cut-off level in predicting mortality range from 114 to 152 mg/L, but the CRP level was only significantly greater in non-survivors beyond 48h [34].

In France, a multicentre randomised controlled trial (RCT), showed that a PCT-guided treatment initiation and discontinuation, in suspected bacterial infections among critically ill patients, provided more antibiotic free days (14.3 vs. 11.6, $p<0.001$), without apparent harm [35]. On the other hand, in a Brazilian RCT, CRP-based algorithm was as useful as PCT-based algorithm in reducing antimicrobial use in septic patients [36]. The debate of which biomarker is better is ongoing and none is specific for infection and all can be altered in other conditions that commonly affect critically-ill patients. But because of its wide availability, good reproducibility and low cost, CRP concentrations remain an attractive biomarker.

Nevertheless, new methods have been developed to improve microbiological analysis, including polymerase chain reaction and mass spectrometry [15]. But, these tests are supplementary to traditional culture-based methods. For instance, in a French case-control study [37], the usefulness of the betaLACTA® (a chromogenic diagnostic device, which detects resistance of Gram-negative bacteria to 3rd generation cephalosporins in less than 20 minutes) was evaluated in critically ill patients. The time between initiation of inadequate antimicrobial treatment and its escalation was 50.5 hours in controls, significantly reduced to 27 hours in cases ($p < 0.01$). The betaLACTA® test also increased antibiotic appropriateness (98% vs. 77%, $p < 0.01$).

Appropriate microbiologic cultures should be collected before starting antimicrobial therapy in patients with suspected sepsis, because antimicrobial therapy can alter the results [38]. Samples from all sites considered to be potential sources of infection should be collected for microbiologic tests in patients with sepsis and septic shock (blood, cerebrospinal fluid, urine, wounds, respiratory secretions and other body fluids), but only if doing so results in no substantial delay in the start of antimicrobials [38].

3.2.2. Empiric Treatment

In the ICU, decision regarding empiric antimicrobial therapy is frequently based on a judgment that the infecting microorganism may be MDR and, thus, broad-spectrum combination therapy is frequently used [15]. Sepsis guidelines also recommend empiric broad-spectrum therapy with one or more antimicrobials to cover all likely pathogens (including bacteria and potentially fungus or virus) [38].

There is some debate regarding the potential benefits of combination versus monotherapy in the empiric management of infection in ICU patients. Observational data showed that initial regimens combining a broad-spectrum β-lactam and an aminoglycoside increased the proportion of appropriately treated patients compared with monotherapy [30]. The disadvantage of combination therapy was increased drug toxicity (especially within

aminoglycosides use), but this is usually an acceptable risk among critically ill patients, which are more susceptible to MDR organisms [15]. Sepsis guidelines suggest that combination therapy should not be routinely used for ongoing treatment of most other serious infections, including bacteremia and sepsis without shock [38].

3.2.3. Pharmacokinetics / Pharmacodynamics

In order to optimize the relationship between antimicrobial dose and efficacy, pharmacokinetics (PK) and pharmacodynamics (PD) characteristics need to be incorporated. Antimicrobials can be distinguish by their killing mechanism: time-dependent or concentration-dependent. With time-dependent antimicrobials (e.g. β-lactams and glycopeptides), maximum bacterial killing occurs when the drug concentration persistently exceeds the minimum inhibitory concentration (MIC) of the pathogen; on the other hand, with concentration-dependent antimicrobials, (e.g. aminoglycosides and fluoroquinolones) maximum bacterial killing occurs when the peak drug concentration exceeds several times the MIC [15].

ICU patients have altered PK secondary to increased volume of distribution and decreased elimination. This can result in insufficient serum aminoglycosides/β-lactam concentrations when standard doses are administered, which emphasizes the need to carefully monitor antimicrobials levels [30]. In a prospective, multinational point-prevalence study, 16% of patients did not maintained PK/PD target-free antibiotic concentration above MIC [39].

Strategies that optimize antimicrobials therapy are required in most ICU patients in order to reach the PK/PD targets (e.g. use of higher than usually recommended antibiotic doses, continuous or extended infusions and daily therapeutic drug monitoring) [30].

3.2.4. De-escalation treatment and decision to stop

For many ICU patients with infections, empiric antimicrobial therapy can be narrowed once pathogen identification and sensitivities are established and/or adequate clinical improvement is noted [38]. It seems that only 30% of all antimicrobials are used for definitive therapy in which the susceptibility patterns for the infection-associated pathogen are known [15].

Longer antimicrobial courses are associated with selection and spread of MDR pathogens, increased risks of toxicity and higher costs, whereas courses that are too short risk inadequate bacterial eradication and relapse [15]. Current sepsis guidelines suggest that an antimicrobial treatment duration of 7 to 10 days is adequate for most serious infections [38]. Longer courses are appropriate in patients who have a slow clinical response, undrainable foci

of infection, bacteremia with *S. aureus*, some fungal and viral infections, or immunologic deficiencies, including neutropenia [38].

Shorter courses are appropriate in some patients, particularly those with rapid clinical resolution following effective source control of intra-abdominal or urinary infection and those with anatomically uncomplicated pyelonephritis [38]. Biomarkers may assist in the decision to stop antimicrobial therapy.

4. Research question

Studies on antimicrobial consumption contribute to rationalize drug use by describing the patterns, detecting early signs of irrational drug prescription and identifying interventions to improve antimicrobial prescription. The *CHU Brugmann* follows the recommendations from the BAPCOC and antimicrobials consumption is evaluated using the ATC/DDD system.

The analysis of antimicrobials consumption in the three units of critical care of the *CHU Brugmann* consist of DDD/1000 patients/day. With this data it is possible to evaluate the global consumption of each antimicrobial group and assess the evolution over time (also to compare with national average). Nevertheless, this type of analysis does not give information regarding the characteristics of the patients and the appropriateness of antimicrobial therapy.

So, the research question for this study was the following:

- ***What is the impact of inadequate antimicrobial treatment on 30-day hospital mortality after ICU admission among patients with infections?***

With this study, it is hoped to contribute with updated data that will help improving the antimicrobial stewardship program in the *CHU Brugmann* and, in some way, contribute to the reduction of AMR. In this sense, the following objectives have been defined:

- To estimate the prevalence and patterns of patients with inadequate antimicrobial therapy in the ICUs;
- To evaluate the relationship between inadequate antimicrobial treatment of infections and 30-day hospital mortality after ICU admission.
- To evaluate the relationship of patient's characteristics, namely age, gender, type of admission, comorbid conditions with the outcome 30-day hospital mortality after ICU admission.

5. Methods

This was an observational study conducted prospectively in an urban university-affiliated teaching hospital: *CHU Brugmann* (850 beds) in Brussels. During a 3-month period (January 2018 to March 2018), all patients admitted to the three ICUs (27 beds) were potentially eligible for this study. The following criteria were used to include (or exclude) patients in the study:

Inclusion criteria

- Patients admitted to the ICU from the 01/01/2018 until the 31/03/2018 and receiving antimicrobial therapy to treat probable/definite infections.

Exclusion criteria

- Age < 18 years;
- Patients with ICU stay of less than 24 hours;
- Patients without antimicrobial treatment during their ICU stay.
- Nominative surgical antibiotic prophylaxis (hospital internal protocol).
- Long-term antimicrobial therapy used as medical prophylaxis (e.g. trimethoprim-sulfamethoxazole used to prevent *Pneumocystis* pneumonia).
- Antimicrobial therapy used as prokinetic therapy (e.g. erythromycin).
- ICU readmissions (if the patient was already included in the study regarding his previous ICU stay).
- Patients admitted to the ICU during the study period, but having antimicrobial therapy prescribed after the 31/03/2018.
- Patients transferred to the ICU temporarily due to a lack of available beds in the post-anesthesia care unit (PACU).

Daily reviews of ICU patients charts were made. Data was collected from admission sheets, medical and nursing records, medication charts, microbiological and radiological testing reports. No interference with the medical team decisions regarding the patient treatment was made. The ICU clinicians were blind to the study objectives, with the exception of the 2 heads of the department.

Assistant from one of the hospital infectious disease specialist was asked in order to evaluate the appropriateness of the antimicrobial therapy.

For all study patients, the following characteristics were prospectively recorded: age, gender, admission diagnosis, the presence of comorbidities, risk factors for infection (e.g. presence of invasive devices), length of ICU stay, severity of illness at admission measured by the Acute Physiology and Chronic Health Evaluation (APACHE II), SOFA scores and CRP

levels. Infection data was also recorded: diagnosis, source of infection (community, HCAI or ICU-acquired) and microbiological documentation.

SOFA scores were calculated for each day by using the worst value of that day. APACHE II score was only calculated for the admission day (worst value of the first 24h). Because measuring the Glasgow Coma Scale (GCS) in the sedated population can lead to incorrect scoring, when possible, assessment of the GSC prior to sedation was made and then this score was used until off sedation for an adequate period of time to clear sedative effects. APACHE II scores and SOFA scores were calculated using a program created with Windows Excel.

The data collected was recorded on individual forms that were created for the purpose (see ***Annex 1***). This instrument of data collection was based on forms from other studies: EPIC III[e] study (extended prevalence of infection in the intensive care) and Global PPS[f] 2017 (global point prevalence survey of antimicrobial consumption and resistance). In order to test and improve the instrument of data collection, a pilot study was conducted during four weeks (between November and December 2017) in one of the three ICUs of the hospital.

This research was conducted in accordance with the Declaration of Helsinki and institutional standards. The study protocol was approved by the Ethics Committee of the hospital (see ***Annex 2***). Due to the non-interventional, observational nature of the study, written informed consent was not required for enrolment in the study. Data collected was treated confidentially and an anonymized computer database was created to compile information.

No sample size calculation was made, due to the fact that this was a clinical series limited by a 3-month period. This limited time was required for completing the master thesis during the academic year.

To know if the patient had at least one episode of inadequate antimicrobial treatment, each patient was followed-up until ICU discharge. During ICU stay, if an episode of inadequate antimicrobial treatment was observed, patient would then be included in the "inadequate antimicrobial treatment" group.

The primary outcome measure was 30-day hospital mortality rate after ICU admission (all-cause). Patients discharged alive from the hospital before 30 days were considered as alive on the 30th day.

[e] https://www2.intensive.org/epic3/Doc/EPIC_III_-_eCRF.pdf
[f] http://www.global-pps.com/

5.1. Definitions

Inadequate antimicrobial treatment of an infection was defined as the microbiological documentation of infection (i.e., a positive culture result) that was not effectively treated at the time the causative microorganism and its antibiotic susceptibility were known. Microbiology result could be any culture and/or sensitivity result from a relevant clinical specimen as well as any other laboratory result like for example Legionella Urinary Antigen.

So, inadequate antimicrobial treatment included the absence of antimicrobial agents covering a specific class of microorganisms (e.g., absence of therapy for atypical pneumonia caused by *Chlamydia pneumoniae*), the administration of an antimicrobial agent to which the microorganism responsible for the infection was resistant (e.g., empiric treatment with oxacillin for bacteraemia subsequently attributed to MRSA) or a delay in starting appropriate antimicrobial treatment [40, 41]. Adequate antimicrobial treatment was considered if the chosen drug covered a particular infection and matched with the *in vitro* susceptibility. Antimicrobials dose and duration of the therapy was not judged. The classification of inadequate antimicrobial treatment used in this study was adapted from Kollef and colleagues [40].

Acquisition of a healthcare-associated infections (HCAI) were defined following current definitions [42]. It included at least one of the following criteria:

- Infection evident ≥ 48h after hospital admission;
- Infection in a patient receiving haemodialysis or intravenous chemotherapy in the 30 days prior to hospital admission;
- Infection in a patient who had been admitted to an acute care hospital for 2 or more days in the 90 days prior to hospital admission;
- Infection in a patient residing in a nursing home or a long-term care facility.

The definition used for ICU-acquired infections (a subgroup of HCAI) was the following: infections occurring ≥ 48 hours in the ICU. With admission day being counted as day 1, infections with onset from day 3 onwards were included in this subgroup [25].

5.2. Statistical analysis

Statistical analysis were performed using *IBM SPSS Statistics*® version 23. Categorical variables were described as numbers and proportions. Continuous variables were described as mean and standard deviation (statistical power); median and inter-quartile range were also presented for variables not normally distributed (robustness).

Firstly, a descriptive analysis was made, comparing the two groups: “inadequate antimicrobial treatment” vs. “adequate antimicrobial treatment”. Differences between the two

groups were assessed using the Student's t-test for continuous variables normally distributed. The Mann-Whitney test was used to compare differences between groups when the variable was not normally distributed. The Pearson chi-square or Fisher's exact tests were used to compare categorical variables. All comparison were unpaired and all tests of significance were two-tailed. The statistical significance threshold was set at $p<0.05$.

Secondary analysis assessed the relationship between the outcome 30-day hospital mortality after ICU admission (dependent variable) and the exposure factor antimicrobial treatment (adequate vs. inadequate). Multiple logistic regression analysis was performed to control for the effects of confounding variables. Variables were included in the multivariate analysis if they were associated with the dependent variable on the univariate analysis with a p-value cut-off point of 0.25 [43]. Covariates included in the analysis were the following:

- Patient's age (<60, 60-74, ≥75);
- Gender (male vs. female);
- Admission type (surgical vs. medical);
- Preexisting comorbidities;
- APACHE II score (<25 vs. ≥ 25). This score is assessed on a scale from 0 to 71, with higher scores indicating an increased risk of death [44]; a score of ≥ 25 has been used as a cut-off point to identify patients at a higher risk for death [45]);
- SOFA score (<7 vs. ≥ 7). This score range from 0 to 24, with higher scores indicating greater severity of illness [22]. According to other authors, SOFA score best cut-off point to predict 30-day hospital mortality is ≥ 7 [23].
- C-reactive protein level according to 3 intervals (<100 mg/l, 100-199 mg/l, ≥200 mg/l).
- Primary source of infection (community-acquired vs. healthcare-associated vs. ICU-acquired).

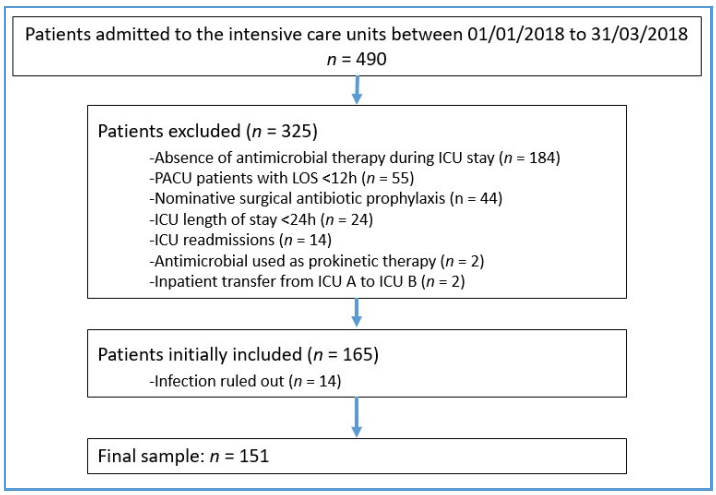
Interaction between covariates was also assessed and multicollinearity among variables was evaluated using Pearson correlation coefficient.

6. Results

A total of 165 consecutive eligible patients were initially included, but infection was ruled out for 14 patients and the antimicrobial therapy was then discontinued (see ***Figure 3***). These 14 patients were then excluded from the impact analysis of antimicrobial treatment of probable/definite infections (final sample: *n*=151).

The mean age of the 151 patients included in the study was 66.6 ±15.6 years (range, 30 to 96 years); the mean APACHE II score was 22.6 ±8.7 (range, 6 to 46); regarding the gender, 57 (37.7%) patients were women and 94 (62.3%) were men; 127 (84.1%) patients were admitted to the ICU with a medical diagnosis, whereas 24 (15.9%) patients were admitted to the ICU following a surgical procedure.

Figure 3 *– Details regarding the patients excluded from the study.*



ICU = intensive care unit.
PACU = post-anaesthesia care unit.

6.1. Inadequate Antimicrobial Treatment

The baseline characteristics of the two groups (adequate antimicrobial treatment vs. inadequate antimicrobial treatment) are presented in the ***Table 3***. Fifty-three patients initially received inadequate antimicrobial treatment during their ICU stay. This represented more than one third (35.1%) of the patients for whom there was a probable/definite infection while in the ICU.

There were no significant differences in the baseline characteristics between the two groups, including age, gender, place before ICU admission and pre-existing comorbidities. The distribution of primary ICU admission diagnosis was not statistical different (p=0.084), but the most common causes of admission in the “adequate antimicrobial treatment” group were respiratory disorders (43.9% vs. 26.4%), while cardiovascular disorders were more frequently in the “inadequate antimicrobial treatment” group (34.0% vs. 23.5%).

Table 3 – Demographic and clinical characteristics of study patients, stratified according to adequate or inadequate antimicrobial treatment.

	Adequate Antimicrobial Treatment (n=98)	Inadequate Antimicrobial Treatment (n=53)	p-value
Age (years)			
Mean ± standard deviation	66.7 ± 15.5	66.5 ± 15.8	0.94
Gender			0.29
Female – no. (%)	40 (40.8%)	17 (32.1%)	
Male – no. (%)	58 (59.2%)	36 (67.9%)	
Type of admission			0.88
Medical – no. (%)	81 (82.7%)	46 (86.8%)	
Elective surgery – no. (%)	7 (7.1%)	3 (5.7%)	
Emergency surgery – no. (%)	10 (10.2%)	4 (7.5%)	
Place before ICU admission			0.10
Emergency department/Home – no. (%)	34 (34.7%)	29 (54.7%)	
Emergency department/Nursing Home – no. (%)	6 (6.1%)	4 (7.5%)	
Hospital floor – no. (%)	38 (38.8%)	11 (20.8%)	
Operating room/recovery – no. (%)	17 (17.3%)	7 (13.2%)	
Other hospital – no. (%)	3 (3.1%)	2 (3.8%)	
Primary ICU admission diagnosis			0.084
Surveillance post-surgery – no. (%)	12 (12.2%)	4 (7.5%)	
Respiratory disorders – no. (%)	43 (43.9%)	14 (26.4%)	
Cardiovascular disorders – no. (%)	23(23.5%)	18 (34.0%)	
Digestive/Liver disorders – no. (%)	8 (8.2%)	10 (18.9%)	
Other medical disorders – no. (%)	12 (12.2%)	7 (13.2%)	
Preexisting condition			
Chronic heart disease – no. (%)	38 (38.8%)	21 (39.6%)	0.92
Chronic arterial hypertension – no. (%)	52 (53.1%)	28 (52.8%)	0.98
Diabetes Mellitus – no. (%)	34 (34.7%)	15 (28.3%)	0.42
COPD – no. (%)	29 (29.6%)	12 (22.6%)	0.36
Cancer – no. (%)	15 (15.3%)	7 (13.2%)	0.73
Chronic renal disease – no. (%)	20 (20.4%)	8 (15.1%)	0.42
Immunocompromised condition – no. (%)	8 (8.2%)	8 (15.1%)	0.19
Liver cirrhosis (Child B/C) – no. (%)	6 (6.1%)	3 (5.7%)	>0.99

P-values for continuous variables were calculated using Students t-test and for binary variables the Pearson chi-square or Fisher's exact tests were used.

COPD = chronic obstructive pulmonary disease; **ICU** = intensive care unit.

Surveillance post-surgery: cardiothoracic surgery (n=4); gastrointestinal/biliary tract surgery (n=5); skin and soft tissue surgery (n=3); other surgery (n=4). **Respiratory disorders**: pneumonia (n=33); acute respiratory failure on chronic pulmonary disease (n=18); acute respiratory distress syndrome (ARDS) (n=6). **Cardiovascular disorders**: shock (n=21); cardiac arrest (n=10); major arrhythmia/myocardial infarction (n=5); other cardiovascular disorders (n=5). **Digestive/Liver disorders**: acute abdomen (n=8); gastrointestinal tract bleeding (n=5); liver failure (n=3); pancreatitis (n=2). **Other disorders**: metabolic disorders (n=9); neurological disorders (n=7); renal failure (n=2); peripartum bleeding (n=1).

Mean APACHE II score at admission was higher in the group with "inadequate antimicrobial treatment" (24.0 vs. 21.8), but this difference was not statistically significant (p=0.13). Similar, there were no significant differences regarding mean SOFA scores (first week highest score) between the two groups. However, when SOFA score (first week highest score) was stratified into two groups the proportions were significantly different: patients in "inadequate antimicrobial treatment" group were more likely to have SOFA score ≥ 7 than patients in "adequate antimicrobial treatment" (73.6% vs. 52.0%, p=0.010).

The highest CRP level during the first week of ICU stay also showed a significant difference between the two groups: median 236.4 mg/L in the "inadequate antimicrobial group" vs. 183.5 mg/L in the "adequate antimicrobial group" (p=0.003).

Patients receiving "inadequate antimicrobial treatment" were statistically more likely to undergo mechanical ventilation (69.8% vs. 36.7%, p<0.001), central vein catheterization (92.5% vs. 67.3%, p=0.001), nasogastric intubation (84.9% vs. 44.9%, p<0.001) and urinary tract catheterization (100% vs. 83.7%, p=0.002).

Respiratory tract (including ventilator-acquired pneumonia) was overall the most common site of initial infection in both groups (61.2% vs. 62.3%), accounting nearly two-thirds of infected patients. Community-acquired infections were more common in the "adequate antimicrobial treatment" group (46.9% vs. 30.2%).

The different types of inadequate antimicrobial treatment are shown in ***Table 4***. The most common was the presence of resistant Gram-negative bacteria not appropriately treated by the prescribed antimicrobial regimen (54.7%); whereas, 26.4% patients were classified as having a resistant Gram-positive bacterial infection.

Table 4 *– Inadequate antimicrobial treatment classification.*

	n (%)
Gram-negative bacteria - CPE resistant to administered antimicrobial	3 (5.7%)
Gram-negative bacteria - ESBL resistant to administered antimicrobial	2 (3.8%)
Other Gram-negative bacteria resistant to administered antimicrobial	24 (45.3%)
Gram-positive bacteria - MRSA resistant to administered antimicrobial	4 (7.5%)
Gram-positive bacteria - *Clostridium difficile* not being treated	1 (1.9%)
Other Gram-positive bacteria resistant to administered antimicrobial	9 (17.0%)
Candida spp. not being treated	3 (5.7%)
Mycobacterium tuberculosis not being treated	1 (1.9%)
No antimicrobial treatment had been initiated	6 (11.3%)
TOTAL	53

Classification adapted from [40].

N.B: Inadequate antimicrobial treatment of an infection was defined as the microbiological documentation of infection (i.e., a positive culture result) that was not effectively treated at the time the causative microorganism and its antibiotic susceptibility were known.

CPE = Carbapenemases-producing *Enterobacteriaceae*; **ESBL** = Extended-spectrum β-lactamase; **MRSA** = Methicillin-resistant *Staphylococcus aureus*; **spp**. = species.

6.2. Patients outcomes

Comparisons of clinical outcomes between patients with "adequate antimicrobial treatment" and patients with "inadequate antimicrobial treatment" are shown in ***Table 5***. The 30-day hospital mortality (all causes) after ICU admission occurred in 40 of the 151 patients (26.5%) in the two groups combined. The occurrence of this outcome was higher in the "inadequate antimicrobial treatment" group (32.1% vs. 23.5%, p=0.25), but this result was not statistically significant. The 30-day ICU mortality rate (all causes) was also higher in the "inadequate antimicrobial treatment" group (26.4% vs. 18.4%, p=0.25). On the other hand, the ICU length of stay showed a significant difference between the two groups. The median ICU length of stay was 7.4 days in the "inadequate antimicrobial treatment" group, as compared with 4.8 days in the "adequate antimicrobial group" (p=0.001). Also, there were significantly fewer patients with hospital discharge at 30-days after ICU admission in the "inadequate antimicrobial treatment" group (20.8% vs. 48.0%, p=0.001).

Table 5 *– Comparisons of illness severity scores, biological characteristics and clinical outcomes between patients with adequate antimicrobial treatment and patients with inadequate antimicrobial treatment.*

	Adequate Antimicrobial Treatment (n=98)	Inadequate Antimicrobial Treatment (n=53)	p-value
APACHE II score - *admission day*			
Mean ± standard deviation	21.8 ± 9.2	24.0 ± 7.5	0.13
APACHE II score - *admission day* (stratified)			0.064
APACHE II score < 25 – no. (%)	65 (66.3%)	27 (50.9%)	
APACHE II score ≥ 25 – no. (%)	33 (33.7%)	26 (49.1%)	
SOFA score			
Admission day - mean ± standard deviation	6.8 ± 3.5	7.5 ± 3.4	0.26
First week highest score - mean ± standard deviation	7.6 ± 3.9	8.8 ± 3.8	0.063
SOFA score (first week highest score)			**0.010**
SOFA score < 7 – no. (%)	47 (48.0%)	14 (26.4%)	
SOFA score ≥ 7 – no. (%)	51 (52.0%)	39 (73.6%)	
CRP (mg/L) – *admission day*			
Mean ± standard deviation	128.8 ± 135.7	134.3 ± 127.3	
Median [interquartile range]	84.6 [16.6 – 207.4]	87.8 [20.4 – 203.1]	0.64
CRP - *first week highest level*			
Mean ± standard deviation	198.5 ± 137.2	265.8 ± 130.4	
Median [interquartile range]	183.5 [84.4 – 294.2]	236.4 [179.8 – 363.9]	**0.003**
CRP - *first week highest level* (stratified)			**0.008**
CRP < 100 mg/L – no. (%)	30 (30.6%)	5 (9.4%)	
CRP 100 – 199 mg/L – no. (%)	26 (26.5%)	14 (26.4%)	
CRP ≥ 200 mg/L – no. (%)	42 (42.9%)	34 (64.2%)	
Use of invasive medical devices			
Mechanical ventilation – no. (%)	36 (36.7%)	37 (69.8%)	**<0.001**
Tracheostomy – no. (%)	2 (2.0%)	2 (3.8%)	0.61
Urinary tract catheterization – no. (%)	82 (83.7%)	53 (100.0%)	**0.002**
Nasogastric intubation – no. (%)	44 (44.9%)	45 (84.9%)	**<0.001**
ECMO or ECCO2R – no. (%)	2 (2.0%)	5 (9.4%)	0.052
Central vein catheterization – no. (%)	66 (67.3%)	49 (92.5%)	**0.001**
Arterial catheterization – no. (%)	91 (92.9%)	51 (96.2%)	0.40
CRRT – no. (%)	15 (15.3%)	8 (15.1%)	0.97
Conventional Hemodialysis – no. (%)	8 (8.2%)	1 (1.9%)	0.16
Surgical drain: none – no. (%)	76 (77.6%)	35 (66.0%)	0.13
Surgical drain: thorax – no. (%)	7 (7.1%)	9 (17.0%)	0.061
Surgical drain: abdominal – no. (%)	10 (10.2%)	10 (18.9%)	0.13
Source or site of initial infection			0.21
Respiratory tract – no. (%)	60 (61.2%)	33 (62.3%)	
Abdomen – no. (%)	10 (10.2%)	7 (13.2%)	
Urinary tract – no. (%)	6 (6.1%)	4 (7.5%)	
Bloodstream infection – no. (%)	3 (3.1%)	4 (7.5%)	
Skin and soft tissue – no. (%)	3 (3.1%)	3 (5.7%)	
Surgical site infection – no. (%)	3 (3.1%)	1 (1.9%)	
Other – no. (%)	13 (13.3%)	1 (1.9%)	
Primary infection – mode of acquisition			0.056
Community-acquired infections – no. (%)	46 (46.9%)	16 (30.2%)	
Healthcare-associated infections – no. (%)	47 (48.0%)	30 (56.6%)	
ICU-acquired infections – no. (%)	5 (5.1%)	7 (13.2%)	
Positive microbiologic culture – no. (%)	59 (60.2%)	53 (100%)	**<0.001**
Primary outcome			
30-day hospital mortality after ICU admission – no. (%)	23 (23.5%)	17 (32.1%)	0.25
Secondary outcomes			
30-day ICU mortality – no. (%)	18 (18.4%)	14 (26.4%)	0.25
ICU length of stay (days)			
Mean ± standard deviation	6.6 ± 5.8	13.9 ± 15.0	
Median [interquartile range]	4.8 [3.0 – 8.0]	7.4 [3.9 – 16.0]	**0.001**
30-day hospital discharge after ICU admission – no. (%)	47 (48.0%)	11 (20.8%)	**0.001**
30-day ICU readmission – no. (%)	4 (4.1%)	6 (11.3%)	0.10

APACHE II score = Acute Physiology and Chronic Health Evaluation; scores range from 0 to 71, with higher scores indicating an increased risk of death; **CRP** = C-reactive protein; **CRRT** = continuous renal replacement therapy; **ECMO** = extracorporeal membrane oxygenation; **$ECCO_2R$** = extracorporeal carbon dioxide removal; **ICU** = intensive care unit; **ICU readmission**: censored at 30 days after ICU first admission; **SOFA score** = sequential organ failure assessment; scores range from 0 to 24, with higher scores indicating more severe illness.

P-values for continuous variables were calculated using Students t-test (except for the variables that were not normally distributed for which the Mann-Whitney test was used). For binary variables the Pearson chi-square test or Fisher's exact test were used.

The 30-day hospital mortality rates (after ICU admission) for patients classified as having a resistant Gram-negative bacteria (n=28; mortality 34.5%) and resistant Gram-positive bacteria (n=14; mortality 28.6%) were also not statistically different from the mortality rates for the remaining patients included in the study (n=108; mortality 24.1%, p = 0.49).

6.2.1. Variables associated with 30-day hospital mortality after ICU admission

Multiple logistic regression demonstrated that inadequate antimicrobial treatment was not significantly associated with hospital mortality (OR=2.61; 95% CI, 0.71 to 9.68; p=0.15) (***Table 7***). APACHE II score (<25 vs. ≥25), SOFA score (<7 vs. ≥7), primary source of infection (CAI vs. HCAI vs. ICU-acquired infections) and having chronic arterial hypertension as pre-existing comorbidity were identified as independent factors associated with 30-day hospital mortality after ICU admission. An interaction was also included in the multivariate analysis, because a significant interaction effect was present with the following binary factors: *APACHE II score (<25 vs. ≥25) * Antimicrobial treatment*. This interaction variable was significantly negative.

The odds of 30-day hospital mortality were almost 6 times higher among patients with APACHE II score ≥ 25 compared with patients who had APACHE II score < 25 (OR: 5.86; 95% CI, 1.61 to 21.38; p=0.007) (if all other variables were kept constant). Also, the probability of hospital mortality for patients having a SOFA score ≥7 (first week highest score) was more than 3 times higher when compared to patients with SOFA score < 7 (OR: 3.55; 95% CI, 1.08 to 11.64; p=0.036) (if all other variables were kept constant).

The adjusted OR regarding the primary source of infection had community-acquired infection (CAI) as referent. Meaning that the odds of 30-day hospital mortality for patients having a HCAI was 4 times higher than for patients having a CAI, while the odds of hospital mortality for patients with an ICU-acquired infection was almost 2 times higher than for patients having a CAI (if all other variables were kept constant).

Table 6 *- Variables associated with 30-day hospital mortality after ICU admission among patients with infection (n=151), using multiple logistic regression.*

	No. of Patients	No. of Deaths (%)	Univariate Analysis (*) OR [95% CI]	p-value	Multivariate Analysis (**) OR [95% CI]	p-value
EXPOSURE VARIABLE						
Adequate antimicrobial treatment	98	23 (23.5)	Reference		Reference	
Inadequate antimicrobial treatment	53	17 (32.1)	1.54 [0.73-3.24]	0.25	2.61 [0.71-9.68]	0.15
COVARIATES						
Age				0.24		0.22
< 60 years	45	11 (24.4)	Reference		Reference	
60 – 74 years	54	11 (20.4)	0.79 [0.31-2.04]		0.38 [0.09-1.59]	
≥ 75 years	52	18 (34.6)	1.68 [0.67-3.98]		0.94 [0.27-3.31]	
Gender				0.12		0.33
Female	57	11 (19.3)	Reference		Reference	
Male	94	29 (30.9)	1.87 [0.85-4.11]		1.63 [0.61-4.38]	
Admission type				0.10		0.37
Surgical	24	3 (12.5)	Reference		Reference	
Medical	127	37 (29.1)	2.88 [0.81-10.24]		1.94 [0.46-8.18]	
Preexisting condition						
Chronic heart disease				0.37		
No	92	22 (23.9)	Reference			
Yes	59	18 (30.5)	1.40 [0.67-2.91]			
Chronic arterial hypertension				0.078		**0.036**
No	71	14 (19.7)	Reference		Reference	
Yes	80	26 (32.5)	1.96 [0.93-4.15]		3.01 [1.08-8.42]	
Diabetes Mellitus				0.69		
No	102	26 (25.5)	Reference			
Yes	49	14 (28.6)	1.17 [0.55-2.51]			
COPD				0.38		
No	110	27 (24.5)	Reference			
Yes	41	13 (31.7)	1.43 [0.65-3.14]			
Cancer				0.26		
No	129	32 (24.8)	Reference			
Yes	22	8 (36.4)	1.73 [0.67-4.51]			
Chronic renal disease				0.22		0.88
No	123	30 (24.4)	Reference		Reference	
Yes	28	10 (35.7)	1.72 [0.72-4.13]		0.92 [0.29-2.88]	
Immunocompromised condition				0.65		
No	135	35 (25.9)	Reference			
Yes	16	5 (31.3)	1.30 [0.42-4.00]			
Liver cirrhosis (Child B/C)				0.22		0.56
No	142	36 (25.4)	Reference		Reference	
Yes	9	4 (44.4)	2.36 [0.60-9.25]		1.75 [0.26-11.52]	
APACHE II score (admission day)				0.001		**0.007**
APACHE II < 25	92	15 (16.3)	Reference		Reference	
APACHE II ≥ 25	59	25 (42.4)	3.78 [1.77-8.04]		5.86 [1.61-21.38]	
SOFA score (1st week highest score)				<0.001		**0.036**
SOFA < 7	61	6 (9.8)	Reference		Reference	
SOFA ≥ 7	90	34 (37.8)	5.57 [2.17-14.31]		3.55 [1.08-11.64]	
C-reactive protein (1st week highest level)				0.32		
< 100 mg/L	35	6 (17.1)	Reference			
100 – 199 mg/L	40	13 (32.5)	2.33 [0.77-6.99]			
≥ 200 mg/L	76	21 (27.6)	1.85 [0.67-5.08]			
Primary source of infection				0.019		**0.018**
Community-acquired infections	62	9 (14.5)	Reference		Reference	
Healthcare-associated infections	77	28 (36.4)	3.37 [1.44-7.84]		4.37 [1.54-12.35]	
ICU-acquired infections	12	3 (25.0)	1.96 [0.44-8.67]		1.83 [0.30-11.25]	
INTERACTION						
APACHE II score * Antimicrobial treatment					0.13 [0.02-0.77]	**0.025**
INTERACTION: subgroup analysis						
Apache II < 25 and Antimicrobial treatment				0.032		
Adequate antimicrobial treatment	65	7 (10.8)	Reference			
Inadequate antimicrobial treatment	27	8 (29.6)	3.49 [1.12-10.90]			
Apache II ≥ 25 and Antimicrobial treatment				0.29		
Adequate antimicrobial treatment	33	16 (48.5)	Reference			
Inadequate antimicrobial treatment	26	9 (34.6)	0.56 [0.20-1.62]			

APACHE II = Acute Physiology and Chronic Health Evaluation II score, range from 0 to 71, with higher scores indicating an increased risk of death; **CAI** = community-acquired infection; **COPD** = chronic obstructive pulmonary disease; **HCAI** = healthcare-associated infection; **ICU** = intensive care unit; **OR** = odds ratio; **SOFA** = sequential organ failure assessment, score range from 0 to 24, with higher scores indicating greater severity of illness.

(*) Variables were included in the multivariate analysis if they were associated with the dependent variable on the univariate analysis with a p-value cut-off point of 0.25.

(**) The model fit was good with a Nagelkerke R^2 value of 0.36, indicating that more than a third of the variability in the model could be explained by the predictors selected. However, the limited sample size has resulted in relatively large 95% CI of odds ratio for some variables. Multicollinearity assessment showed that none of the variables was strongly correlated (r <0.95).

6.3. Infection: types, causes and treatment

Overall, 408 clinical pathogens were identified by microbiological tests. Clinical infectious diseases were supported by positive cultures in 112 (74.2%) patients. In the "adequate antimicrobial treatment group" 60.2% patients had positive microbiologic culture vs. 100% of patients in the "inadequate antimicrobial group" ($p<0.001$). For more information regarding the frequency and distribution of the pathogens associated with clinically recognized CAI, HCAI and ICU-acquired infections see ***Annex 3***.

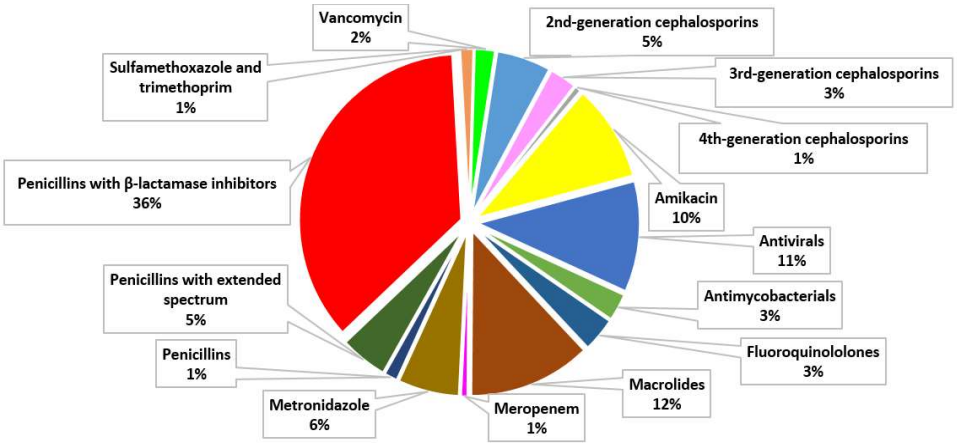
E. coli was the most common Gram-negative pathogen isolated from patients in both groups: inadequate antimicrobial therapy group 24.5% (n = 13) and adequate antimicrobial therapy group 9.2% (n = 9). Regarding Gram-positive bacteria, MSSA was the most frequent isolated pathogen in both groups: inadequate antimicrobial therapy group 35.8% (n = 19) and adequate antimicrobial therapy group 13.3% (n = 13). The prevalence of Influenza virus was also important, especially among patients with community-acquired pneumonia. The prevalence of the most threatening bacteria was the following: 6 patients (4.0%) with ESBL positive isolates, 4 patients (2.6%) with CPE positive isolates and 2 patients (1.3%) with P. aeruginosa multidrug resistant.

Globally, 62 (41.1%) patients had a CAI as primary type of infection, 77 (51.0%) patients developed a HCAI and 12 (7.9%) patients had an ICU-acquired infection. Respiratory tract infections were the most frequent ones (61.2% vs. 62.3% in the "inadequate antimicrobial treatment" group), but these data only concerned the source of initial infection (some patients had multiple infection sources).

Among the 151 patients with infection, there were 390 antimicrobials prescriptions issued. Antibiotics accounted for 350 (89.7%), antivirals for 27 (6.9%), antifungals for 7 (1.8%) and antimycobacterials for 6 (1.5%). Globally, the two most commonly prescribed antimicrobials were penicillins with a β-lactamase inhibitor: amoxicillin/clavulanic acid (20.0%) and piperacillin/tazobactam (13.3%). The 3rd and 4th most commonly prescribed antimicrobials were amikacin (aminoglycoside) with 8.2% and clarithromycin (macrolide) with 6.2%.

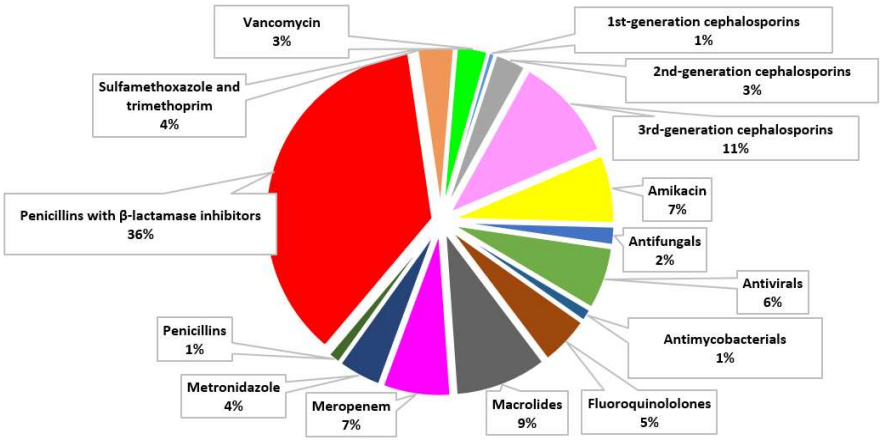
The ***Figure 4*** illustrates the proportion of prescribed antimicrobials for CAI. The most prescribed class of antimicrobials for CAI were penicillins with a β-lactamase inhibitor (36.1%), of which the majority (79.2%) was amoxicillin/clavulanic acid while the piperacillin/tazobactam accounted for the other 20.8%. Macrolides were the second most prescribed class with 12.2% (mainly clarithromycin), followed by antivirals with 10.9% (essentially oseltamivir).

Figure 4 *– Proportion of prescribed antimicrobials for systemic use in community-acquired infections.*



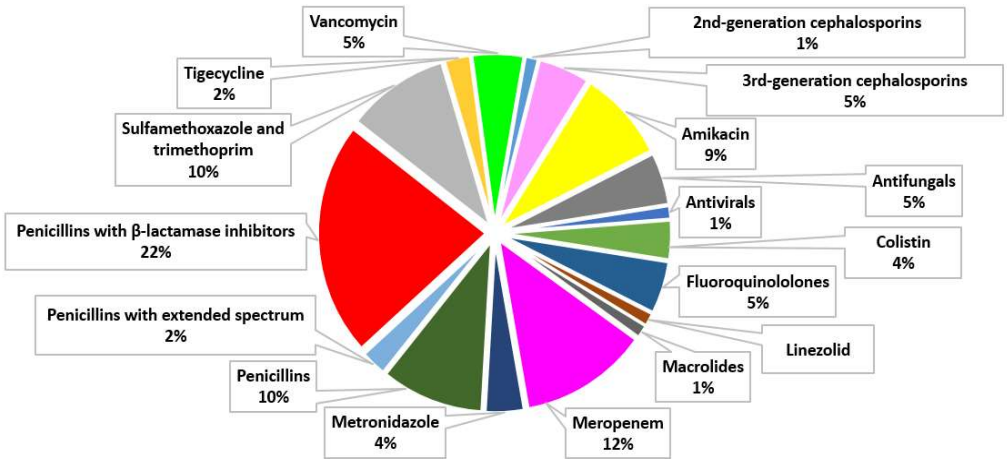
The ***Figure 5*** concerns HCAI. It shows that the most commonly prescribed class of antimicrobials was also penicillins with a β-lactamase inhibitor (36.4%), of which piperacillin/tazobactam accounted for 54.2% and amoxicillin/clavulanic acid accounted for the other 45.8%. Third-generation cephalosporins was the second most commonly prescribed class of antimicrobials with 10.5% (essentially ceftriaxone and ceftazidime), followed by macrolides with 9.3% (mainly clarithromycin).

Figure 5 *– Proportion of prescribed antimicrobials for systemic use in healthcare associated infections.*



Regarding ICU-acquired infections, the most prescribed class of antimicrobials was also penicillins with a β-lactamase inhibitor accounting for 22.2% (***Figure 6***). But when regarding individually each type of antimicrobial, meropenem (carbapenem class) was the most commonly prescribed with 12.3%, followed by piperacillin/tazobactam accounting for 11.1% and amoxicillin/clavulanic acid also with 11.1%.

Figure 6 *– Proportion of prescribed antimicrobials for systemic use in ICU-acquired infections.*



Patients having HCAI or ICU-acquired infections as primary source were more likely to have an antibiotic-resistant Gram-negative bacteria infection (23.4% and 25.0% respectively) than the patients having CAI as primary type of infection (12.9%), but this difference was not significant (p=0.26). Also, no statistical difference was found between groups for patients acquiring an antibiotic-resistant Gram-positive bacterial infection (CAI: 8.1%, HCAI: 9.1%, ICU-acquired infection: 16.7%; p=0.52).

7. Discussion

According to the descriptive analysis of the infected patients with antimicrobial therapy, 35.1% patients had at least one episode of inadequate antimicrobial treatment. The mean age of these patients was 66 years old, showing that infection can be an important cause of morbidity in older people admitted to the ICU. With the demographic transition, patients are becoming increasingly older and with multiple comorbidities, so this subgroup of population is being admitted more frequently into the ICU and their treatment can pose serious challenge to the medical team.

The 30-day hospital mortality after ICU admission was higher in the elderly group, but when using multiple logistic regression analysis the variable age (stratified) was not considered an independent risk factor of hospital mortality. Other authors have shown that older age was independently associated with a greater risk of hospital death in patients with infection admitted to the ICU [21].

The descriptive analysis also showed that the use of invasive medical devices (e.g. mechanical ventilation, urinary tract catheterization, nasogastric intubation, central vein catheterization) was significantly more common in the “inadequate antimicrobial treatment” group. For instance, mechanical ventilation proportion was almost the double in the “inadequate antimicrobial treatment” group when compared to the “adequate antimicrobial treatment” group. Two hypotheses emerge from these observations. On the one hand, the use of invasive medical devices can be a risk factor for infections, which can lead to inadequate antimicrobial treatment. On the other hand, the inadequate antimicrobial treatment can increase the severity of illness requiring the use of invasive medical devices. In the EUROBACT study, mechanical ventilation was present in 89.1% of the patients when the diagnosis of hospital-acquired bloodstream infection was made and catheter-related infection was present in 21.4% of the patients [27]. However, data collected in the present study is limited and insufficient to draw definite conclusions about the link between inadequate antimicrobial treatment and the use of invasive medical devices. In fact, it would require to have more information regarding the beginning and ending of invasive medical devices use and to compare it with the episode of inadequate antimicrobial treatment.

The ICU length of stay also showed a significant difference between the two groups. The median ICU length of stay was significantly higher in the “inadequate antimicrobial treatment” group, when compared to the “adequate antimicrobial treatment” group. Some authors have showed that patients with appropriate empiric antimicrobial treatment of ventilator-associated pneumonia had a significantly shorter total length of stay ($p=0.022$),

while others have found no differences in the total length of stay of patients with community-acquired bloodstream infections [16].

The highest CRP level during ICU first week also showed a significant difference between the two groups: median CRP level was significantly increased in the "inadequate antimicrobial treatment" group. However, in the multiple logistic regression analysis, CRP (stratified) was not a variable independently associated with hospital mortality. The main advantages of serum CRP levels are the availability in almost every hospital laboratory and the low cost assays when compared to other inflammation biomarkers. The main disadvantage is that CRP is not specific for infection, so elevated values are not necessarily related to the presence of infection. CRP levels are more useful to rule out infection, because a normal value makes a diagnosis of infection more improbable. In the critical care setting, when deciding about antimicrobial treatment, CRP levels should be considered in association with other clinical findings (e.g. temperature, imaging signs, increasing SOFA score, etc.), but never alone.

Other authors have tried to evaluate the variables associated with inadequate antimicrobial treatment and found that prior administration of antibiotic, increasing APACHE II score, decreasing patient age, bloodstream infections and presence of pneumonia where variables independently associated with inadequate antimicrobial treatment [40].

30-day hospital mortality after ICU admission

This study research question concerned the impact of inadequate antimicrobial treatment on 30-day hospital mortality after ICU admission. The study results do not support the hypothesis that 30-day hospital mortality after ICU admission is significantly different in patients with inadequate antimicrobial treatment than in patients with adequate antimicrobial treatment. Even when using multiple logistic regression analysis for controlling potential confounding variables, it was not possible to demonstrate a statistically significant association between the administration of inadequate antimicrobial treatment and 30-day hospital mortality after ICU admission for patients with infection.

Randomized controlled trials represent the "gold standard" study, but using one to evaluate the consequences of inadequate antimicrobial therapy would be unethical. So, observational studies like this one allow insight into its impact. In 2010, a meta-analysis, including 70 prospective cohort studies, demonstrated that inadequate empirical antimicrobial treatment was associated with significantly higher mortality among patients with sepsis [14]. In 2015, similar results were presented in another meta-analysis which reported significantly

higher mortality rates in patients receiving inadequate antimicrobial treatment for severe infection [16].

Additionally, the multiple logistic regression analysis demonstrated that having chronic arterial hypertension as pre-existing comorbidity, first week highest SOFA score (<7 vs. ≥7), APACHE II score on admission day (<25 vs. ≥25) and primary source of infection (CAI, HCAI or ICU-acquired infection) were independent variables associated with 30-day hospital mortality after ICU admission.

The APACHE II score is a classification system, which was designed to measure the severity of disease for adult patients admitted to the ICU [44]. Because it takes into consideration various parameters, such as age, physiological variables, vital signs and comorbid conditions, APACHE II score can be a useful instrument as predictor of ICU mortality. A systematic review regarding severity scoring systems found that APACHE II score was slightly superior to SOFA score in predicting ICU mortality and that the combination of sequential SOFA derivatives with APACHE II models clearly improved prognostic performance of either model alone [46].

The international guidelines for sepsis point out that organ dysfunction is represented by an increase in the SOFA score of ≥2 points [22], but SOFA score is not routinely used in the critical care units studied. So, the results of this study may be important in order to promote the regular and repeated SOFA scoring allowing the identification of patients at risk of infection or at risk of inadequate antimicrobial treatment.

Chronic arterial hypertension was also an independent variable associated with 30-day hospital mortality. In the general population, it is one of the leading risk factors associated with significant morbidity and mortality [47]. In the Netherlands, an epidemiological study in the critical care setting also reported hypertension along with ischaemic heart disease, atherosclerosis, chronic obstructive pulmonary disease and cancer as the most frequently pre-ICU admission comorbidities occurring for complication or death among patients with low APACHE II scores [48].

The mode of infection acquisition (HCAI, ICU-acquired or CAI) was also considered an independent variable associated with hospital mortality. In fact, the adjusted odds ratio of hospital mortality for patients having an HCAI was 4 times higher than for patients having a CAI, while the adjusted OR for ICU-acquired infections was only 2 times higher than for patients having a CAI. This shows that the place before ICU admission plays an important role in the outcome of patients and that there may be systematic difficulties in recognizing and managing patients with infection in general wards. A recent study also demonstrated that

patients being transferred from general wards were more likely to die, because they were more severely ill [49].

Contrary to the initial hypothesis, the interaction variable (inadequate antimicrobial treatment * APACHE II score) introduced in the model was significantly negative (antagonistic interaction), meaning that the association between inadequate antimicrobial treatment and mortality increased if an APACHE II score <25 was present (if all other variables were kept constant). The analysis of the two subgroups of the interaction showed that inadequate antimicrobial treatment was an important outcome determinant for patients less severely ill (APACHE II score <25), but not a significant one in more severely ill patients (APACHE II score ≥25). Therefore, particular attention must be paid to this subgroup of patients when deciding about antimicrobial therapy.

Infection: types causes and treatment

More than two-thirds of the patients had positive microbiological isolates and most isolated pathogens were Gram-negative bacteria. This proportion was in line with a recent retrospective study that analysed the outcomes of ICU patients with sepsis, which showed that microbiology was positive in 68.1% of all patients [50].

Respiratory tract infections were the most frequent ones, including patients with ventilator-associated pneumonia (VAP). However, these data only concerned the primary type of infection (some of the patients had multiple infection sources during ICU stay). In the EPIC II study, respiratory tract was also reported as the most common site of infection, accounting for 64% of infections [21]. The season may be important in pulmonary infections, which are more frequent in winter and represent a leading cause of sepsis [32]. Therefore, these results point out the importance of implementing effective strategies in order to prevent both community-acquired pneumonia (e.g., vaccination against influenza in high risk population) and healthcare-associated pneumonia (e.g. programmes to promote hand hygiene).

Combinations of penicillins with a β-lactamase inhibitor were the most frequently antimicrobials prescribed in this study. These findings were in line with those of the global point prevalence survey of 2015, which revealed that penicillins with a β-lactamase inhibitor had high prescribing rates in northern and western Europe (particularly in Belgian hospitals) [51]. Amoxicillin/clavulanic acid was the drug of choice for CAI, while piperacillin/tazobactam was reserved for more severe infections or for HCAI. These pattern of prescription seemed quite reasonable, particularly since they were generally in accord with the guidelines established by the BAPCOC [52].

Piperacillin/tazobactam is a broad spectrum antibiotic with activity against most Gram-positive and Gram-negative bacteria. Pathogens resistant to piperacillin/tazobactam are becoming more frequent in Europe and it is problematic. This increases the consumption of last-line antimicrobials like carbapenems, thus favouring the further dissemination of CPE [5]. Infections with CPE are associated with increased morbidity and mortality because they are extremely difficult to treat.

There were a few cases where the use of broad spectrum antibiotics seemed extreme (e.g. Meropenem for community-acquired infection). This approach is sometimes used in the critical care setting to ensure that all possible causative pathogens are initially covered. The risk of this conduct is the selection of extremely resistant bacteria, if the excessive (unnecessary) prescription of broad spectrum antimicrobials is used during long periods.

Therefore, it appears important to promote the strategy of "de-escalation" to a simpler antimicrobial treatment after identification of the causative microorganism and antimicrobial susceptibilities are known [15]. Yet, caution must be made since studies have reported conflicting effects on outcomes with de-escalation in some groups of critically ill patients and evidence seems to be insufficient to determine whether de-escalation is effective and safe [15].

This study results clearly showed that ICU-acquired infections were more frequently associated with multidrug-resistant pathogens. This was also illustrated by the use of antimicrobials of last resort, like colistin, tigecycline and linezolid. Also higher proportions of vancomycin, amikacin and meropenem were used to treat ICU-acquired infections when compared to antimicrobials used for CAI and for HCAI.

Amikacin (aminoglycoside) was also one of the most commonly prescribed antimicrobials. With the antimicrobial resistance increasing, particularly for Gram-negative bacteria, empiric β-lactam and aminoglycoside combination are often considered for critically ill patients with healthcare-associated infections [53]. This strategy is important to improve patient outcomes, but the misuse of this principle can lead to unnecessary exposure to broad-spectrum antimicrobials which could lead to further development of resistance and increased rates of nephrotoxicity [53].

7.1. Study limitations

The study limitations are inherent to the methods used, which aimed to describe the patterns of antimicrobials usage among the critically ill patients.

First, it was a single centre study, so the results presented may not be generalized to other types of ICUs with different contexts.

Second, the study period was short (3 months) and during winter season, so caution must be made with the interpretation of the reported rates.

Third, the sample size was relatively small and included patients initially admitted for a non-infectious condition and patients with sepsis on admission. These two types of patients may have large differences between them, including different exposure to antimicrobial therapy, which may represent two subgroups with completely different outcomes.

Fourth, one of the exclusion criteria was ICU length of stay < 24h which could have the effect of excluding some of the sickest patients who have died early and might have bias study results.

Fifth, the definition used to classify inadequate antimicrobial treatment focused only on the drug used (matching microbiological results), excluding dose and duration of the therapy. Nevertheless, adequate antimicrobial treatment is related not only to the substance itself but also to dosing and/or administration route [16].

Sixth, the list of variables used to predict 30-day hospital mortality after ICU admission was non-exhaustive since only a limited number of variables that could explain this outcome were tested.

Notwithstanding these limitations, the strengths of this study include the uniformity of data collection and the fact that it was a prospective study. Also, the majority of patients had microbiological documentation to corroborate the diagnosis of an infectious process.

8. Conclusion

Inadequate antimicrobial treatment was present in more than a third of infected patients. This group of patients had higher CRP levels and were more likely to have SOFA score ≥ 7 during the first week of ICU stay when compared to the others. Patients receiving "inadequate antimicrobial treatment" were also statistically more likely to have longer ICU length of stay and to use invasive medical devices (including mechanical ventilation, central vein catheterization, nasogastric intubation and urinary tract catheterization). Community-acquired infections were less common among patients with inadequate antimicrobial treatment. Most of these findings can be helpful in the early detection of patients at risk of inadequate antimicrobial treatment, especially with the increasing prevalence of antimicrobial resistant micro-organisms like ESBL and CPE.

This study demonstrated that having chronic arterial hypertension as pre-existing comorbidity, SOFA score, APACHE II score and primary source of infection were independent variables associated with 30-day hospital mortality after ICU admission. Inadequate antimicrobial treatment was not significantly associated with hospital mortality. Even with no statistically significant difference between the two groups, inadequate antimicrobial treatment should not be a negligible phenomenon. In fact, particular attention must be paid to patients with APACHE II score <25, since the impact of inadequate antimicrobial treatment on 30-day hospital mortality was significant among this subgroup of patients.

This study opened a series of questions for further research. Having relied solely on a single centre, it would be interesting to transform this research in a multicentre study. Also, having a longer study period (for instance one year) could give more reliable data.

In further research, other questions should be added to the form like the duration of invasive devices and if they were present before or after the exposure to inadequate antimicrobial treatment. Also, it would be interesting to differentiate between patients with non-infectious admission diagnosis and patients with sepsis admission diagnosis.

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Annex 1 – Patient Form

Data collection instrument: *Patient form*

Patient Form

Master in Public Health Sciences (UCL) - 2017/2018

Ethics committee reference: 2017/129 – B077201733832

Survey Nbr	Patient Nbr	ICU	Age (years)	Gender	ICU Length of stay	End-of-life decisions (DNR or withdraw/withhold therapy during ICU stay)
		02 ☐ 10 ☐ 20 ☐		F ☐1 M ☐0	____ days	Yes ☐1 No ☐0

Follow-up during 30 days				
Still alive in ICU ☐1	ICU discharged ☐2	Death in ICU ☐3	Death in hospital ☐4	Hospital Discharged ☐5

Type of admission	Primary ICU admission diagnosis(1)	Place before ICU admission	APACHE II *(admission day)*
Medical ☐1 Trauma ☐2 Elective surgery ☐3 Emergency surgery ☐4 Other ☐5	_____ _____ _____ ☐☐☐☐	ER/Ambu *(Home)* ☐1 ER/Ambu *(Nursing home)* ☐2 Hospital floor ☐3 OR/recovery ☐4 Other hospital ☐5	

Comorbidities					
Yes ☐1 No ☐0 UNK ☐99	Chronic heart disease ☐1/0 Diabetes Mellitus ☐1/0 COPD ☐1/0	HTA ☐1/0 Cancer ☐1/0 Chronic Renal disease ☐1/0	Immunosuppression ☐1/0 Cirrhosis (child B/C) ☐1/0		

Invasive Devices Used

Invasive MV	Tracheostomy	Urinary KT	Nasogastric tube	ECMO	$ECCO_2R$	Surgical Drains	
Yes ☐1 No ☐0	Yes ☐1 No ☐0	Yes ☐1 No ☐0	Yes ☐1 No ☐0	Yes ☐1 No ☐0	Yes ☐1 No ☐0	None ☐1/0 Thorax ☐1/0	Abdominal ☐1/0 Other ☐1/0

CVC	Pulm. art. KT "swan"	Art. KT	HD	CRRT
Yes ☐1 No ☐0	Yes ☐1 No ☐0	Yes ☐1 No ☐0	Yes ☐1 No ☐0	Yes ☐1 No ☐0

SOFA score and CRP values during ICU stay

AM changing = switching from one AM to another / adding another AM

	SOFA	CRP	AM changing		SOFA	CRP	AM Changing		SOFA	CRP	AM Changing		SOFA	CRP	AM Changing
Day 1				Day 6				Day 11				Day16			
Day 2				Day 7				Day 12				Day17			
Day 3				Day 8				Day 13				Day18			
Day 4				Day 9				Day 14				Day19			
Day 5				Day 10				Day 15				Day20			

Antimicrobial (AM) Name	(1)	(2)	(3)
AM initiated before ICU	Yes ☐1 No ☐0	Yes ☐1 No ☐0	Yes ☐1 No ☐0
	Nbr of days ___ <24h ☐99 // N.A. ☐0	Nbr of days ___ <24h ☐99 // N.A. ☐0	Nbr of days ___ <24h ☐99 // N.A. ☐0
START | STOP	__/__/__ | __/__/__	__/__/__ | __/__/__	__/__/__ | __/__/__
ICU-AM duration	____ *days*	____ *days*	____ *days*
Start IV	Yes ☐1 No ☐0	Yes ☐1 No ☐0	Yes ☐1 No ☐0
Switch to oral alternative	Yes ☐1 No ☐0 NA ☐99	Yes ☐1 No ☐0 NA ☐99	Yes ☐1 No ☐0 NA ☐99
Infection(2)	BSI ☐1 CVS ☐2 VAP ☐3 RESP ☐4 SSI ☐5 GI ☐6 SST ☐7 UTI ☐8 CNS ☐9 OTH ☐10 SEPSIS ☐11 UNK ☐99	BSI ☐1 CVS ☐2 VAP ☐3 RESP ☐4 SSI ☐5 GI ☐6 SST ☐7 UTI ☐8 CNS ☐9 OTH ☐10 SEPSIS ☐11 UNK ☐99	BSI ☐1 CVS ☐2 VAP ☐3 RESP ☐4 SSI ☐5 GI ☐6 SST ☐7 UTI ☐8 CNS ☐9 OTH ☐10 SEPSIS ☐11 UNK ☐99
Infection: mode of acquisition(3)	HCAI ☐1 CAI ☐2 ICU acquired ☐3 UNK ☐99	HCAI ☐1 CAI ☐2 ICU acquired ☐3 UNK ☐99	HCAI ☐1 CAI ☐2 ICU acquired ☐3 UNK ☐99
Type of prescription	Empirical ☐1 Culture-directed ☐2 Other ☐99	Empirical ☐1 Culture-directed ☐2 Other ☐99	Empirical ☐1 Culture-directed ☐2 Other ☐99
ID specialist advice	Yes ☐1 No ☐0	Yes ☐1 No ☐0	Yes ☐1 No ☐0
Reason in Notes to start the AM on day 1(4)	Yes ☐1 No ☐0	Yes ☐1 No ☐0	Yes ☐1 No ☐0
AM therapy appropriate(5)	Yes ☐1 No ☐0 NA ☐99	Yes ☐1 No ☐0 NA ☐99	Yes ☐1 No ☐0 NA ☐99
Cultures before AM initiation	Adequate ☐1 Inadequate ☐0 UNK ☐99	Adequate ☐1 Inadequate ☐0 UNK ☐99	Adequate ☐1 Inadequate ☐0 UNK ☐99
Reason to stop AM	**1)** Narrowing the spectrum of AM therapy (de-escalation) **2)** Completion of full AM treatment course **3)** Infection ruled out/AM treatment not indicated **4)** Isolation of a resistant pathogen **5)** Adverse effects **6)** Failure with AM treatment (escalation) **7)** ID specialist advice – switch to alternative **8)** Single dose treatment **9)** Patient transferred with the AM treatment prescribed **10)** Other reason **11)** Patient died or End-of-life decisions		

Pathogen Detection during ICU Stay

(Evaluate frequency of positive results during ICU stay, pathogens detected, culture sites)

Date	Fluid sample(6)	Pathogens detected
__/__/__	Blood ☐1 Urine ☐2 Respiratory ☐3 Other ☐4 Screening swab ☐5 Other swab ☐6	
__/__/__	Blood ☐1 Urine ☐2 Respiratory ☐3 Other ☐4 Screening swab ☐5 Other swab ☐6	
__/__/__	Blood ☐1 Urine ☐2 Respiratory ☐3 Other ☐4 Screening swab ☐5 Other swab ☐6	
__/__/__	Blood ☐1 Urine ☐2 Respiratory ☐3 Other ☐4 Screening swab ☐5 Other swab ☐6	
__/__/__	Blood ☐1 Urine ☐2 Respiratory ☐3 Other ☐4 Screening swab ☐5 Other swab ☐6	
__/__/__	Blood ☐1 Urine ☐2 Respiratory ☐3 Other ☐4 Screening swab ☐5 Other swab ☐6	
__/__/__	Blood ☐1 Urine ☐2 Respiratory ☐3 Other ☐4 Screening swab ☐5 Other swab ☐6	
__/__/__	Blood ☐1 Urine ☐2 Respiratory ☐3 Other ☐4 Screening swab ☐5 Other swab ☐6	
__/__/__	Blood ☐1 Urine ☐2 Respiratory ☐3 Other ☐4 Screening swab ☐5 Other swab ☐6	
__/__/__	Blood ☐1 Urine ☐2 Respiratory ☐3 Other ☐4 Screening swab ☐5 Other swab ☐6	
__/__/__	Blood ☐1 Urine ☐2 Respiratory ☐3 Other ☐4 Screening swab ☐5 Other swab ☐6	

Screening swab *Day 1 (first 24h)*: **CPE** Yes ☐1 No ☐0 // **MRSA** Yes ☐1 No ☐0

(1) Diagnoses list

Adapted from the EPIC III case report form
(https://www2.intensive.org/epic3/Doc/EPIC_III_-_eCRF.pdf)

100 Surveillance post-surgery
101 Pneumonectomy or lobectomy
102 Pleural surgery: includes all surgery on pleura either for tumor or pneumothorax
103 Valvular, without CABG
104 Valvular with CABG
105 CABG without valvular repair
106 Other: pericardial effusion, congenital anomaly, ventricular aneurysm, neoplastic disease, vena cava clipping/filter.
107 Major aortic surgery: includes all surgery on aorta for dissection, atheroma, and aneurysm.
108 Carotid endarterectomy: includes all surgery on the carotid artery
109 Other major vascular surgery: includes all surgery on intra thoracic or intra-abdominal vessels
110 Peripheral vascular surgery: includes all surgery on non-intracranial, non-intrathoracic, non-intraabdominal vessels, either arteries or veins with or without by-pass graft
111 Renal surgery
112 Urological surgery
113 Upper gastrointestinal surgery (up to and including the jejunum)
114 Lower gastrointestinal surgery
115 Biliary tract: surgery of gallbladder and/or biliary tract
116 Liver: partial hepatectomy, portal-systemic shunt surgery
117 Pancreas
118 Endocrine surgery (thyroid, adrenal, pancreas etc)
119 0bstetric surgery: Cesarean section; surgery for ectopic pregnancy, peri or post-partum haemorrhage, intra-uterine death
120 Gynecological surgery: surgery on uterus, ovaries, cervix uteri, genitalia
121 Thorax trauma: surgery of intra-thoracic organs (either cardiac, respiratory or digestive tract) and vessels.
122 Trauma Abdomen
123 Trauma Limb
124 Surgery for necrotizing fasciitis
125 Other skin or soft tissue surgery
126 Other

200 Neurological
201 Coma, stupor, obtunded patient, vigilance disturbances, confusion, agitation, delirium
202 Seizures
203 Ischemic stroke
204 Spontaneous intracranial hemorrhage
205 Focal neurological deficit (hemiplegia, paraplegia, tetraplegia) of other origin
206 lntracranial mass effect
207 Meningitis/encephalitis
208 Non-traumatic subarachnoid haemorrhage

300 Respiratory
301 ARDS: Syndrome of inflammation and increased permeability associated with clinical, radiological and physiological abnormalities: arterial hypoxemia resistant to oxygen therapy (PaO2/FiO2 < 300 mmHg) and diffuse bilateral radiological infiltrates without signs of cardiac failure (or increased left-sided filling pressures)
302 Acute respiratory failure on chronic pulmonary disease (obstructive or restrictive)
303 Acute respiratory failure without chronic pulmonary disease
304 Pneumonia

400 Cardiovascular
401 Out-of-hospital cardiac arrest: Needing cardiopulmonary resuscitation (CPR) prior to admission to ICU. CPR must include chest compression, defibrillation or cardiac massage.
402 In-hospital cardiac arrest: Needing cardiopulmonary resuscitation (CPR) prior to admission to ICU. CPR must include chest compression, defibrillation or cardiac massage.
403 Shock: SBP) <90 mmHg or a drop in SBP of >40 mmHg from baseline with presence of organ hypoperfusion (altered cutaneous perfusion, oliguria, encephalopathy, lactic acidosis) requiring the use of vasopressor agents.
404 Acute coronary syndrome: STEMI, NSTEMI …
405 Hypertensive crisis
406 Major arrhythmia (e.g. AV block …)
407 Cardiac failure without shock (left, right or global) (e.g. pulmonary oedema)

408 Cardiovascular infection (endocarditis, pacemaker infection, graft infection …)
500 Renal
501 Pre-renal (or functional) renal failure
502 Obstructive renal failure (post-renal)
503 Organic acute renal failure
504 Pyelonephriis
600 Hematological
601 Hemorrhagic syndrome
602 Coagulopathy including severe thrombocytopenia and/or increase in prothrombin lime and/or APTT.
603 Severe hemolysis
700 Digestive/Liver
701 Bleeding: Either upper or lower gastrointestinal tract
702 Acute abdomen: Related to infection, ischemia, perforation, inflammation, either upper or lower gastrointestinal tract. Excludes severe pancreatitis
703 Severe pancreatitis
704 Liver failure: hepatic failure inducing metabolic disturbances and/or encephalopathy
800 Metabolic
801 Acid-base and/or electrolyte disturbance
802 Hypo and hyperthermia
803 Hypo and hyperglycemia (includes diabetic coma)
804 Hypo/hyperthyroidism
900 Ob/gyn
901 Eclampsia
902 Peripartum bleeding
903 Other peripartum complication
904 Other obstetric problem
905 Gynecological problem
1000 Trauma
1001 Brain
1002 Thorax
1003 Abdomen
1004 Limb
1005 Polytrauma
1010 Sepsis of unknown origin

Infection code[(2)]

Code	Description	Code	Description
BSI	Bloodstream infection	**GI**	Gastro-intestinal infection
CVS	Cardiovascular infection (endocarditis, pacemaker, vascular graft)	**SST**	Skin and soft tissue infection
		UTI	Urinary tract infection
VAP	Ventilator-associated pneumonia	**CNS**	Central nervous system infection
RESP	Pneumonia (excluding VAP) & lower respiratory tract infection	**OTH**	Other type of infection
		SEPSIS	Sepsis, septic choc of unknown origin
SSI	Surgical Site infection	**UNK**	Infection of unknown origin

[(4)] A diagnosis / indication for treatment is recorded in the patient's documentation (treatment chart, notes, etc.) at the start of antimicrobial treatment.

[(5)] To know if the patient had at least one episode of inadequate AM treatment. If the patient has more than one inadequate AM treatment the most pertinent will be considered.

[(6)] **Fluid sample**
Respiratory = sputum samples, endotracheal aspirates or bronchoalveolar-lavage specimens

Annex 2 – Ethics committee approval

C H U I U V C
BRUGMANN

Réf. : CE 2017/129

Melle Liliana Teixeira Lopes

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14/11/2017

Chère Melle Liliana Teixeira Lopes,

Concerne :
Antimicrobial prescription characteristics and changing pattern in the intensive care units
B077201733832

Le Comité d'Ethique Hospitalier du C.H.U. BRUGMANN a pris connaissance du dossier de soumission de l'étude dont l'intitulé est repris sous rubrique.

Documents examinés:

Formulaire de demande interne
Protocole
Curriculum vitae
Demande d'assurance Ethias

Le comité d'éthique marque son accord.

Nous vous prions de croire, Mademoiselle, en l'assurance de nos sentiments les meilleurs.

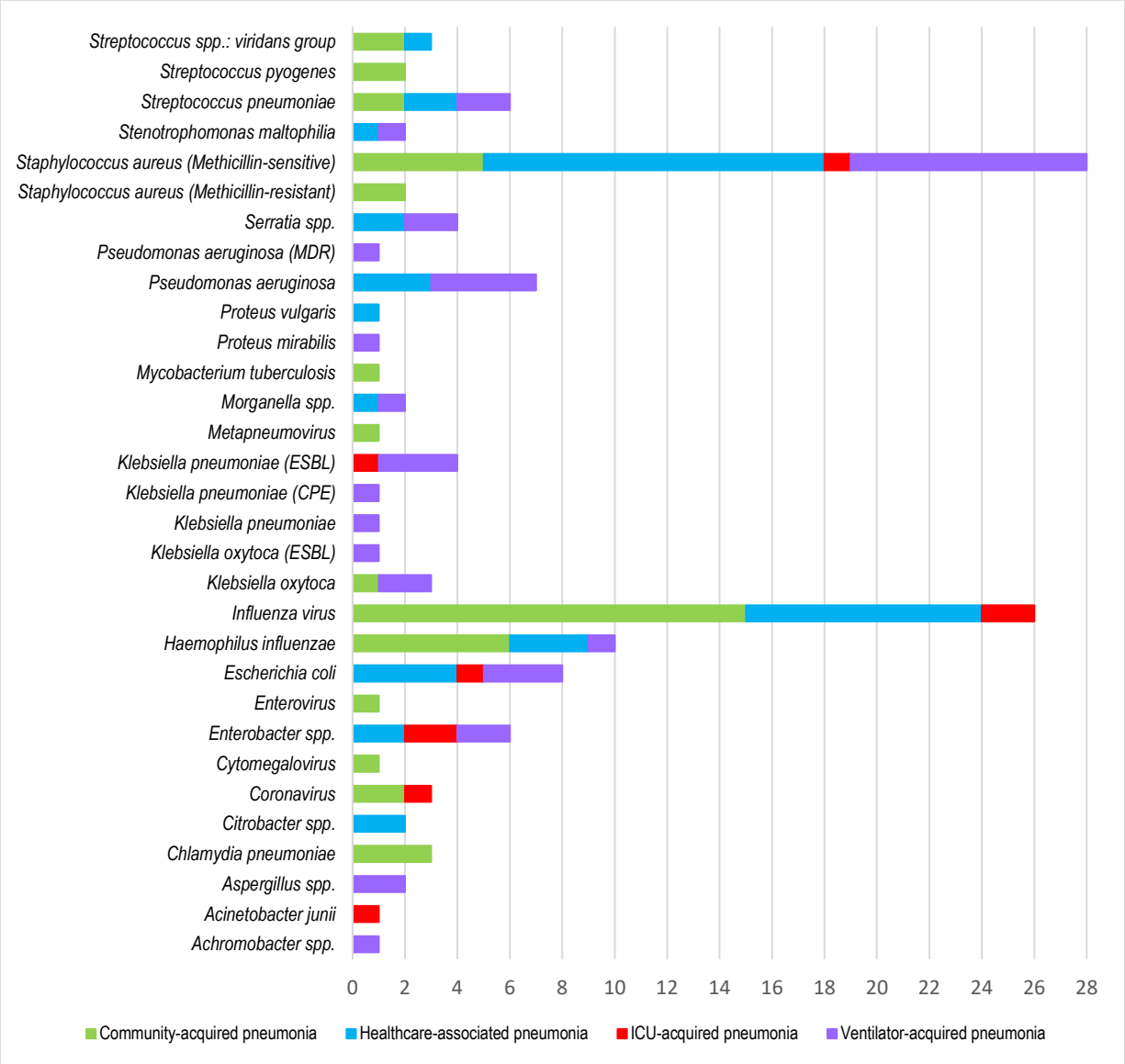
Docteur P. VERBANCK,
Secrétaire

Docteur J. VALSAMIS,
Président

Le Comité d'Ethique rappelle que les amendements substantiels et les notifications de sécurité, comme décrites dans la loi du 7 mai 2004, doivent lui être soumis.

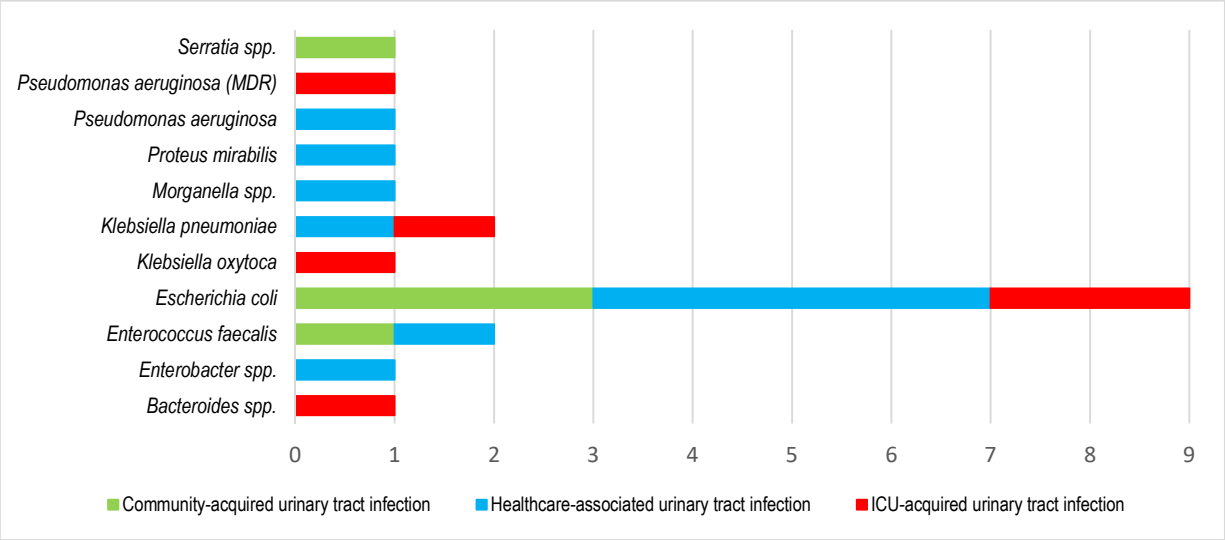
Annex 3 – Frequency of the pathogens identified

Figure 7 *- Number of pathogens associated with Pneumonia (some infections being polymicrobial).*



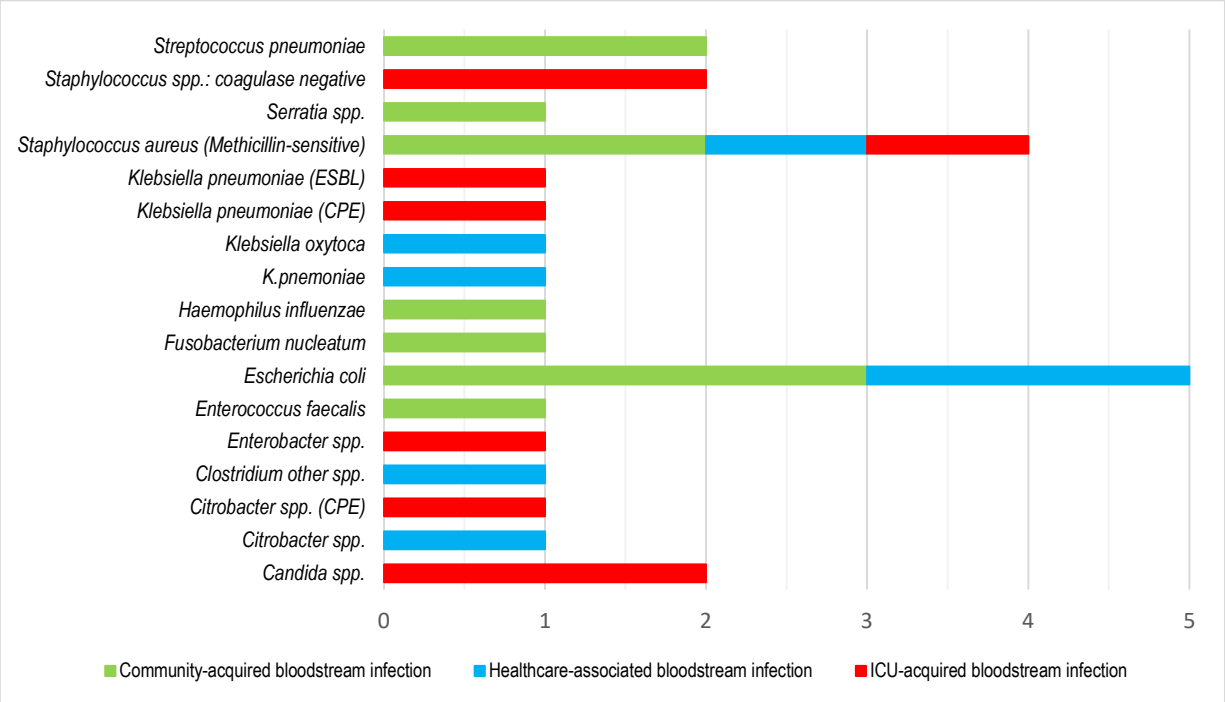
Pathogens associated with ventilator-acquired pneumonia were counted separately from the other ICU-acquired pneumonia.
CPE = Carbapenemase-producing *Enterobacteriaceae*.
ESBL = Extended-spectrum β-lactamase.
MDR = Multidrug-resistant (i.e. bacteria non-susceptible to as least one agent in ≥ 3 antimicrobial classes).

Figure 8 *- Number of pathogens associated with urinary tract infections (some infections being polymicrobial).*



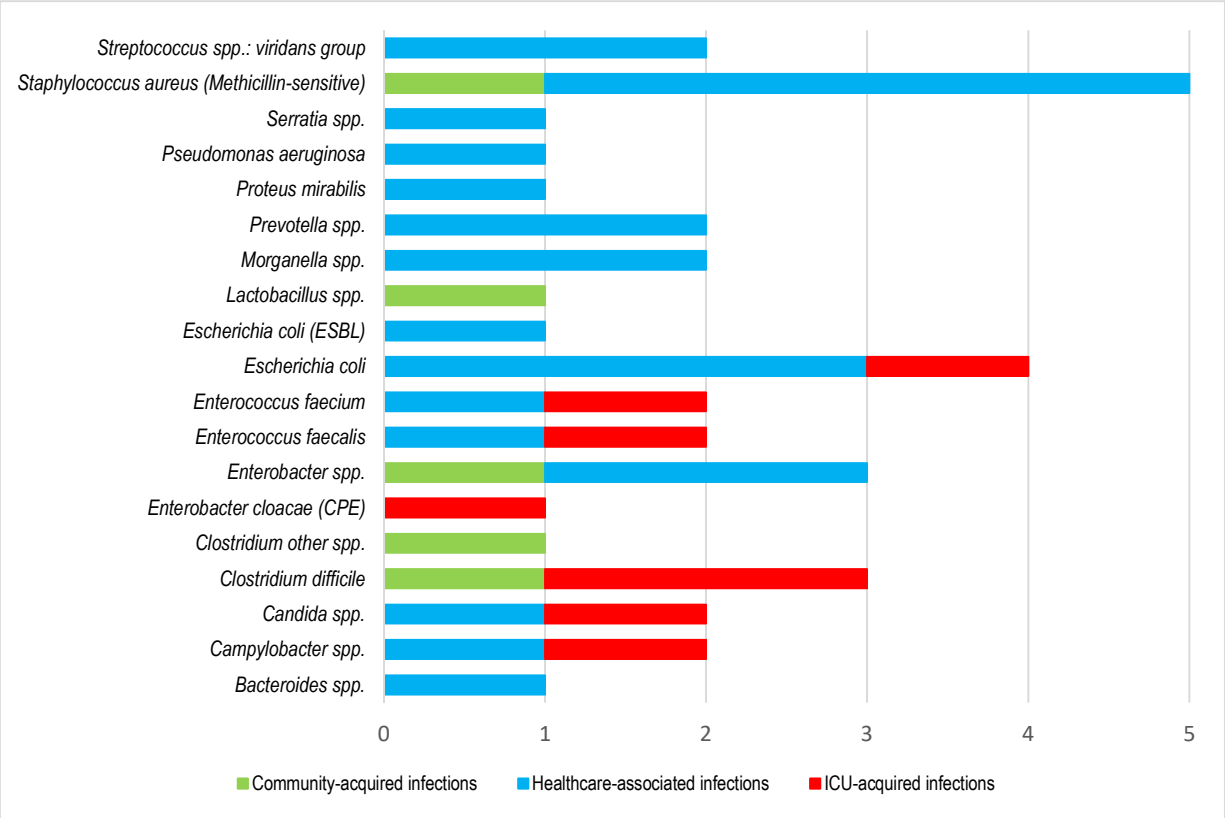
MDR = Multidrug-resistant (i.e. bacteria non-susceptible to as least one agent in ≥ 3 antimicrobial classes).

Figure 9 *– Number of pathogens associated with bloodstream infections (some infections being polymicrobial).*



CPE = Carbapenemase-producing *Enterobacteriaceae*.
ESBL = Extended-spectrum β-lactamase.

Figure 10 *- Number of pathogens associated with infections other than pneumonia, bloodstream or urinary tract infections (some infections being polymicrobial).*



CPE = Carbapenemase-producing *Enterobacteriaceae*.
ESBL = Extended-spectrum β-lactamase.

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