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

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ABSTRACT

This prospective, observational multicentre ($n = 24$) 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 the case of favourable 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 β-lactamase (EBSL)-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 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 reflecting 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.

1. Introduction

Avoiding nosocomial infection remains a daily challenge for healthcare workers involved in the care of the critically ill [1]. Despite several large-scale efforts to improve prevention of healthcare-associated infection [2–7], in general about 20–50% of patients hospitalised 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 hospitalisation [10–13]. In addition, severe infection seriously compromises survival. Attributable mortality varies from 0% to as much as 50% depending on a variety of factors [13–21]. Early initiation of

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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, whilst 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 of combining high rates of empiric appropriate therapy with reduced consumption of antibiotics in pneumonia and bacteraemia [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 β-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 adapted?

2. Methods

2.1. Study design

A prospective multicentre 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 centres antimicrobial prescribing was done or supervised by the attending senior intensivist.

2.2. Inclusion criteria

Eligible patients were those who gave informed consent, were at least 18 years of age, were hospitalised 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. bacteraemia secondary to urinary tract infection or sinusitis).

2.3. Definitions

Infections were considered hospital- or ICU-acquired when diagnosed at least 48 h 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 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 infections secondary to other sources than pneumonia or intra-abdominal infections 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 5 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 tumour), and neutropenia (absolute neutrophil count <1500 cells/mm^3).

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 antipseumononal 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 1 month preceding the current infectious episode. Prior hospitalisation was defined as a hospital admission within the 4 months preceding the current ICU admission.

Table 1
Empirical antibiotic regimens clustered in six major groups according to the pathogens covered.

Coverage	Empirical regimens	*n*
ESBL-producing Enterobacteriaceae + *Pseudomonas aeruginosa* + MRSA (*n* = 6)	MER + VAN	5
	MER + VAN + AMI	1
ESBL-producing Enterobacteriaceae + *P. aeruginosa* (*n* = 31)	MER	18
	MER + AMI	9
	MER + OXA	1
	MER + CIP + AMI	1
	MER + PIP/TAZ + AMI	2
P. aeruginosa + MRSA (*n* = 7)	PIP/TAZ + VAN + LEV	1
	PIP/TAZ + VAN	1
	CAZ + VAN	1
	CEP + VAN	2
	CEP + VAN + AMI	2
P. aeruginosa (*n* = 74)	PIP/TAZ	12
	PIP/TAZ + AMI	12
	PIP/TAZ + FLU	2
	PIP/TAZ + AMC	1
	AMC + AMI	4
	CAZ	2
	CEP	8
	CIP	2
	LEV	3
	CEP + AMI	6
	CAZ + AMI	7
	CEP + CIP	3
	CAZ + MOX	2
	CEP + FLU	1
	CIP + AMC	2
	LEV + AMC	3
	LEV + AMC + CLA	1
	LEV + AMI	1
	CIP + OXA	1
	OXA + AZT	1
MRSA (*n* = 1)	VAN	1
Non-MDR pathogens or *P. aeruginosa* (*n* = 51)	AMC	32
	AMC + MTR	1
	CEF	7
	MOX	1
	CFX	1
	CFX + MTR	3
	CEF + CLA	1
	TMO	3
	OXA	2
No empirical therapy (*n* = 1)		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.

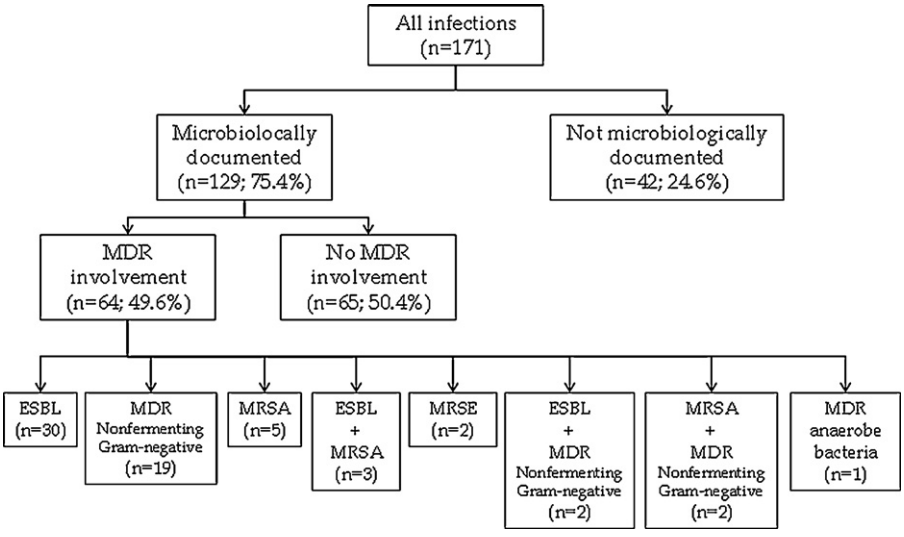

Fig. 1. Review of 171 nosocomial infections distributed for microbiological documentation and multidrug resistance involvement. MDR, multidrug resistance or multidrug resistant; ESBL, extended-spectrum β-lactamase producing Enterobacteriaceae; MRSA, meticillin-resistant *Staphylococcus aureus*; MRSE,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

Table 2
Characteristics of 171 Intensive Care Unit (ICU) patients with nosocomial infections.

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

IQR, interquartile range; APACHE, Acute Physiology and Chronic Health Evaluation.
[a] Data are *n* (%) unless otherwise stated.

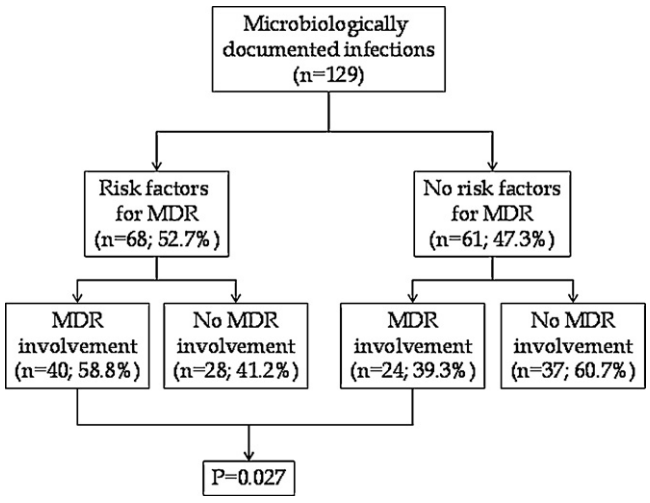

Fig. 2. Breakdown of microbiologically documented infections according to the presence of risk factors for multidrug resistance, and multidrug resistance involvement. MDR, multidrug resistance.

2.4. Data analyses

For comparisons between groups of continuous variables the Mann–Whitney *U*-test and Fisher's 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 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 empiric antibiotic schemes. Results of the regression analysis are reported as odds ratios (OR) and 95% confidence intervals (CI).

3. Results

3.1. 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 (Fig. 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 oxytocca* ($n = 7$) as 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. In 64 of the 129 microbiologically documented infections MDR pathogens were involved (49.6%).

3.2. 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). Hospitalisation in another ward prior to ICU admission was also recognised as significantly associated with MDR involvement (59.0% vs. 40.9%, $p = 0.041$; relative risk 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 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), 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 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 Fig. 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 adapted: in 60 cases following initial inappropriate or inadequate therapy, and in 46 patients in order to refine empiric therapy.

3.4. 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 was administered in 14 cases, but in only 3 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 analysed rates of empiric appropriate or adequate therapy irrespective of the coverage of MRSA (Fig. 4a).

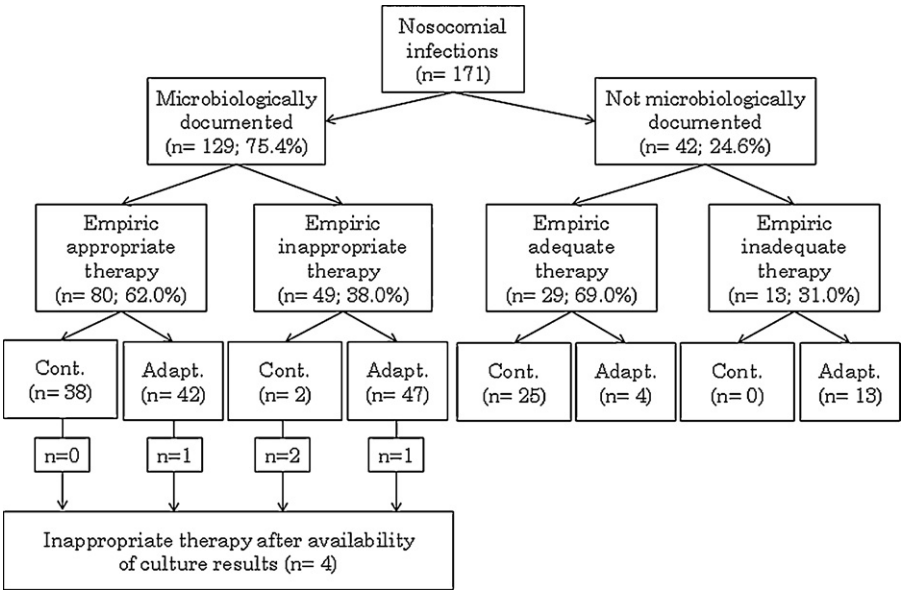

Fig. 3. Rates of empiric appropriate or adequate therapy in ICU patients with nosocomial infections. Cont., continuation of empiric therapy; Adapt., adaptation of empiric therapy.

Coverage of ESBL-producing Enterobacteriaceae (by MER-based empiric schemes) allowed for significantly higher rates of appropriate or adequate therapy. We hypothesised 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 ESBL-producing Enterobacteriaceae remained superior (Fig. 4b).

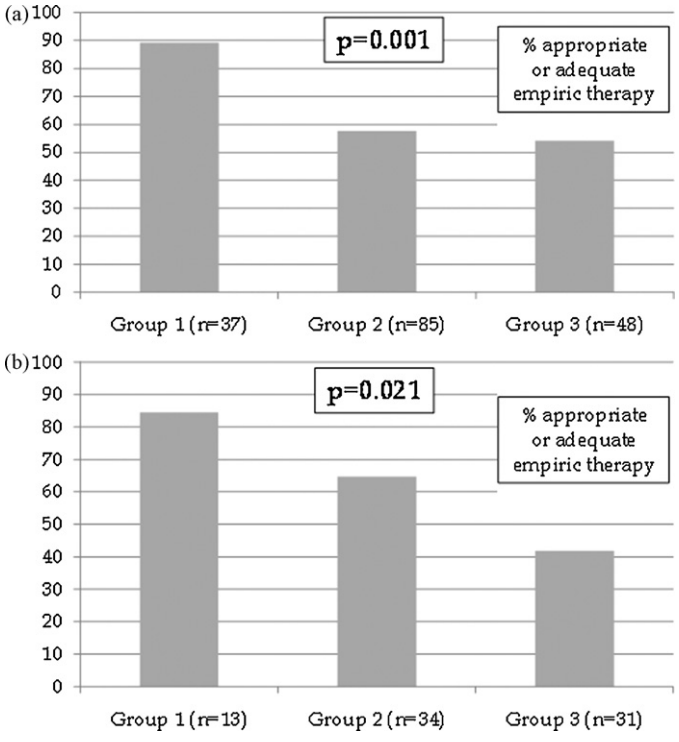

Fig. 4. Rates of empiric appropriate or adequate therapy according to three major groups of empiric antibiotic regimens (coverage of meticillin-resistant pathogens not considered). (a) All patients considered ($n = 170$; in one patient no empiric therapy was initiated). (b) Only patients considered without risk factors for multidrug resistance involvement (hospitalisation at a general ward prior to ICU admission and prior antibiotic exposure) ($n = 78$). Group 1: coverage 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).

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 4.8–68.1; $p < 0.001$) and the presence of MDR pathogens (OR 0.04, 95% CI 0.01–0.10; $p < 0.001$). No other variables reached statistical significance.

4. 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 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 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 recognised 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/hospitalisation can also be taken into account. However, in our cohort of ICU patients with nosocomial infection some of the recognised 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 *E. aerogenes* with an increasing resistance pattern was noticed in Belgian hospitals [54,55].

Following the high rate 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 (Fig. 2). Hence, the present study suggests coverage of both 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 colonisation 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 (Fig. 1). In MER-based empiric schemes ($n = 37$) therapy was continued in 23 and adapted 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 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.

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Competing interests: None declared.

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

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