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Patterns of Antimicrobial Therapy in Severe Nosocomial Infections: Empiric Choices, Proportion of Appropriate Therapy, and Adaptation Rates – A Multicenter, Observational Survey in Critically Ill Patients.

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Abstract
This prospective, observational multicenter (n=24) study investigated relationships between antimicrobial choices and rates of empiric appropriate or adequate therapy, and subsequent adaptation of therapy in 171 ICU patients with severe nosocomial infections. Appropriate antibiotic therapy was defined as in-vitro susceptibility of the causative pathogen and clinical response to the agent administered. In non-microbiologically documented infections, therapy was considered adequate in case of favorable clinical response <5 days. Patients had pneumonia (n=127; 66 ventilator-associated), intra-abdominal infection (n=23), and bloodstream infection (n=21).

Predominant pathogens were Pseudomonas aeruginosa (n=29) Escherichia coli (n=26), Staphylococcus aureus (n=22), and Enterobacter aerogenes (n=21). In 49.6% of infections multidrug resistant (MDR) bacteria were involved, mostly extended-spectrum Beta-lactamase producing Enterobacteriaceae and MDR non-fermenting Gram-negative bacteria. Prior antibiotic exposure and hospitalization in a general ward prior to ICU admission were risk factors for MDR. Empiric therapy was appropriate/adequate in 63.7% of cases. Empiric schemes were classified according to coverage of (i) ESBL-Enterobacteriaceae + non-fermenting Gram-negative bacteria (meropenem-based), (ii) non-fermenting Gram-negative bacteria (schemes with antipseudomonal agent), and (iii) first-line agents not covering ESBL-Enterobacteriaceae nor non-fermenting Gram-negative bacteria. Meropenem-based schemes allowed for significantly higher rates of appropriate/adequate therapy (p<0.001). This benefit remained when only patients without risk factors for MDR were considered (p=0.021). In 106 patients (61%) empiric therapy was adapted: in 60 cases following initial
inappropriate/inadequate therapy, in 46 patients in order to fine-tune empiric therapy. In this study reflecting real-life practice first-line use of meropenem provided significantly higher rates of appropriate/adequate therapy, irrespective of presence of risk factors for MDR.

**Keywords:** antibiotic resistance – multidrug resistance – intensive care – infection – appropriate therapy
Introduction

To avoid nosocomial infection remains a daily challenge for healthcare workers involved in the care of critically ill [1]. The prevalence of infection strongly depends on the presence of particular iatrogenic risk factors such as the use of indwelling devices and extensive surgery, as well as the severity of underlying disease and critical illness. Despite several large scaled efforts to improve prevention of healthcare-associated infection [2-7], in general about 20% to 50% of patients hospitalized in intensive care units (ICUs) experience infection, either hospital or ICU-acquired [8, 9].

Severe nosocomial infection carries a substantial economic burden due to extensive antimicrobial consumption and, even more importantly, increased length of hospitalization [10-13]. In addition, severe infection seriously compromises the odds of survival. Attributable mortality rates vary from as low as zero percent to a dramatic 50% dependent of the type of infection, the causative pathogen, patient age, associated co-morbidities, and overall quality of the anti-infective approach [13-21]. Among all the modalities that are to be fulfilled in the aim to optimize clinical patient outcomes, early initiation of the proper antimicrobial agent is a cornerstone [1]. Failure to timely administer appropriate antimicrobial therapy results in a dramatic increase in fatality rates [22-25]. Selecting an empiric regimen which covers the causative pathogen, however, is hampered by the presence of multidrug resistant (MDR) micro-organisms which is the utmost important cause of empiric inappropriate therapy. Since antimicrobial consumption in itself is a major trigger for
MDR development, physicians are frequently urged to thoughtfully use ‘last-line antibiotics’. In fact, the challenge is to achieve high rates of empiric appropriate therapy in order to optimize patient survival, while avoiding unnecessary use of antibiotics with the intention to minimize microbial selection pressure, and hence, MDR development [1, 26].

In order to accomplish this goal, in the past decade two main strategies have been proposed. In the surveillance-assisted strategy, the empiric regimen is selected mainly based on the presence or absence of MDR pathogens in routine surveillance cultures. The strength of this approach is the high negative predictive value of surveillance cultures to predict MDR involvement in subsequent infection. On the condition that cultures are taken at least twice weekly, this strategy is capable to combine high rates of empiric appropriate therapy with reduced consumption of antibiotics in pneumonia and bacteremia [27-33]. The cost-effectiveness of this approach, however, remains questionable. Another approach is the so-called ‘de-escalation strategy’ which, on the condition of risk factors for MDR involvement, recommends empiric start with a regimen which covers most potential MDR pathogens such as extended-spectrum beta-lactamase producing (ESBL) Enterobacteriaceae, non-fermenting Gram-negative bacteria, and methicillin-resistant Staphylococcus aureus (MRSA) [34-36]. Once culture results are available, and if feasible, narrowing the antimicrobial spectrum is advised. This concept, often referred to as ‘de-escalation’, is widely used and advocated [37-40]. This strategy has been demonstrated to be successful and safe, and may also reduce antibiotic use and hence limiting the emergence of MDR [36, 41].
The objective of the present study was to prospectively investigate patterns of antimicrobial therapy in critically ill patients with nosocomial infection. More precisely, we formulated the following research questions: (i) What is the rate of empiric appropriate or adequate therapy achieved? (ii) Which antibiotic selections allow for the highest rates of empiric appropriate or adequate therapy, either in the presence or absence of risk factors for MDR pathogens? (iii) What is the rate by which empiric therapy (either appropriate/adequate or not) is adapted?
Methods

Study design. A prospective multicenter observational study was performed between February 2006 and June 2007. In total 24 Belgian ICUs participated. In all centers the study was approved by the local ethics committee and informed consent was requested. In all centers antimicrobial prescribing was done or supervised by the attending senior intensivist.

Inclusion criteria. Eligible patients were those who provided informed consent, were at least 18 year of age, were hospitalized in the ICU, and experienced severe hospital- or ICU-acquired infection, either pneumonia, intra-abdominal infection, primary bloodstream infection, or secondary bloodstream infection originating from another source than pneumonia or intra-abdominal infection (e.g. bacteremia secondary to urinary tract infection or sinusitis).

Definitions. Infections were considered hospital- or ICU-acquired when diagnosed at least 48 hours after respectively hospital or ICU admission. Severe bacterial infections were defined following the International Sepsis Forum Consensus Conference on Definitions of Infection in the ICU [42]. Definitions of invasive fungal infections are described elsewhere [43, 44]. Pneumonia was considered ventilator-associated when occurring after at least 48 hours of mechanical ventilation. For the purpose of the study, only the first episode per patient was considered. Pneumonia or intra-abdominal infection with bacteremic breakthrough (i.e. positive blood cultures) were classified according to the primary infection. Bloodstream infections
secondary to other sources than pneumonia or intra-abdominal infection were
classified as secondary bloodstream infection.

Definitions of MDR are described elsewhere [10, 32, 45]. *Candida* spp. were
considered MDR when resistant to fluconazole.

Following the epidemiological scope of the study aiming at insights into empiric
therapy in general, we also wanted to include microbiologically undocumented
infections with obvious signs of clinical sepsis. For this purpose we made a difference
between appropriate and adequate empiric therapy. The term appropriate therapy
was valid for microbiologically documented infectious episodes and was defined as
*in vitro* susceptibility of the causative pathogen and clinical response to the agent
administered. The term adequate therapy was used in non-microbiologically
documented infections and was defined as favorable clinical response within five
days of therapy (resolution of signs of sepsis).

Severity of disease was assessed by means of the acute physiology and chronic health
evaluation (APACHE) II score [46]. The following co-morbid conditions were
registered: respiratory disease (chronic restrictive, obstructive or pulmonary vascular
disease resulting in severe exercise restriction), cardiac disease (New York Heart
Association Class IV), diabetes mellitus, hepatic disease (cirrhosis and portal
hypertension; episodes of past upper gastro-intestinal bleeding attributed to portal
hypertension or prior episodes of hepatic failure or encephalopathy), renal disease
(chronic glomerulonephritis, nephropathy, or chronic kidney disease), neurologic
disease (impairment of alertness or confusion) malignancy (hematologic cancer or solid tumor), and neutropenia (absolute neutrophil count <1500 cells/mm³).

To assess relationships between empiric antibiotic selection and rates of appropriate or adequate therapy, the empiric antimicrobial schemes were grouped according to the spectrum of pathogens covered. Table 1 describes the classification of empiric antimicrobial schemes. Because of the small numbers of empiric schemes covering MRSA and the relative low occurrence rate of MRSA in the cohort, empiric antibiotic schemes were classified in three major groups: (i) coverage of ESBL-Enterobacteriaceae + non-fermenting Gram-negative bacteria (meropenem [MER]-based schemes), (ii) coverage of non-fermenting Gram-negative bacteria (schemes including an antipseudomonal agent), and (iii) schemes without coverage of either ESBL-Enterobacteriaceae nor non-fermenting Gram-negative bacteria (first line agents). In this analysis the added value of vancomycin as empiric therapy in order to cover methicillin resistant Gram-positive pathogens was investigated separately.

Prior antibiotic exposure was defined as the administration of antimicrobial agents within one month preceding the current infectious episode. Prior hospitalization was defined as an hospital admission within the four months preceding the current ICU admission.

Data analyses. Continuous variables are described as median (interquartile range [IQR]) and discrete variables as n (%). For comparisons between groups the Mann Whitney U test and Fisher Exact test or Chi-square test were used as appropriate.

Independent relationships with empiric appropriate or adequate therapy were
assessed by means of a logistic regression analysis. Variables taken into account in the logistic regression analysis either showed a moderate relationship in univariate analysis or a logical relationship with the dependent variable. Variables considered were: age, APACHE II score, underlying diseases, hospitalization in another ward prior to ICU admission, prior antibiotic exposure, and empiric antibiotic schemes. Results of the regression analysis are reported as odds ratios (OR) and 95% confidence intervals (CI).
Results

Demographics. During the study period 198 patients were included. Due to incomplete patient files 27 patients were excluded, resulting in a final database containing 171 patients. Patient characteristics are described in Table 2. Primary infections were pneumonia (n=127, of which 66 ventilator-associated), intra-abdominal infection (n=23) bloodstream infection (n=21, of which 9 primary, 1 catheter-related, and 12 secondary to another source than pneumonia or intra-abdominal infection). One hundred and fifteen infections were ICU-acquired (66.7%). About 75% of infections were microbiologically documented (Figure 1). This represented 129 microbiologically documented infections in which 165 microorganisms were isolated. Gram-negative bacteria were most common (n=122, 73.9%) with Pseudomonas aeruginosa (n=29), Escherichia coli (n=26), Enterobacter aerogenes (n=21), Klebsiella pneumonia (n=7), and Klebsiella oxytocca (n=7) as predominant pathogens. Among the 42 Gram-positive bacteria, Staphylococcus aureus (n=22), Streptococcus pneumoniae (n=11), and Enterococci (n=5) were most frequently isolated. One fungal pathogen was isolated. In 64 of the 129 microbiologically documented infections MDR pathogens were involved (49.6%). Figure 1 describes the breakdown of the different types of resistance involved in these infections.

Risk factors for multidrug resistance (MDR). Risk factors for MDR were assessed in order to evaluate empiric antimicrobial regimens relative to their presence. No specific underlying conditions appeared to predispose for MDR involvement. MDR involvement was more frequent in patients with compared to without prior
antibiotic exposure (74.3% vs. 41.3%, p=0.001; relative risk 4.26, 95% CI: 1.80-10.09).

Hospitalization in another ward prior to ICU admission was also recognized as significantly associated with MDR involvement (59.0% vs. 40.9%, p=0.041; relative risk 2.08, 95% CI: 1.03-4.22). Figure 3 shows a breakdown of microbiologically documented infections according to the presence of these two risk factors for MDR, and subsequent MDR involvement.

Length of ICU stay prior to the development of infection, however, was negatively associated with the risk of MDR involvement. Patients who experienced infections without MDR pathogens developed this infection after a median of 3 days (IQR: 2-7 days), while infections caused by MDR pathogens occurred after a median of 2 days (IQR: 0-4.25 days), (p=0.002).

Rates of empiric appropriate or adequate therapy and subsequent adaptation. The presence of MDR pathogens in infections was associated with a significant lower rate of empiric appropriate therapy: 87.7% vs. 35.9% (p<0.001). Rates of empiric appropriate and adequate therapy are illustrated in Figure 2. In 80 of the 129 microbiologically documented infections empiric therapy was appropriate (62.0%). In non-microbiologically documented infections, empiric therapy was judged adequate in 29 of 42 infections (69.0%). In 106 patients (62.0%) empiric therapy was adapted: in 60 cases following initial inappropriate or inadequate therapy, and in 46 patients in order to fine tune empiric therapy.
Empiric antimicrobial selection and rates of appropriate or adequate therapy. In 12 infections the causative pathogen was methicillin-resistant (10 MRSA, 2 methicillin-resistant \textit{Staphylococcus epidermidis}). Vancomycin was 14 times administered as an empiric agent, but in only three cases in which a methicillin-resistant pathogen proved to be involved. As such the rate of inappropriate therapy in case of methicillin-resistance involvement was 75%. Due to the relative low prevalence of methicillin-resistance as well as the low added value of initiating a glycopeptide, the association (or not) of such an agent did not alter the study results in this particular cohort. Therefore, we analyzed rates of empiric appropriate or adequate therapy irrespective of the coverage of MRSA. This is illustrated by Figure 4a. Coverage of ESBL-\textit{Enterobacteriaceae} (by MER-based empiric schemes) allowed for significantly higher rates of appropriate or adequate therapy. Because the advantage of an antibiotic agent which covers ESBL-\textit{Enterobacteriaceae} is obvious in settings with a high prevalence of MDR, we hypothesized that the benefit of using a MER-based empiric scheme would fade away when only patients without risk factors for MDR were taken into account. However, in this analysis empiric schemes covering ESBL-\textit{Enterobacteriaceae} remained superior (Figure 4b).

When MER-based empiric schemes were compared to other empiric regimens, a difference of approximately 30% in empiric appropriate or adequate therapy was observed when all patients were taken into account (89.2% vs. 56.0%; p<0.001), and this distinction remained when only patients without risk factors for MDR were considered (83.6% vs. 53.8%; p=0.040).
In a multivariable logistic regression analysis, the only factors independently associated with empiric appropriate or adequate therapy were a MER-based empiric scheme (OR 18.1, 95% CI 4.8 to 68.1; p<0.001) and the presence of MDR pathogens (OR 0.04, 95% CI 0.01 to 0.10; p<0.001). No other variables reached the level of significance.
Discussion

In this prospective, observational study, which aims to reflect real life daily practice, rates of empiric appropriate or adequate therapy were only 63.7%. About half of the infections were caused by MDR micro-organisms, mostly ESBL-Enterobacteriaceae and P. aeruginosa. As such, only the inclusion of meropenem in the empiric scheme, allowed for acceptable rates of appropriate therapy (approximately 90%).

Several reasons for the low rate of appropriate or adequate therapy can be proposed. The overall prevalence of MDR in this particular cohort is high (~50%) and the rate of appropriate or adequate therapy in infections caused by MDR pathogens was very poor (35.9%). MDR is well recognized as a major determinant of inappropriate therapy [47-52]. However, to a certain extent the involvement of MDR can be predicted on basis of some typical risk factors of which the most essential are prior antibiotic exposure and a length of ICU stay (or mechanical ventilation in case of pneumonia) of >7 days [32, 53]. Other risk factors such as particular underlying diseases (e.g. chronic obstructive pulmonary disease) and recent surgery/hospitalization can also be taken into account but generally are not included in the principal risk factors. Strangely enough, in this cohort of ICU patients with nosocomial infection some of the classic patterns failed to predict the involvement of MDR. For instance, prior hospitalization (<4 months of the current hospital admission) was not associated with a higher likelihood of MDR, while length of ICU stay was even inversely related to MDR involvement. On the other hand, prior antibiotic exposure and hospitalization in a general ward prior to ICU admission
appeared to have a significant relationship with MDR involvement. Importantly, however, although these relationships were statistically significant, MDR pathogens were isolated in about 40% of patients in the absence of these risk factors. As a consequence, the predictive value of these risk factors was low. As such, the generally accepted concepts of risk perception for MDR involvement failed in this particular cohort. We have no plausible explanation for this observation. Given the relationship between prior hospitalization at a general ward and MDR, the relative high number of infections already present at time of ICU admission, and the short length of stay in the ICU prior to infection, it appears that there exists a serious problem of MDR in general wards in Belgian hospitals, thereby contributing to the low rate of empiric appropriate therapy in ICUs. Indeed, already a decade ago a higher incidence of *Enterobacter aerogenes* with an increasing resistance pattern has been noticed in Belgian hospitals [54, 55].

Following the high rate of ESBL-*Enterobacteriaceae* and *P. aeruginosa*, an MER-based empiric scheme allowed for the highest rates of appropriate/adequate therapy. Due to the failure of classic risk factors to predict MDR involvement performance rates of empiric schemes did not substantially alter when only patients without risk factors were considered (Figure 3). Hence, based on the present study an approach including coverage of both ESBL-*Enterobacteriaceae* and *P. aeruginosa* seems highly warranted. Without firm supportive knowledge of local ecology in ICU and non-ICU settings indicating low MDR levels, an empiric strategy which does not cover ESBL-*Enterobacteriaceae* and *P. aeruginosa* is potentially dangerous, and as such supports the de-escalation strategy. The present findings however, with the failure of MDR
prediction based on general characteristics in particular, provide perspectives for the surveillance assisted approach in which individual colonization status is a major element in steering empiric therapy.

In 62% of patients empiric therapy was adapted (n=106). In 60 cases adaptation followed initial inappropriate or inadequate therapy, whereas in 46 patients empiric therapy could be fine-tuned (true de-escalation). Noteworthy, when only microbiologically documented infections are considered, 4 out of 129 patients received inappropriate therapy even after the availability of culture results (Figure 1). In MER-based empiric schemes (n=37) therapy was continued in 23 and adapted in 14 patients (in 4 cases because of initial inappropriate therapy and in 10 cases in order to narrow down the spectrum). As this study supports the approach of empiric coverage of ESBL-Enterobacteriaceae and P. aeruginosa, we stress the importance of de-escalation whenever possible. Baran et al. found that previous exposition to carbapenems was 44% in patients with infections caused by imipenem-resistant Acinetobacter baumannii, whereas only 12% in patients infected by imipenem-susceptible A. baumannii isolates [56]. Yet, in multivariate analysis, previous antibiotic exposure and not carbapenem exposure in particular appeared to be an independent risk factor for imipenem-resistance. The link between exposure and specific resistance development is obvious and should not be disregarded, but this suggests that the mission to reduce microbial selection pressure is valid for all antimicrobial agents and not only for carbapenems. Further, based on the
Surveillance of Antimicrobial Use and Antimicrobial Resistance in German ICUs (SARI project), Meyer E et al. identified carbapenem use as an independent predictor for a higher Stenotrophomonas maltophilia incidence [57]. Although this data do not disclose a causal relationship, it is highly suggestive for the specific selection pressure of this pathogen. Therefore, excessive use of carbapenems is to be avoided by a strict de-escalation strategy and by avoidance of unnecessary long therapies.

The most important advantage of this study is its non-interventional design, reflecting real daily practice, thereby disclosing the true pain points in empiric antibiotic therapy in critically ill patients. Due to the multicenter approach the data might be valid for many tertiary care centers in Belgium and abroad.

This study has limitations. First, no outcome data are available as the primary aim of the study was to describe antibiotic prescription patterns and how they perform in terms of appropriate therapy. Yet, the relationship between initial empiric failure to cover the causative pathogen and adverse outcomes has been demonstrated repeatedly and is generally accepted as an important quality indicator [58, 59]. Secondly, the cohort does not represent a consecutive series of ICU patients with nosocomial infections. Probably this might have lead to the selection bias towards more severe infections, with a higher likelihood of MDR involvement. Yet, for what concerns risk factors for MDR, including less severe infections would probably not have changed the observations regarding the relationship between MDR infection and risk factors.
In conclusion, in this prospective study reflecting real life practice in ICU patients with nosocomial infections, the rate of appropriate or adequate empiric therapy was 63.7%. This study demonstrated that classic risk factors for MDR such as prior antibiotic exposure and length of ICU stay, may be insufficient to predict MDR involvement. As such, empiric first-line use of MER allowed for significantly higher rates of appropriate or adequate therapy, irrespective of presence of these risk factors, and may be recommended in settings with a high prevalence of MDR pathogens. In addition, these data illustrate the necessity for strict infection prevention and control.

Declarations

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Competing Interests: No conflicts of interest to declare

Ethical Approval: For this non-interventional, observational study, ethical approval was given by the local ethics committees of the participating centres (n=24).
References


Figure Legends

Figure 1 - Review of 171 nosocomial infections distributed for microbiological documentation and multidrug resistance involvement.

- MDR, multidrug resistance or multidrug resistant
- ESBL, extended spectrum beta-lactamase producing Enterobacteriaceae
- MRSA, methicillin- resistant Staphylococcus aureus
- MRSE, methicillin-resistant Staphylococcus epidermidis

Figure 2 - Rates of empiric appropriate or adequate therapy in ICU patients with nosocomial infections.

- Cont., continuation of empiric therapy
- Adapt., adaptation of empiric therapy

Figure 3 – Breakdown of microbiologically documented infections according to the presence of risk factors for multidrug resistance, and multidrug resistance involvement.

- MDR, multidrug resistance

Figure 4 – Rates of empiric appropriate or adequate therapy according to three major groups of empiric antibiotic regimens (coverage of methicillin-resistant pathogens not considered).

- Figure 4a, all patients considered (n=170; in one patient no empiric therapy was initiated)
- Figure 4b, only patients considered without risk factors for multidrug resistance involvement (hospitalization at a general ward prior to ICU admission and prior antibiotic exposure), (n=78).
- Group 1: coverage of ESBL-Enterobacteriaceae + P. aeruginosa (meropenem-based schemes)
- Group 2: coverage of P. aeruginosa (schemes containing an antipseudomonal agent)
Group 3: no coverage of ESBL nor non-fermenting Gram-negative bacteria (first line agents)
Table 1 - Empiric antibiotic regimens clustered in six major groups according to the pathogens covered.

<table>
<thead>
<tr>
<th>Coverage</th>
<th>Empiric regimens</th>
<th>n</th>
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<td>MER+CIP+AMI</td>
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</tr>
<tr>
<td></td>
<td>CAZ+VAN</td>
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<tr>
<td></td>
<td>CEF+VAN</td>
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<td></td>
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<td>Pathogen Description</td>
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<td>Frequency</td>
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**Legend:**

MER, meropenem
AMI, aminoglycoside
VAN, vancomycin
OXA, oxacillin
CIP, ciprofloxacin
PIPtaz, piperacillin/tazobactam
LEVO, levofloxacin
FLU, fluconazole
AMOXIclav, amoxicillin/clavulanate
CEF, cefuroxim
CAZ, ceftazidime
CTX, ceftriaxone
CEFE, cefepim
MOXI, moxifloxacin
CLA, clarithromycin
Figure 2
Click here to download high resolution image
Figure 3

Microbiologically documented infections (n=129)

- Risk factors for MDR (n=68; 52.7%)
  - MDR involvement (n=40; 58.8%)
  - No MDR involvement (n=28; 41.2%)

- No risk factors for MDR (n=61; 47.3%)
  - MDR involvement (n=24; 39.3%)
  - No MDR involvement (n=37; 60.7%)

P=0.027
Patterns of Antimicrobial Therapy in Severe Nosocomial Infections:
Empiric Choices, Proportion of Appropriate Therapy, and Modification Rates –
A Multicenter, Observational Survey in Critically Ill Patients.

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Abstract

This prospective, observational multicenter (n=24) study investigated relationships between antimicrobial choices and rates of empiric appropriate or adequate therapy, and subsequent modification of therapy in 171 ICU patients with severe nosocomial infections. Appropriate antibiotic therapy was defined as in-vitro susceptibility of the causative pathogen and clinical response to the agent administered. In non-microbiologically documented infections, therapy was considered adequate in the case of favorable clinical response <5 days. Patients had pneumonia (n=127; 66), ventilator-associated), intra-abdominal infection (n=23), and bloodstream infection (n=21). Predominant pathogens were *Pseudomonas aeruginosa* (n=29) *Escherichia coli* (n=26), *Staphylococcus aureus* (n=22), and *Enterobacter aerogenes* (n=21). In 49.6% of infections multidrug resistant (MDR) bacteria were involved, mostly extended-spectrum Beta-lactamase producing Enterobacteriaceae and MDR non-fermenting Gram-negative bacteria. Prior antibiotic exposure and hospitalization in a general ward prior to ICU admission were risk factors for MDR. Empiric therapy was appropriate/adequate in 63.7% of cases. Empiric schemes were classified according to coverage of (i) ESBL-producing Enterobacteriaceae and non-fermenting Gram-negative bacteria (“meropenem-based”), (ii) non-fermenting Gram-negative bacteria (schemes with an antipseudomonal agent), and (iii) first-line agents not covering ESBL-Enterobacteriaceae nor non-fermenting Gram-negative bacteria. Meropenem-based schemes allowed for significantly higher rates of appropriate/adequate therapy (p<0.001). This benefit remained when only patients without risk factors for MDR were considered (p=0.021). In 106 patients (61%) empiric therapy was
modified: in 60 cases following initial inappropriate/inadequate therapy, in 46 patients in order to refine empiric therapy. In this study which reflects real-life practice, first-line use of meropenem provided significantly higher rates of the appropriate/adequate therapy, irrespective of presence of risk factors for MDR.

**Keywords:** antibiotic resistance – multidrug resistance – intensive care – infection – appropriate therapy
Introduction

Avoiding nosocomial infection remains a daily challenge for healthcare workers involved in the care of critically ill [1]. Despite several large scaled efforts to improve prevention of healthcare-associated infection [2-7], in general about 20% to 50% of patients hospitalized in intensive care units (ICUs) experience infection, either hospital or ICU-acquired [8, 9].

Severe nosocomial infection carries a substantial economic burden due to antimicrobial consumption and increased length of hospitalization [10-13]. In addition, severe infection seriously compromises survival. Attributable mortality varies from zero, to as much as 50% depending on a variety of factors [13-21]. Early initiation of the appropriate antimicrobial agents is a cornerstone in optimising clinical patient outcomes, [1]. Failure of timely administration of appropriate antimicrobial therapy results in a dramatic increase in mortality [22-25]. Selecting an empiric regimen which covers causative pathogens, however, is hampered by the presence of multidrug resistant (MDR) micro-organisms which is the utmost important cause of empiric inappropriate therapy. Since antimicrobial consumption itself is a major trigger for MDR development, physicians are frequently urged to use ‘last-resort antibiotics’ thoughtfully. The challenge is to achieve high rates of empiric appropriate therapy, while avoiding unnecessary use of antibiotics, and hence, MDR development [1, 26].

In order to achieve this goal, two main strategies have been proposed. In the surveillance-assisted strategy, the empiric regimen is selected mainly based on the
presence or absence of MDR pathogens in routine surveillance cultures. The strength of this approach is the high negative predictive value of surveillance cultures to predict MDR involvement in subsequent infection. If cultures are taken at least twice weekly, this strategy is capable to combine high rates of empiric appropriate therapy with reduced consumption of antibiotics in pneumonia and bacteremia [27-33]. The cost-effectiveness of this approach, however, remains unclear. Another approach is the ‘de-escalation strategy’ which, if there are risk factors for MDR, recommends an empiric start with a regimen which covers most potential MDR pathogens such as extended-spectrum beta-lactamase producing (ESBL) Enterobacteriaceae, non-fermenting Gram-negative bacteria, and meticillin-resistant Staphylococcus aureus (MRSA) [34-36]. Once culture results are available, and if feasible, narrowing the antimicrobial spectrum is advised. This concept, often referred to as ‘de-escalation’, is widely used and advocated [37-40]. This strategy has been shown to be successful and safe, and may also reduce antibiotic use and hence limit the emergence of MDR [36, 41].

The objective of the present study was prospectively to investigate patterns of antimicrobial therapy in critically ill patients with nosocomial infection. More precisely we formulated the following research questions: (i) What is the rate of empiric appropriate or adequate therapy achieved? (ii) Which antibiotic selections allow for the highest rates of empiric appropriate or adequate therapy, either in the presence or absence of risk factors for MDR pathogens? (iii) What is the rate by which empiric therapy (either appropriate/adequate or not) is subsequently modified?
Methods

Study design. A prospective multicenter observational study was performed between February 2006 and June 2007. 24 Belgian ICUs participated. In all centres the study was approved by the local ethics committee and informed consent was requested. In all centers antimicrobial prescribing was by, or supervised by, the attending senior intensivist.

Inclusion criteria. Eligible patients were those who gave informed consent, were at least 18 years of age, were hospitalized in the ICU, and experienced severe hospital-acquired infection; either pneumonia, intra-abdominal infection, primary or secondary bloodstream infection originating from a source other than pneumonia or intra-abdominal infection (e.g. bacteremia secondary to urinary tract infection or sinusitis).

Definitions. Infections were considered hospital- or ICU-acquired when diagnosed at least 48 hours after hospital or ICU admission respectively. Severe bacterial infections were defined according to the International Sepsis Forum Consensus Conference on Definitions of Infection in the ICU [42]. Definitions of invasive fungal infections are described elsewhere [43, 44]. Pneumonia was considered ventilator-associated when occurring after at least 48 hours of mechanical ventilation. For the purpose of the study, only the first episode per patient was considered. Pneumonia or intra-abdominal infection with bacteraemic breakthrough (i.e. positive blood cultures) were classified according to the primary infection. Bloodstream infections
secondary to other sources than pneumonia or intra-abdominal infection were classified as secondary bloodstream infection.

Definitions of MDR are described elsewhere [10, 32, 45]. *Candida* spp. were considered MDR when resistant to fluconazole.

Following the epidemiological scope of the study, aiming at insights into empiric therapy in general, we also wanted to include microbiologically unconfirmed infections with obvious signs of clinical sepsis. For this purpose we made a difference between appropriate and adequate empiric therapy. The term appropriate therapy was used for microbiologically documented infectious episodes and was defined as *in vitro* susceptibility of the causative pathogen with clinical response to the agent administered. The term adequate therapy was used in non-microbiologically confirmed infections, and was defined as favourable clinical response within five days of treatment (resolution of signs of sepsis).

Severity of disease was assessed by means of the acute physiology and chronic health evaluation (APACHE) II score [46]. The following co-morbid conditions were recorded: respiratory disease (chronic restrictive, obstructive or pulmonary vascular disease resulting in severe exercise restriction), cardiac disease (New York Heart Association Class IV), diabetes mellitus, hepatic disease (cirrhosis and portal hypertension; episodes of past upper gastro-intestinal bleeding attributed to portal hypertension or prior episodes of hepatic failure or encephalopathy), renal disease (chronic glomerulonephritis, nephropathy, or chronic kidney disease), neurologic
disease (impairment of alertness or confusion) malignancy (haematologic or solid tumor), and neutropenia (absolute neutrophil count <1500 cells/mm³).

To assess relationships between empiric antibiotic selection and rates of appropriate and adequate therapy, the empiric antimicrobial schemes were grouped according to the spectrum of pathogens covered. Table 1 gives the classification of empiric antimicrobial schemes. Because of the small numbers of empiric schemes covering MRSA and the relative low occurrence rate of MRSA in the cohort, empiric antibiotic schemes were classified in three major groups: (i) coverage of ESBL-producing Enterobacteriaceae and non-fermenting Gram-negative bacteria (“meropenem [MER]-based” schemes), (ii) coverage of non-fermenting Gram-negative bacteria (schemes including an antipseudomonal agent), and (iii) schemes without coverage of either of ESBL-producing Enterobacteriaceae nor non-fermenting Gram-negative bacteria (first line agents). In this analysis the added value of vancomycin as empiric therapy in order to cover meticillin resistant Gram-positive pathogens was investigated separately.

Prior antibiotic exposure was defined as the administration of antimicrobial agents within one month preceding the current infectious episode. Prior hospitalization was defined as an hospital admission within the four months preceding the current ICU admission.

Data analyses. For comparisons between groups of continuous variables the Mann Whitney U test and Fisher Exact test or Chi-square test were used as appropriate.

Independent relationships with empiric appropriate or adequate therapy were
assessed by means of a logistic regression analysis. Variables taken into account in the logistic regression analysis either showed a moderate relationship in univariate analysis or a logical relationship with the dependent variable. Variables considered were: age, APACHE II score, underlying diseases, hospitalization in another ward prior to ICU admission, prior antibiotic exposure, and empiric antibiotic schemes. Results of the regression analysis are reported as odds ratios (OR) and 95% confidence intervals (CI).
Results

Demographics. During the study period 198 patients were included. Due to incomplete patient files 27 patients were excluded, resulting in a final database containing 171 patients. Patient characteristics are given in Table 2. Primary infections were pneumonia (n=127, of which 66 ventilator-associated), intra-abdominal infection (n=23) bloodstream infection (n=21, of which 9 primary, 1 catheter-related, and 12 secondary to a source other than pneumonia or intra-abdominal infection). 115 infections were ICU-acquired (66.7%). Approximately 75% of infections were microbiologically documented (Figure 1). This represented 129 microbiologically documented with 165 micro-organisms. Gram-negative bacteria were most common (n=122, 73.9%) with Pseudomonas aeruginosa (n=29), Escherichia coli (n=26), Enterobacter aerogenes (n=21), Klebsiella pneumonia (n=7), and Klebsiella oxytoca (n=7) as predominant pathogens. Among the 42 Gram-positive bacteria, Staphylococcus aureus (n=22), Streptococcus pneumoniae (n=11), and enterococci (n=5) were most frequently isolated. One fungal pathogen was isolated. In 64 of the 129 microbiologically documented infections MDR pathogens were involved (49.6%).

Risk factors for multidrug resistance (MDR). Risk factors for MDR were assessed in order to evaluate empiric antimicrobial regimens relative to their presence. No specific underlying conditions appeared to predispose for MDR involvement. MDR involvement was more frequent in patients with prior antibiotic exposure (74.3% vs. 41.3%, p=0.001; relative risk 4.26, 95% CI: 1.80-10.09). Hospitalization in another ward prior to ICU admission was also recognized as significantly associated with
MDR involvement (59.0% vs. 40.9%, p=0.041; relative risk 2.08, 95% CI: 1.03-4.22).

Figure 2 shows a breakdown of microbiologically documented infections according to the presence of these two risk factors for MDR, and subsequent MDR involvement.

Length of ICU stay prior to the development of infection, however, was negatively associated with the risk of MDR involvement. Patients who experienced infections without MDR pathogens developed this infection after a median of 3 days (IQR: 2-7 days), while infections caused by MDR pathogens occurred after a median of 2 days (IQR: 0-4.25 days), (p=0.002).

Rates of empiric appropriate or adequate therapy and subsequent modification. The presence of MDR pathogens in infections was associated with a significant lower rate of empiric appropriate therapy: 87.7% vs. 35.9% (p<0.001). Rates of empiric appropriate and adequate therapy are illustrated in Figure 3. In 80 of the 129 microbiologically documented infections, empiric therapy was appropriate (62.0%). In non-microbiologically documented infections, empiric therapy was judged adequate in 29 of 42 infections (69.0%). In 106 patients (62.0%) empiric therapy was modified: in 60 cases following initial inappropriate or inadequate therapy, and in 46 patients in order to refine empiric therapy.

Empiric antimicrobial selection and rates of appropriate or adequate therapy. In 12 infections the causative pathogen was meticillin-resistant (10 MRSA, 2 meticillin-resistant Staphylococcus epidermidis). Vancomycin administered empirically in 14 cases, but in only was a meticillin-resistant pathogen involved. The rate of inappropriate therapy
in case of meticillin-resistance involvement was thus 75%. Due to the relative low prevalence of meticillin-resistance and the low added value of initiating a glycopeptide, the association of such an agent did not alter the study results in this particular cohort. Therefore, we analyzed rates of empiric appropriate or adequate therapy irrespective of the coverage of MRSA (Figure 4a). Coverage of of ESBL-producing Enterobacteriaceae (by MER-based empiric schemes) allowed for significantly higher rates of appropriate or adequate therapy. We hypothesized that the benefit of using a MER-based empiric scheme would disappear when only patients without risk factors for MDR were taken into account. However, in this analysis empiric schemes covering of ESBL-producing Enterobacteriaceae remained superior (Figure 4b).

When MER-based empiric schemes were compared with others, a difference of approximately 30% in empiric appropriate or adequate therapy was observed when all patients were included (89.2% vs. 56.0%; p<0.001), and this distinction remained when only patients without risk factors for MDR were considered (83.6% vs. 53.8%; p=0.040).

In a multivariable logistic regression analysis, the only factors independently associated with empiric appropriate or adequate therapy were a MER-based empiric scheme (OR 18.1, 95% CI 4.8 to 68.1; p<0.001) and the presence of MDR pathogens (OR 0.04, 95% CI 0.01 to 0.10; p<0.001). No other variables reached statistical significance.
Discussion

In this prospective, observational study, rates of empiric appropriate or adequate therapy were only 63.7%. About half of the infections were caused by MDR microorganisms, mostly ESBL-Enterobacteriaceae and P. aeruginosa. As such, only the inclusion of meropenem in the empiric scheme, allowed for acceptable rates of appropriate therapy (approximately 90%).

Several reasons for the low rate of appropriate or adequate therapy are possible. The overall prevalence of MDR in this particular cohort is high (~50%) and the rate of appropriate or adequate therapy in infections caused by MDR pathogens was low (35.9%). MDR is recognized as a determinant of inappropriate therapy [47-52]. The involvement of MDR can be partly predicted by some typical risk factors such as prior antibiotic exposure and length of ICU stay (or mechanical ventilation in case of pneumonia) of >7 days [32, 53]. Other risk factors such as underlying diseases and recent surgery/hospitalization can also be taken into account. However, in our cohort of ICU patients with nosocomial infection some of the recognized risk factors failed to predict the involvement of MDR. Also, MDR pathogens were isolated in about 40% of patients in the absence of these risk factors. As a consequence, the predictive value of these risk factors was low. As such, the generally accepted concepts of risk for MDR involvement were not supported by this particular cohort.

It appears that there exists a serious problem of MDR in general wards in Belgian hospitals, thereby contributing to the low rate of appropriate empiric therapy.
Indeed, a decade ago a higher incidence of *Enterobacter aerogenes* with an increasing resistance pattern was noticed in Belgian hospitals [54, 55].

Following the high rate of of ESBL-producing Enterobacteriaceae and *P. aeruginosa*, a MER-based empiric scheme gave the highest rates of appropriate/adequate therapy. Due to the failure of classic risk factors to predict MDR involvement, performance of empiric schemes did not substantially alter when only patients without risk factors were examined (Figure 2). Hence, the present study suggests coverage of both of ESBL-producing Enterobacteriaceae and *P. aeruginosa* is warranted and supports the de-escalation strategy. The present findings however, with the failure of MDR prediction based on general characteristics in particular, provide perspectives for the surveillance assisted approach in which individual colonization status is a major element in steering empiric therapy.

In 62% (n=106) of patients empiric therapy was modified. In 60 cases modification followed initial inappropriate or inadequate therapy, in the other 46 patients empiric therapy could be refined (true de-escalation). It is noteworthy that when only microbiologically documented infections are considered, four of 129 patients received inappropriate therapy even after culture results were available (Figure 1). In MER-based empiric schemes (n=37) therapy was continued in 23 and modified in 14 patients (in four cases because of initial inappropriate therapy and in 10 to narrow the spectrum). This supports the approach of empiric antibiotic coverage followed by de-escalation. Likewise Baran et al. found that previous exposure to carbapenems
was 44% in patients with infections caused by imipenem-resistant *Acinetobacter baumannii*, but only 12% in patients infected by imipenem-susceptible strains [56].

However multivariate analysis showed it was previous antibiotic exposure, and not carbapenem exposure specifically, that was an independent risk factor for imipenem-resistance. The link between exposure and specific resistance development is intuitive, but such findings suggest the aim of reducing microbial selection pressure is valid for all antimicrobial agents. Further, based on the Surveillance of Antimicrobial Use and Antimicrobial Resistance in German ICUs (SARI project), Meyer E *et al.* identified carbapenem use as an independent predictor for increased incidence of *Stenotrophomonas maltophilia* [57].

This study has its limitations. Firstly, no outcome data are available since the primary aim of the study was to describe antibiotic prescription patterns and how they perform in terms of appropriate therapy. However, the relationship between initial empiric failure to cover the causative pathogen and adverse outcomes was demonstrated repeatedly, and is generally accepted as an important quality indicator [58, 59]. Secondly, the cohort does not represent a consecutive series of ICU patients with nosocomial infections. This may have led to selection bias for more severe infections, with a higher likelihood of MDR involvement, although there is no reason to believe this would have changed the relationship between MDR infection and risk factors.

In conclusion, in this prospective study, which reflects real life practice in ICU patients with nosocomial infections, the rate of appropriate or adequate empiric
therapy was 63.7%. This study demonstrated that classic risk factors for MDR such as prior antibiotic exposure and length of ICU stay, may be insufficient to predict MDR involvement. As such, empiric first-line use of MER allowed for significantly higher rates of appropriate or adequate therapy, irrespective of presence of these risk factors, and may be recommended in settings with a high prevalence of MDR pathogens. In addition, these data illustrate the necessity for strict infection prevention and control.

324 Declarations
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Competing Interests: No conflicts of interest to declare

Ethical Approval: For this non-interventional, observational study, ethical approval was given by the local ethics committees of the participating centres (n=24).
References


Figure Legends

Figure 1 – Review of 171 nosocomial infections distributed for microbiological documentation and multidrug resistance involvement.

MDR, multidrug resistance or multidrug resistant

ESBL, extended spectrum beta-lactamase producing Enterobacteriaceae

MRSA, meticillin- resistant *Staphylococcus aureus*

MRSE, meticillin-resistant *Staphylococcus epidermidis*

Figure 3 - Rates of empiric appropriate or adequate therapy in ICU patients with nosocomial infections.

Cont., continuation of empiric therapy

Modif., modification of empiric therapy

Figure 2 – Breakdown of microbiologically documented infections according to the presence of risk factors for multidrug resistance, and multidrug resistance involvement.

MDR, multidrug resistance

Figure 4 – Rates of empiric appropriate or adequate therapy according to three major groups of empiric antibiotic regimens (coverage of meticillin-resistant pathogens not considered).

Figure 4a, all patients considered (n=170; in one patient no empiric therapy was initiated)

Figure 4b, only patients considered without risk factors for multidrug resistance involvement (hospitalization at a general ward prior to ICU admission and prior antibiotic exposure), (n=78).

Group 1: coverage of of ESBL-producing and *Pseudomonas aeruginosa* (meropenem-based schemes)
Group 2: coverage of *P. aeruginosa* (schemes containing an antipseudomonal agent)

Group 3: no coverage of ESBL-producing, or non-fermenting, Gram-negative bacteria (first line agents)
Table 1 – Empiric antibiotic regimens clustered in six major groups according to the pathogens covered.

<table>
<thead>
<tr>
<th>Coverage</th>
<th>Empiric regimens</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESBL- <em>Enterobacteriaceae</em> + <em>P. aeruginosa</em> + MRSA (n=6)</td>
<td>MER+VAN</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>MER+VAN+AMI</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>MER+AMI</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>MER+OXA</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>MER+CIP+AMI</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>MER+PIPtaz+AMI</td>
<td>2</td>
</tr>
<tr>
<td>ESBL- <em>Enterobacteriaceae</em> + <em>P. aeruginosa</em> (n=31)</td>
<td>MER</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>MER+AMI</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>MER+OXA</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>MER+CIP+AMI</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>MER+PIPtaz+AMI</td>
<td>2</td>
</tr>
<tr>
<td><em>P. aeruginosa</em> + MRSA (n=7)</td>
<td>PIPtaz+VAN+LEVO</td>
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</tr>
<tr>
<td></td>
<td>PIPtaz+VAN</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>CAZ+VAN</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>CEF+VAN</td>
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</tr>
<tr>
<td></td>
<td>CEF+VAN+AMI</td>
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</tr>
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<td><em>P. aeruginosa</em> (n=74)</td>
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<tr>
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<td>PIPtaz+AMI</td>
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<td>LEVO</td>
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<td></td>
<td>CEF+AMI</td>
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<td>CEF+CIP</td>
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<td></td>
<td>CIP+AMOXclav</td>
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<tr>
<td></td>
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<tr>
<td>Pathogen Description</td>
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<td>Count</td>
</tr>
<tr>
<td>-----------------------------------------------------------</td>
<td>--------------------</td>
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<tr>
<td>MRSA (n=1)</td>
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<tr>
<td>Non-MDR pathogens or <em>P. aeruginosa</em> (n=51)</td>
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<td></td>
<td>AMOXIclav</td>
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<td>AMOXIclav+metronidazole</td>
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<tr>
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<td>CEF</td>
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</tr>
<tr>
<td></td>
<td>MOXI</td>
<td>1</td>
</tr>
<tr>
<td></td>
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<tr>
<td></td>
<td>CTX+metronidazole</td>
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<tr>
<td></td>
<td>CEF+CLA</td>
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<tr>
<td></td>
<td>OXA</td>
<td>2</td>
</tr>
<tr>
<td>No empiric therapy (n=1)</td>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>

Legend:
MER, meropenem
AMI, aminoglycoside
VAN, vancomycin
OXA, oxacillin
CIP, ciprofloxacin
PIPtaz, piperacillin/tazobactam
LEVO, levofloxacin
FLU, fluconazole
AMOXIclav, amoxicillin/clavulanate
CEF, cefuroxim
CAZ, ceftazidime
CTX, ceftriaxone
CEFE, cefepim
MOXI, moxifloxacin
CLA, clarithromycin
Table 2 – Characteristics of 171 ICU patients with a nosocomial infection.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n (%)</th>
</tr>
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<tbody>
<tr>
<td>Gender (male)</td>
<td>107 (62.0)</td>
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<tr>
<td>Age (years)</td>
<td>67 (55 – 76)</td>
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<tr>
<td>APACHE II score</td>
<td>20 (15 – 24)</td>
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<td>Recent trauma / surgery</td>
<td>39 (22.8)</td>
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<td>Co-morbidities</td>
<td>139 (81.3)</td>
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<td>Respiratory disease</td>
<td>66 (38.6)</td>
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<td>Cardiac disease</td>
<td>59 (34.5)</td>
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<td>Neurologic disease</td>
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<td>Diabetes mellitus</td>
<td>36 (21.1)</td>
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<td>Hepatic disease</td>
<td>11 (6.4)</td>
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<tr>
<td>Renal disease</td>
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<td>Malignancy</td>
<td>28 (16.4)</td>
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<tr>
<td>Neutropenia</td>
<td>1 (0.6)</td>
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<td>Corticosteroid therapy</td>
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<td>Prior hospitalization</td>
<td>51 (30.4)</td>
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<tr>
<td>Hospitalization at another ward prior to ICU admission</td>
<td>84 (50.0)</td>
</tr>
<tr>
<td>Prior antibiotic use</td>
<td>49 (28.7)</td>
</tr>
<tr>
<td>ICU-acquired infection</td>
<td>115 (66.7)</td>
</tr>
<tr>
<td>ICU stay before onset of infection (days)</td>
<td>3.8 (0 - 6)</td>
</tr>
</tbody>
</table>

Data are described as n (%) or median (interquartile range)
Figure 1
Click here to download high resolution image
Microbiologically documented infections (n=129)

Risk factors for MDR (n=68; 52.7%)
- MDR involvement (n=40; 58.8%)
- No MDR involvement (n=28; 41.2%)

No risk factors for MDR (n=61; 47.3%)
- MDR involvement (n=24; 39.3%)
- No MDR involvement (n=37; 60.7%)

P=0.027
fig 3 (prev fig2)

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Figure 4

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Patterns of antimicrobial therapy in severe nosocomial infections: empirical choices, proportion of appropriate therapy and adaptation rates—a multicentre observational survey in critically ill patients

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ABSTRACT

This prospective, multicentre, observational study investigated relationships between antimicrobial choices and rates of empirical appropriate or adequate therapy as well as subsequent adaptation of therapy in 171 Intensive Care Unit (ICU) patients with severe nosocomial infections. Appropriate antibiotic therapy was defined as in vitro susceptibility of the causative pathogen and clinical response to the agent administered. In non-microbiologically documented infections, therapy was considered adequate in the case of a favourable clinical response within 5 days. Patients had pneumonia (n = 127; 66 ventilator-associated), intra-abdominal infection (n = 23) and bloodstream infection (n = 21). Predominant pathogens were *Pseudomonas aeruginosa* (n = 29), *Escherichia coli* (n = 26), *Staphylococcus aureus* (n = 22) and *Enterobacter aerogenes* (n = 21). Multidrug-resistant (MDR) bacteria were involved in 49.6% of infections, mostly extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae and MDR non-fermenting Gram-negative bacteria. Prior antibiotic exposure and hospitalisation in a general ward prior to ICU admission were risk factors for multidrug resistance. Empirical therapy was appropriate/adequate in 63.7% of cases. Empirical schemes were classified according to coverage of (i) ESBL-producing Enterobacteriaceae + non-fermenting Gram-negative bacteria (meropenem-based), (ii) non-fermenting Gram-negative bacteria (schemes with an antipseudomonal agent) and (iii) first-line agents not covering ESBL-producing Enterobacteriaceae or non-fermenting Gram-negative bacteria. Meropenem-based schemes allowed for significantly higher rates of appropriate/adequate therapy (*P* < 0.001). This benefit remained when only patients without risk factors for MDR infection were considered (*P* = 0.021). Empirical therapy was adapted in 106 patients (62%), in 60 cases following initial
inappropriate/inadequate therapy and in 46 patients to fine-tune empirical therapy. In this study reflecting real-life practice, first-line use of meropenem provided significantly higher rates of appropriate/adequate therapy, irrespective of presence of risk factors for multidrug resistance.
1. Introduction

Avoiding nosocomial infection remains a daily challenge for healthcare workers involved in care of the critically ill [1]. The prevalence of infection strongly depends on the presence of particular iatrogenic risk factors, such as the use of indwelling devices and extensive surgery, as well as the severity of underlying disease and critical illness. Despite several large-scale efforts to improve the prevention of healthcare-associated infection [2–7], in general ca. 20–50% of patients hospitalised in the Intensive Care Unit (ICU) experience infection, either hospital- or ICU-acquired [8,9].

Severe nosocomial infection carries a substantial economic burden owing to extensive antimicrobial consumption and, even more importantly, increased length of hospitalisation [10–13]. In addition, severe infection seriously compromises the likelihood of survival. Attributable mortality rates vary from as low as 0% to a dramatic 50% depending of the type of infection, the causative pathogen, patient age, associated co-morbidities and overall quality of the anti-infective approach [13–21]. Among all the processes that should be fulfilled with the aim of optimising clinical patient outcome, early initiation of the proper antimicrobial agent is a cornerstone [1]. Failure to administer appropriate antimicrobial therapy in a timely manner results in a dramatic increase in the fatality rate [22–25]. However, selecting an empirical regimen that covers the causative pathogen is hampered by the presence of multidrug-resistant (MDR) microorganisms, which is the most important cause of inappropriate empirical therapy. Since antimicrobial consumption in itself is a major trigger for the development of multidrug resistance, physicians are frequently urged
to use ‘last-line antibiotics’ carefully. In fact, the challenge is to achieve high rates of appropriate empirical therapy in order to optimise patient survival whilst avoiding unnecessary use of antibiotics with the intention to minimise microbial selection pressure and hence development of multidrug resistance [1,26].

To accomplish this goal, in the past decade two main strategies have been proposed. In the surveillance-assisted strategy, the empirical regimen is selected mainly based on the presence or absence of MDR pathogens in routine surveillance cultures. The strength of this approach is the high negative predictive value of surveillance cultures in predicting the involvement of MDR microorganisms in subsequent infection. On the condition that cultures are taken at least twice weekly, this strategy is able to combine high rates of appropriate empirical therapy with reduced consumption of antibiotics in pneumonia and bacteremia [27–33]. However, the cost effectiveness of this approach remains questionable. Another approach is the so-called ‘de-escalation strategy’ that, on the condition of risk factors for MDR involvement, recommends initiation of empirical therapy with a regimen that covers most potential MDR pathogens such as extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae, non-fermenting Gram-negative bacteria and meticillin-resistant Staphylococcus aureus (MRSA) [34–36]. Once culture results are available, and if feasible, narrowing the antimicrobial spectrum is advised. This concept, often referred to as ‘de-escalation’, is widely used and advocated [37–40]. This strategy has been demonstrated to be successful and safe and may also reduce antibiotic use and hence limit the emergence of multidrug resistance [36,41].
The objective of the present study was prospectively to investigate patterns of antimicrobial therapy in critically ill patients with nosocomial infection. More precisely, the following research questions were formulated. (i) What is the rate of empirical appropriate or adequate therapy achieved? (ii) Which antibiotic selections allow for the highest rates of empirical appropriate or adequate therapy, either in the presence or absence of risk factors for MDR pathogens? And (iii) what is the rate by which empirical therapy (either appropriate/adequate or not) is adapted?

2. Methods

2.1. Study design

A prospective, multicentre observational study was performed between February 2006 and June 2007. In total, 24 Belgian ICUs participated. Informed consent was requested from all patients. In all centres, antimicrobial prescribing was done or supervised by the attending senior intensive care physician.

2.2. Inclusion criteria

Eligible patients were those who provided informed consent, were at least 18 year of age, hospitalised in the ICU and experienced severe hospital-acquired infection, either pneumonia, intra-abdominal infection, primary bloodstream infection or secondary bloodstream infection originating from a source other than pneumonia or intra-abdominal infection (e.g. bacteraemia secondary to urinary tract infection or sinusitis).
2.3. Definitions

Infections were considered hospital- or ICU-acquired when they were diagnosed >48 h after hospital or ICU admission, respectively. Severe bacterial infections were defined following the International Sepsis Forum Consensus Conference on Definitions of Infection in the ICU [42]. Definitions of invasive fungal infections are described elsewhere [43,44]. Pneumonia was considered ventilator-associated when occurring after >48 h of mechanical ventilation. For the purpose of the study, only the first episode per patient was considered. Pneumonia or intra-abdominal infections with bacteraemic breakthrough (i.e. positive blood cultures) were classified according to the primary infection. Bloodstream infection secondary to sources other than pneumonia or intra-abdominal infection were classified as secondary bloodstream infection.

Definitions of multidrug resistance are described elsewhere [10,32,45]. Candida spp. were considered MDR when resistant to fluconazole.

Following the epidemiological scope of the study aiming at insights into empirical therapy in general, we also wanted to include microbiologically undocumented infections with obvious signs of clinical sepsis. For this purpose, a difference was made between appropriate and adequate empirical therapy. The term appropriate therapy was valid for microbiologically documented infectious episodes and was defined as in vitro susceptibility of the causative pathogen and clinical response to the agent administered. The term adequate therapy was used in non-microbiologically documented infections and was defined as favourable clinical response within 5 days of therapy (resolution of signs of sepsis).
Severity of disease was assessed by means of the Acute Physiology and Chronic Health Evaluation (APACHE) II score [46]. The following co-morbid conditions were registered: respiratory disease (chronic restrictive, obstructive or pulmonary vascular disease resulting in severe exercise restriction); cardiac disease (New York Heart Association Class IV); diabetes mellitus; hepatic disease (cirrhosis and portal hypertension, episodes of past upper gastrointestinal bleeding attributed to portal hypertension or prior episodes of hepatic failure or encephalopathy); renal disease (chronic glomerulonephritis, nephropathy or chronic kidney disease); neurological disease (impairment of alertness or confusion); malignancy (haematological cancer or solid tumour); and neutropenia (absolute neutrophil count <1500 cells/mm$^3$).

To assess relationships between empirical antibiotic selection and rates of appropriate or adequate therapy, the empirical antimicrobial schemes were grouped according to the spectrum of pathogens covered. Table 1 describes the classification of empirical antimicrobial schemes. Because of the small number of empirical schemes covering MRSA and the relative low occurrence rate of MRSA in the cohort, empirical antibiotic schemes were classified in three major groups: (i) coverage of ESBL-producing Enterobacteriaceae + non-fermenting Gram-negative bacteria (meropenem-based schemes); (ii) coverage of non-fermenting Gram-negative bacteria (schemes including an antipseudomonal agent); and (iii) schemes without coverage of either ESBL-producing Enterobacteriaceae or non-fermenting Gram-negative bacteria (first-line agents). In this analysis, the added value of vancomycin as empirical therapy to cover meticillin-resistant Gram-positive pathogens was investigated separately.
Prior antibiotic exposure was defined as administration of antimicrobial agents within 1 month preceding the current infectious episode. Prior hospitalisation was defined as a hospital admission within the 4 months preceding the current ICU admission.

2.4. Data analysis

Continuous variables are described as median [interquartile range (IQR)] and discrete variables as number (%). For comparison between groups, the Mann–Whitney U-test and Fisher’s exact test or $\chi^2$ test were used as appropriate. Independent relationships with empirical appropriate or adequate therapy were assessed by means of logistic regression analysis. Variables taken into account in the logistic regression analysis either showed a moderate relationship in the univariate analysis or a logic relationship with the dependent variable. Variables considered were age, APACHE II score, underlying diseases, hospitalisation in another ward prior to ICU admission, prior antibiotic exposure and empirical antibiotic schemes. Results of the regression analysis are reported as odds ratios (OR) and 95% confidence interval (CI).

3. Results

3.1. Demographics

During the study period, 198 patients were included. Owing to incomplete patient files, 27 patients were excluded, resulting in a final database containing 171 patients. Patient characteristics are described in Table 2. Primary infections were pneumonia
(n = 127, of which 66 were ventilator-associated), intra-abdominal infection (n = 23) and bloodstream infection (n = 21, of which 9 were primary, 1 was catheter-related and 11 secondary to a source other than pneumonia or intra-abdominal infection). One hundred and fifteen infections (67.3%) were ICU-acquired. Approximately 75% of infections were microbiologically documented (Fig. 1). This represented 129 microbiologically documented infections in which 165 microorganisms were isolated. Gram-negative bacteria were most common (n = 122; 73.9%), with *Pseudomonas aeruginosa* (n = 29), *Escherichia coli* (n = 26), *Enterobacter aerogenes* (n = 21), *Klebsiella pneumonia* (n = 7) and *Klebsiella oxytoca* (n = 7) being the predominant pathogens. Among the 42 Gram-positive bacteria, *S. aureus* (n = 22), *Streptococcus pneumoniae* (n = 11) and enterococci (n = 5) were most frequently isolated. One fungal pathogen was isolated. MDR pathogens were involved in 64 (49.6%) of the 129 microbiologically documented infections. Fig. 1 shows the breakdown of the different types of resistance involved in these infections.

### 3.2. Risk factors for multidrug resistance

Risk factors for multidrug resistance were assessed in order to evaluate empirical antimicrobial regimens relative to their presence. No specific underlying conditions appeared to predispose for involvement of MDR organisms. MDR involvement was more frequent in patients with prior antibiotic exposure compared with patients without prior antibiotic exposure [74.3% vs. 41.3%; *P* = 0.001; relative risk (RR) = 4.26, 95% CI 1.80–10.09]. Hospitalisation in another ward prior to ICU admission was also recognised as significantly associated with MDR involvement (59.0% vs. 40.9%; *P* = 0.041; RR = 2.08, 95% CI 1.03–4.22). Fig. 2 shows a breakdown of
microbiologically documented infections according to the presence of these two risk factors for multidrug resistance and subsequent MDR involvement.

Length of ICU stay prior to the development of infection was negatively associated with the risk of MDR involvement. Patients who experienced infections without MDR pathogens developed this infection after a median of 3 days (IQR 2–7 days), whilst infections caused by MDR pathogens occurred after a median of 2 days (IQR 0–4.25 days) ($P = 0.002$).

3.3. Rates of empirical appropriate or adequate therapy and subsequent adaptation

The presence of MDR pathogens in infections was associated with a significant lower rate of empirical appropriate therapy (87.7% vs. 35.9%; $P < 0.001$). Rates of empirical appropriate and adequate therapy are illustrated in Fig. 3. Empirical therapy was appropriate in 80 (62.0%) of the 129 microbiologically documented infections. In the 42 non-microbiologically documented infections, empirical therapy was judged adequate in 29 (69.0%). Empirical therapy was adapted in 106 patients (62.0%), in 60 cases following initial inappropriate or inadequate therapy and in 46 patients to fine-tune empirical therapy.

3.4. Empirical antimicrobial selection and rates of appropriate or adequate therapy

In 12 infections the causative pathogen was meticillin-resistant (10 MRSA and 2 meticillin-resistant Staphylococcus epidermidis). Vancomycin was administered 14 times as an empirical agent, but in only 3 cases in which a meticillin-resistant pathogen proved to be involved. As such, the rate of inappropriate therapy in the
case of meticillin resistance involvement was 75%. Owing to the relative low prevalence of meticillin resistance as well as the low added value of initiating a glycopeptide, the association (or not) of such an agent did not alter the study results in this particular cohort. Therefore, rates of empirical appropriate or adequate therapy were analysed irrespective of the coverage of MRSA. This is illustrated in Fig. 4a. Coverage of ESBL-producing Enterobacteriaceae (by meropenem-based empirical schemes) allowed for significantly higher rates of appropriate or adequate therapy. Because the advantage of an antibiotic agent that covers ESBL-producing Enterobacteriaceae is obvious in settings with a high prevalence of multidrug resistance, it was hypothesised that the benefit of using a meropenem-based empirical scheme would fade away when only patients without risk factors for MDR were taken into account. However, in this analysis empirical schemes covering ESBL-producing Enterobacteriaceae remained superior (Fig. 4b).

When meropenem-based empirical schemes were compared with other empirical regimens, a difference of ca. 30% in empirical appropriate or adequate therapy was observed when all patients were taken into account (89.2% vs. 56.0%; $P < 0.001$) and this distinction remained when only patients without risk factors for MDR infection were considered (83.6% vs. 53.8%; $P = 0.040$).

In a multivariate logistic regression analysis, the only factors independently associated with empirical appropriate or adequate therapy were a meropenem-based empirical scheme (OR $= 18.1$, 95% CI 4.8–68.1; $P < 0.001$) and the presence of MDR pathogens (OR 0.04, 95% CI 0.01–0.10; $P < 0.001$). No other variables reached the level of significance.
4. Discussion

In this prospective, observational study that aimed to reflect real-life daily practice, rates of empirical appropriate or adequate therapy were only 63.7%. Approximately one-half of the infections were caused by MDR microorganisms, mostly ESBL-producing Enterobacteriaceae and P. aeruginosa. As such, only the inclusion of meropenem in the empirical scheme allowed for acceptable rates of appropriate therapy (ca. 90%).

Several reasons for the low rate of appropriate or adequate therapy can be proposed. The overall prevalence of multidrug resistance in this particular cohort is high (ca. 50%) and the rate of appropriate or adequate therapy in infections caused by MDR pathogens was very poor (35.9%). Multidrug resistance is well recognised as a major determinant of inappropriate therapy [47–52]. However, to a certain extent the involvement of multidrug resistance can be predicted on the basis of some typical risk factors, of which the most essential are prior antibiotic exposure and length of ICU stay (or mechanical ventilation in the case of pneumonia) of >7 days [32,53]. Other risk factors, such as a particular underlying diseases (e.g. chronic obstructive pulmonary disease) and recent surgery/hospitalisation, can also be taken into account but generally are not included in the principal risk factors. Strangely enough, in this cohort of ICU patients with nosocomial infection some of the classic patterns failed to predict the involvement of multidrug resistance. For instance, prior hospitalisation (within 4 months of the current hospital admission) was not associated with a higher likelihood of multidrug resistance, whilst length of ICU stay was even
inversely related to MDR involvement. On the other hand, prior antibiotic exposure and hospitalisation in a general ward prior to ICU admission appeared to have a significant relationship with MDR involvement. Importantly, however, although these relationships were statistically significant, MDR pathogens were isolated in ca. 40% of patients in the absence of these risk factors. As a consequence, the predictive value of these risk factors was low. As such, the generally accepted concepts of risk perception for MDR involvement failed in this particular cohort. We have no plausible explanation for this observation. Given the relationship between prior hospitalisation in a general ward and multidrug resistance, the relatively high number of infections already present at the time of ICU admission and the short length of stay in the ICU prior to infection, it appears that there exists a serious problem of multidrug resistance in general wards in Belgian hospitals, thereby contributing to the low rate of empirical appropriate therapy in ICUs. Indeed, already a decade ago a higher incidence of *E. aerogenes* with an increasing resistance pattern had been noticed in Belgian hospitals [54,55].

Following the high prevalence rate of ESBL-producing Enterobacteriaceae and *P. aeruginosa*, a meropenem-based empirical scheme allowed for the highest rates of appropriate/adequate therapy. Owing to the failure of classic risk factors to predict MDR involvement (Fig. 2), performance rates of empirical schemes did not substantially alter when only patients without risk factors were considered (Fig. 4b). Hence, based on the present study, an approach including coverage both of ESBL-producing Enterobacteriaceae and *P. aeruginosa* seems highly warranted. Without firm supportive knowledge of local ecology in ICU and non-ICU settings indicating low MDR levels, an empirical strategy that does not cover ESBL-producing
Enterobacteriaceae and *P. aeruginosa* is potentially dangerous and as such supports the de-escalation strategy. However, the present findings, with the failure of MDR prediction based on general characteristics in particular, provide perspectives for the surveillance-assisted approach in which individual colonisation status is a major element in steering empirical therapy.

Empirical therapy was adapted in 62% of patients (*n*= 106). In 60 cases adaptation followed initial inappropriate or inadequate therapy, whereas in 46 patients empirical therapy could be fine tuned (true de-escalation). Of note is that when only microbiologically documented infections are considered, 4 of 129 patients received inappropriate therapy even after the availability of culture results (Fig. 3). In meropenem-based empirical schemes (*n*= 37), therapy was continued in 23 patients and adapted in 14 patients (in 4 cases because of initial inappropriate therapy and in 10 cases to narrow down the spectrum). As this study supports the approach of empirical coverage of ESBL-producing Enterobacteriaceae and *P. aeruginosa*, we stress the importance of de-escalation whenever possible. Baran et al. [56] reported that the rate of previous exposure to carbapenems was 44% in patients with infections caused by imipenem-resistant *Acinetobacter baumannii* whereas it was only 12% in patients infected by imipenem-susceptible *A. baumannii* isolates. Yet in multivariate analysis, previous antibiotic exposure and not carbapenem exposure in particular appeared to be an independent risk factor for imipenem resistance. The link between exposure and specific resistance development is obvious and should not be disregarded, but this suggests that the mission to reduce microbial selection pressure is valid for all antimicrobial agents and not only for carbapenems. Furthermore, based on the Surveillance of Antimicrobial Use and Antimicrobial
Resistance in German ICUs (SARI project), Meyer et al. [57] identified carbapenem use as an independent predictor for a higher *Stenotrophomonas maltophilia* incidence. Although these data do not disclose a causal relationship, they are highly suggestive for the specific selection pressure of this pathogen. Therefore, excessive use of carbapenems is to be avoided by a strict de-escalation strategy and by avoidance of unnecessary long therapies.

The most important advantage of this study is its non-interventional design, reflecting real daily practice, thereby disclosing the true problem points in empirical antibiotic therapy in critically ill patients. Owing to the multicentre approach, the data might be valid for many tertiary care centres in Belgium and abroad.

However, the study has limitations. First, no outcome data are available as the primary aim of the study was to describe antibiotic prescription patterns and how they perform in terms of appropriate therapy. However, the relationship between failure of initial empirical therapy to cover the causative pathogen and adverse outcomes has been demonstrated repeatedly and is generally accepted as an important quality indicator [58,59]. Second, the cohort does not represent a consecutive series of ICU patients with nosocomial infections. It is possible that this might have led to a selection bias towards more severe infections, with a higher likelihood of MDR involvement.

In conclusion, in this prospective study reflecting real-life practice in ICU patients with nosocomial infections, the rate of appropriate or adequate empirical therapy was 63.7%. This study demonstrated that classic risk factors for multidrug resistance such
as prior antibiotic exposure and length of ICU stay may be insufficient to predict MDR involvement. As such, empirical first-line use of meropenem allowed for significantly higher rates of appropriate or adequate therapy, irrespective of the presence of these risk factors, and may be recommended in settings with a high prevalence of MDR pathogens. In addition, these data illustrate the necessity for strict infection prevention and control.

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Competing interests
None declared.

Ethical approval
Ethical approval was given by the local ethics committees of the participating centres \((n = 24)\).
References


caused by antibiotic-resistant Gram-negative bacteria in an intensive care unit.


**Fig. 1.** Review of 171 nosocomial infections by microbiological documentation and multidrug resistance involvement. MDR, multidrug resistance or multidrug resistant; ESBL, extended-spectrum β-lactamase-producing Enterobacteriaceae; MRSA, meticillin-resistant *Staphylococcus aureus*; MRSE, meticillin-resistant *Staphylococcus epidermidis*.

**Fig. 2.** Breakdown of microbiologically documented infections according to the presence of risk factors for multidrug resistance (MDR) and MDR involvement.

**Fig. 3.** Rates of empirical appropriate or adequate therapy in Intensive Care Unit patients with nosocomial infections. Cont., continuation of empirical therapy; Adapt., adaptation of empirical therapy.

**Fig. 4.** Rates of empirical appropriate or adequate therapy according to three major groups of empirical antibiotic regimens (coverage of meticillin-resistant pathogens not considered): (a) all patients considered (*n* = 170; in 1 patient no empirical therapy was initiated); and (b) only patients without risk factors for multidrug resistance involvement considered (hospitalisation in a general ward prior to Intensive Care Unit admission and prior antibiotic exposure) (*n* = 78). Group 1, coverage of extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae + *Pseudomonas aeruginosa* (meropenem-based schemes); Group 2, coverage of *P. aeruginosa* (schemes containing an antipseudomonal agent); and Group 3, no coverage of ESBL-producing or non-fermenting Gram-negative bacteria (first-line agents).
Table 1

Empirical antibiotic regimens clustered in six major groups according to the pathogens covered

<table>
<thead>
<tr>
<th>Coverage</th>
<th>Empirical regimens</th>
<th>n</th>
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<td>18</td>
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<tr>
<td></td>
<td>MER+OXA</td>
<td>1</td>
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<tr>
<td></td>
<td>MER+CIP+AMI</td>
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<tr>
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<tr>
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<td></td>
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<tr>
<td>CFX</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>CFX+MTR</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>CEF+CLA</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>TMO</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>OXA</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

**MRSA (n = 1)**

**Non-MDR pathogens or P. aeruginosa (n = 51)**

**No empirical therapy (n = 1)**

ESBL, extended-spectrum β-lactamase; MRSA, meticillin-resistant *Staphylococcus aureus*; MDR, multidrug-resistant; MER, meropenem; VAN, vancomycin; AMI, aminoglycoside; OXA, oxacillin; CIP, ciprofloxacin; PIP/TAZ, piperacillin/tazobactam; LEV, levofloxacin; CAZ, ceftazidime; CEP, cefepime; FLU, fluconazole; AMC, amoxicillin/clavulanic acid; MOX, moxifloxacin; CLA, clarithromycin; AZT, aztreonam; MTR, metronidazole; CEF, cefuroxime; CFX, ceftriaxone; TMO, temocillin.
Table 2

Characteristics of 171 Intensive Care Unit (ICU) patients with nosocomial infections

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male)</td>
<td>107 (62.6)</td>
</tr>
<tr>
<td>Age (years) [median (IQR)]</td>
<td>67 (55–76)</td>
</tr>
<tr>
<td>APACHE II score [median (IQR)]</td>
<td>20 (15–24)</td>
</tr>
<tr>
<td>Recent trauma/surgery</td>
<td>39 (22.8)</td>
</tr>
<tr>
<td>Co-morbidities</td>
<td>139 (81.3)</td>
</tr>
<tr>
<td>Respiratory disease</td>
<td>66 (38.6)</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>59 (34.5)</td>
</tr>
<tr>
<td>Neurological disease</td>
<td>28 (16.4)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>36 (21.1)</td>
</tr>
<tr>
<td>Hepatic disease</td>
<td>11 (6.4)</td>
</tr>
<tr>
<td>Renal disease</td>
<td>20 (11.7)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>28 (16.4)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Corticosteroid therapy</td>
<td>20 (11.7)</td>
</tr>
<tr>
<td>Prior hospitalisation</td>
<td>51 (29.8)</td>
</tr>
<tr>
<td>Hospitalisation at another ward prior to ICU admission</td>
<td>84 (49.1)</td>
</tr>
<tr>
<td>Prior antibiotic use</td>
<td>49 (28.7)</td>
</tr>
<tr>
<td>ICU-acquired infection</td>
<td>115 (67.3)</td>
</tr>
<tr>
<td>ICU stay before onset of infection (days) [median (IQR)]</td>
<td>3.8 (0–6)</td>
</tr>
</tbody>
</table>

IQR, interquartile range; APACHE, Acute Physiology and Chronic Health Evaluation.

aData are n (%) unless otherwise stated.
All infections (n=171)

Microbiologically documented (n=129; 75.4%)

- MDR involvement (n=64; 49.6%)
  - ESBL (n=30)
  - MDR Nonfermenting Gram-negative (n=19)
  - MRSA (n=5)

- No MDR involvement (n=65; 50.4%)
  - ESBL + MRSA (n=2)
  - MRSE (n=2)
  - MRSA + MDR Nonfermenting Gram-negative (n=2)
  - MDR anaerobe bacteria (n=1)

Not microbiologically documented (n=42; 24.6%)
Microbiologically documented infections (n=129)

Risk factors for MDR (n=68; 52.7%)
- MDR involvement (n=40; 58.8%)
- No MDR involvement (n=28; 41.2%)

No risk factors for MDR (n=61; 47.3%)
- MDR involvement (n=24; 39.3%)
- No MDR involvement (n=37; 60.7%)

P=0.027
**Figure 4a**

Percentage of appropriate or adequate empiric therapy:

- Group 1 (n=37): 90%
- Group 2 (n=85): 80%
- Group 3 (n=48): 70%

*P* = 0.001

**Figure 4b**

Percentage of appropriate or adequate empiric therapy:

- Group 1 (n=13): 90%
- Group 2 (n=34): 80%
- Group 3 (n=31): 70%

*P* = 0.021