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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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► To cite this version:

Dirk Vogelaers, David de Bels, Frédéric Forêt, Sophie Cran, Eric Gilbert, et al.. 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.. International Journal of Antimicrobial Agents, 2010, 35 (4), pp.375. 10.1016/j.ijantimicag.2009.11.015 . hal-00567278

HAL Id: hal-00567278

<https://hal.science/hal-00567278>

Submitted on 20 Feb 2011

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Accepted Manuscript

Title: 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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PII: S0924-8579(09)00549-4
DOI: doi:10.1016/j.ijantimicag.2009.11.015
Reference: ANTAGE 3193

To appear in: *International Journal of Antimicrobial Agents*

Received date: 17-9-2009
Revised date: 22-10-2009
Accepted date: 23-11-2009

Please cite this article as: Vogelaers D, De Bels D, Forêt F, Cran S, Gilbert E, Schoonheydt K, Blot S, 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., *International Journal of Antimicrobial Agents* (2008), doi:10.1016/j.ijantimicag.2009.11.015

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

4
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20 Word count: 3146

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33 **Abstract**

34 This prospective, observational multicenter (n=24) study investigated relationships
35 between antimicrobial choices and rates of empiric appropriate or adequate therapy,
36 and subsequent adaptation of therapy in 171 ICU patients with severe nosocomial
37 infections. Appropriate antibiotic therapy was defined as in-vitro susceptibility of the
38 causative pathogen and clinical response to the agent administered. In non-
39 microbiologically documented infections, therapy was considered adequate in case of
40 favorable clinical response <5 days. Patients had pneumonia (n=127; 66 ventilator-
41 associated), intra-abdominal infection (n=23), and bloodstream infection (n=21).
42 Predominant pathogens were *Pseudomonas aeruginosa* (n=29) *Escherichia coli* (n=26),
43 *Staphylococcus aureus* (n=22), and *Enterobacter aerogenes* (n=21). In 49.6% of infections
44 multidrug resistant (MDR) bacteria were involved, mostly extended-spectrum Beta-
45 lactamase producing *Enterobacteriaceae* and MDR non-fermenting Gram-negative
46 bacteria. Prior antibiotic exposure and hospitalization in a general ward prior to ICU
47 admission were risk factors for MDR. Empiric therapy was appropriate/adequate in
48 63.7% of cases. Empiric schemes were classified according to coverage of (i) ESBL-
49 *Enterobacteriaceae* + non-fermenting Gram-negative bacteria (meropenem-based), (ii)
50 non-fermenting Gram-negative bacteria (schemes with antipseudomonal agent), and
51 (iii) first-line agents not covering ESBL-*Enterobacteriaceae* nor non-fermenting Gram-
52 negative bacteria. Meropenem-based schemes allowed for significantly higher rates
53 of appropriate/adequate therapy (p<0.001). This benefit remained when only
54 patients without risk factors for MDR were considered (p=0.021). In 106 patients
55 (61%) empiric therapy was adapted: in 60 cases following initial

56 inappropriate/inadequate therapy, in 46 patients in order to fine-tune empiric
57 therapy. In this study reflecting real-life practice first-line use of meropenem
58 provided significantly higher rates of appropriate/adequate therapy, irrespective of
59 presence of risk factors for MDR.

60

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

63 Introduction

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

72 Severe nosocomial infection carries a substantial economic burden due to extensive
73 antimicrobial consumption and, even more importantly, increased length of
74 hospitalization [10-13]. In addition, severe infection seriously compromises the odds
75 of survival. Attributable mortality rates vary from as low as zero percent to a
76 dramatic 50% dependent of the type of infection, the causative pathogen, patient age,
77 associated co-morbidities, and overall quality of the anti-infective approach [13-21].

78 Among all the modalities that are to be fulfilled in the aim to optimize clinical patient
79 outcomes, early initiation of the proper antimicrobial agent is a cornerstone [1].

80 Failure to timely administer appropriate antimicrobial therapy results in a dramatic
81 increase in fatality rates [22-25]. Selecting an empiric regimen which covers the
82 causative pathogen, however, is hampered by the presence of multidrug resistant
83 (MDR) micro-organisms which is the utmost important cause of empiric
84 inappropriate therapy. Since antimicrobial consumption in itself is a major trigger for

85 MDR development, physicians are frequently urged to thoughtfully use 'last-line
86 antibiotics'. In fact, the challenge is to achieve high rates of empiric appropriate
87 therapy in order to optimize patient survival, while avoiding unnecessary use of
88 antibiotics with the intention to minimize microbial selection pressure, and hence,
89 MDR development [1, 26].

90 In order to accomplish this goal, in the past decade two main strategies have been
91 proposed. In the surveillance-assisted strategy, the empiric regimen is selected
92 mainly based on the presence or absence of MDR pathogens in routine surveillance
93 cultures. The strength of this approach is the high negative predictive value of
94 surveillance cultures to predict MDR involvement in subsequent infection. On the
95 condition that cultures are taken at least twice weekly, this strategy is capable to
96 combine high rates of empiric appropriate therapy with reduced consumption of
97 antibiotics in pneumonia and bacteremia [27-33]. The cost-effectiveness of this
98 approach, however, remains questionable. Another approach is the so-called 'de-
99 escalation strategy' which, on the condition of risk factors for MDR involvement,
100 recommends empiric start with a regimen which covers most potential MDR
101 pathogens such as extended-spectrum beta-lactamase producing (ESBL)
102 *Enterobacteriaceae*, non-fermenting Gram-negative bacteria, and methicillin-resistant
103 *Staphylococcus aureus* (MRSA) [34-36]. Once culture results are available, and if
104 feasible, narrowing the antimicrobial spectrum is advised. This concept, often
105 referred to as 'de-escalation', is widely used and advocated [37-40]. This strategy has
106 been demonstrated to be successful and safe, and may also reduce antibiotic use and
107 hence limiting the emergence of MDR [36, 41].

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

115

116

117 **Methods**

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

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

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

138 secondary to other sources than pneumonia or intra-abdominal infection were
139 classified as secondary bloodstream infection.

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

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

151 Severity of disease was assessed by means of the acute physiology and chronic health
152 evaluation (APACHE) II score [46]. The following co-morbid conditions were
153 registered: respiratory disease (chronic restrictive, obstructive or pulmonary vascular
154 disease resulting in severe exercise restriction), cardiac disease (New York Heart
155 Association Class IV), diabetes mellitus, hepatic disease (cirrhosis and portal
156 hypertension; episodes of past upper gastro-intestinal bleeding attributed to portal
157 hypertension or prior episodes of hepatic failure or encephalopathy), renal disease
158 (chronic glomerulonephritis, nephropathy, or chronic kidney disease), neurologic

159 disease (impairment of alertness or confusion) malignancy (hematologic cancer or
160 solid tumor), and neutropenia (absolute neutrophil count <1500 cells/mm³).

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

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

177 *Data analyses.* Continuous variables are described as median (interquartile range
178 [IQR]) and discrete variables as n (%). For comparisons between groups the Mann
179 Whitney U test and Fisher Exact test or Chi-square test were used as appropriate.
180 Independent relationships with empiric appropriate or adequate therapy were

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

188

189

190 Results

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

208 *Risk factors for multidrug resistance (MDR).* Risk factors for MDR were assessed in
209 order to evaluate empiric antimicrobial regimens relative to their presence. No
210 specific underlying conditions appeared to predispose for MDR involvement. MDR
211 involvement was more frequent in patients with compared to without prior

212 antibiotic exposure (74.3% vs. 41.3%, $p=0.001$; relative risk 4.26, 95% CI: 1.80-10.09).
213 Hospitalization in another ward prior to ICU admission was also recognized as
214 significantly associated with MDR involvement (59.0% vs. 40.9%, $p=0.041$; relative
215 risk 2.08, 95% CI: 1.03-4.22). Figure 3 shows a breakdown of microbiologically
216 documented infections according to the presence of these two risk factors for MDR,
217 and subsequent MDR involvement.

218

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

224 *Rates of empiric appropriate or adequate therapy and subsequent adaptation.* The presence
225 of MDR pathogens in infections was associated with a significant lower rate of
226 empiric appropriate therapy: 87.7% vs. 35.9% ($p<0.001$). Rates of empiric appropriate
227 and adequate therapy are illustrated in Figure 2. In 80 of the 129 microbiologically
228 documented infections empiric therapy was appropriate (62.0%). In non-
229 microbiologically documented infections, empiric therapy was judged adequate in 29
230 of 42 infections (69.0%). In 106 patients (62.0%) empiric therapy was adapted: in 60
231 cases following initial inappropriate or inadequate therapy, and in 46 patients in
232 order to fine tune empiric therapy.

233 *Empiric antimicrobial selection and rates of appropriate or adequate therapy.* In 12 infections
234 the causative pathogen was methicillin-resistant (10 MRSA, 2 methicillin-resistant
235 *Staphylococcus epidermidis*). Vancomycin was 14 times administered as an empiric
236 agent, but in only three cases in which a methicillin-resistant pathogen proved to be
237 involved. As such the rate of inappropriate therapy in case of methicillin-resistance
238 involvement was 75%. Due to the relative low prevalence of methicillin-resistance as
239 well as the low added value of initiating a glycopeptide, the association (or not) of
240 such an agent did not alter the study results in this particular cohort. Therefore, we
241 analyzed rates of empiric appropriate or adequate therapy irrespective of the
242 coverage of MRSA. This is illustrated by Figure 4a. Coverage of ESBL-
243 *Enterobacteriaceae* (by MER-based empiric schemes) allowed for significantly higher
244 rates of appropriate or adequate therapy. Because the advantage of an antibiotic
245 agent which covers ESBL-*Enterobacteriaceae* is obvious in settings with a high
246 prevalence of MDR, we hypothesized that the benefit of using a MER-based empiric
247 scheme would fade away when only patients without risk factors for MDR were
248 taken into account. However, in this analysis empiric schemes covering ESBL-
249 *Enterobacteriaceae* remained superior (Figure 4b).

250 When MER-based empiric schemes were compared to other empiric regimens, a
251 difference of approximately 30% in empiric appropriate or adequate therapy was
252 observed when all patients were taken into account (89.2% vs. 56.0%; $p < 0.001$), and
253 this distinction remained when only patients without risk factors for MDR were
254 considered (83.6% vs. 53.8%; $p = 0.040$).

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

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261 **Discussion**

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

267 Several reasons for the low rate of appropriate or adequate therapy can be proposed.
268 The overall prevalence of MDR in this particular cohort is high (~50%) and the rate of
269 appropriate or adequate therapy in infections caused by MDR pathogens was very
270 poor (35.9%). MDR is well recognized as a major determinant of inappropriate
271 therapy [47-52]. However, to a certain extent the involvement of MDR can be
272 predicted on basis of some typical risk factors of which the most essential are prior
273 antibiotic exposure and a length of ICU stay (or mechanical ventilation in case of
274 pneumonia) of >7 days [32, 53]. Other risk factors such as particular underlying
275 diseases (e.g. chronic obstructive pulmonary disease) and recent
276 surgery/hospitalization can also be taken into account but generally are not included
277 in the principal risk factors. Strangely enough, in this cohort of ICU patients with
278 nosocomial infection some of the classic patterns failed to predict the involvement of
279 MDR. For instance, prior hospitalization (<4 months of the current hospital
280 admission) was not associated with a higher likelihood of MDR, while length of ICU
281 stay was even inversely related to MDR involvement. On the other hand, prior
282 antibiotic exposure and hospitalization in a general ward prior to ICU admission

283 appeared to have a significant relationship with MDR involvement. Importantly,
284 however, although these relationships were statistically significant, MDR pathogens
285 were isolated in about 40% of patients in the absence of these risk factors. As a
286 consequence, the predictive value of these risk factors was low. As such, the
287 generally accepted concepts of risk perception for MDR involvement failed in this
288 particular cohort. We have no plausible explanation for this observation. Given the
289 relationship between prior hospitalization at a general ward and MDR, the relative
290 high number of infections already present at time of ICU admission, and the short
291 length of stay in the ICU prior to infection, it appears that there exists a serious
292 problem of MDR in general wards in Belgian hospitals, thereby contributing to the
293 low rate of empiric appropriate therapy in ICUs. Indeed, already a decade ago a
294 higher incidence of *Enterobacter aerogenes* with an increasing resistance pattern has
295 been noticed in Belgian hospitals [54, 55].

296 Following the high rate of ESBL-*Enterobacteriaceae* and *P. aeruginosa*, an MER-based
297 empiric scheme allowed for the highest rates of appropriate/adequate therapy. Due
298 to the failure of classic risk factors to predict MDR involvement performance rates of
299 empiric schemes did not substantially alter when only patients without risk factors
300 were considered (Figure 3). Hence, based on the present study an approach
301 including coverage of both ESBL-*Enterobacteriaceae* and *P. aeruginosa* seems highly
302 warranted. Without firm supportive knowledge of local ecology in ICU and non-ICU
303 settings indicating low MDR levels, an empiric strategy which does not cover ESBL-
304 *Enterobacteriaceae* and *P. aeruginosa* is potentially dangerous, and as such supports the
305 de-escalation strategy. The present findings however, with the failure of MDR

306 prediction based on general characteristics in particular, provide perspectives for the
307 surveillance assisted approach in which individual colonization status is a major
308 element in steering empiric therapy.

309

310 In 62% of patients empiric therapy was adapted (n=106). In 60 cases adaptation
311 followed initial inappropriate or inadequate therapy, whereas in 46 patients empiric
312 therapy could be fine-tuned (true de-escalation). Noteworthy, when only
313 microbiologically documented infections are considered, 4 out of 129 patients
314 received inappropriate therapy even after the availability of culture results (Figure 1).

315 In MER-based empiric schemes (n=37) therapy was continued in 23 and adapted in
316 14 patients (in 4 cases because of initial inappropriate therapy and in 10 cases in
317 order to narrow down the spectrum). As this study supports the approach of empiric

318 coverage of ESBL-*Enterobacteriaceae* and *P. aeruginosa*, we stress the importance of de-

319 escalation whenever possible. Baran et al. found that previous exposition to

320 carbapenems was 44% in patients with infections caused by imipenem-resistant

321 *Acinetobacter baumannii*, whereas only 12% in patients infected by imipenem-

322 susceptible *A. baumannii* isolates [56]. Yet, in multivariate analysis, previous

323 antibiotic exposure and not carbapenem exposure in particular appeared to be an

324 independent risk factor for imipenem-resistance. The link between exposure and

325 specific resistance development is obvious and should not be disregarded, but this

326 suggests that the mission to reduce microbial selection pressure is valid for all

327 antimicrobial agents and not only for carbapenems. Further, based on the

328 Surveillance of Antimicrobial Use and Antimicrobial Resistance in German ICUs
329 (SARI project), Meyer E et al. identified carbapenem use as an independent predictor
330 for a higher *Stenotrophomonas maltophilia* incidence [57]. Although this data do not
331 disclose a causal relationship, it is highly suggestive for the specific selection
332 pressure of this pathogen. Therefore, excessive use of carbapenems is to be avoided
333 by a strict de-escalation strategy and by avoidance of unnecessary long therapies.

334

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

339 This study has limitations. First, no outcome data are available as the primary aim of
340 the study was to describe antibiotic prescription patterns and how they perform in
341 terms of appropriate therapy. Yet, the relationship between initial empiric failure to
342 cover the causative pathogen and adverse outcomes has been demonstrated
343 repeatedly and is generally accepted as an important quality indicator [58, 59].

344 Secondly, the cohort does not represent a consecutive series of ICU patients with
345 nosocomial infections. Probably this might have lead to the selection bias towards
346 more severe infections, with a higher likelihood of MDR involvement. Yet, for what
347 concerns risk factors for MDR, including less severe infections would probably not
348 have changed the observations regarding the relationship between MDR infection
349 and risk factors.

350 In conclusion, in this prospective study reflecting real life practice in ICU patients
351 with nosocomial infections, the rate of appropriate or adequate empiric therapy was
352 63.7%. This study demonstrated that classic risk factors for MDR such as prior
353 antibiotic exposure and length of ICU stay, may be insufficient to predict MDR
354 involvement. As such, empiric first-line use of MER allowed for significantly higher
355 rates of appropriate or adequate therapy, irrespective of presence of these risk
356 factors, and may be recommended in settings with a high prevalence of MDR
357 pathogens. In addition, these data illustrate the necessity for strict infection
358 prevention and control.

359

360

361 **Declarations**

362 **Funding:** This study was sponsored by an unrestricted grant by AstraZeneca,
363 Belgium. Dr. Blot is supported by a grant from the European Society of Intensive
364 Care Medicine and iMDsoft Patient Safety Research Award 2008.

365 **Competing Interests:** No conflicts of interest to declare

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

368

369

370

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385

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- 543
- 544
- 545

546 **Figure Legends**

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

549 MDR, multidrug resistance or multidrug resistant

550 ESBL, extended spectrum beta-lactamase producing *Enterobacteriaceae*

551 MRSA, methicillin- resistant *Staphylococcus aureus*

552 MRSE, methicillin-resistant *Staphylococcus epidermidis*

553

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

556 Cont., continuation of empiric therapy

557 Adapt., adaptation of empiric therapy

558

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

562 MDR, multidrug resistance

563

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

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

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

571 Group 1: coverage of ESBL-*Enterobacteriaceae* + *P. aeruginosa* (meropenem-based schemes)

572 Group 2: coverage of *P. aeruginosa* (schemes containing an antipseudomonal agent)

573 Group 3: no coverage of ESBL nor non-fermenting Gram-negative bacteria (first line agents)

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

Coverage	Empiric regimens	n
ESBL- <i>Enterobacteriaceae</i> + <i>P. aeruginosa</i> + MRSA (n=6)	MER+VAN	5
	MER+VAN+AMI	1
ESBL- <i>Enterobacteriaceae</i> + <i>P. aeruginosa</i> (n=31)	MER	18
	MER+AMI	9
	MER+OXA	1
	MER+CIP+AMI	1
	MER+PIPtaz+AMI	2
<i>P. aeruginosa</i> + MRSA (n=7)	PIPtaz+VAN+LEVO	1
	PIPtaz+VAN	1
	CAZ+VAN	1
	CEFE+VAN	2
	CEFE+VAN+AMI	2
<i>P. aeruginosa</i> (n=74)	PIPtaz	12
	PIPtaz+AMI	12
	PIPtaz+FLU	2
	PIPtaz+AMOXIclav	1
	AMOXIclav+AMI	4
	CAZ	2
	CEFE	8
	CIP	2
	LEVO	3
	CEFE+AMI	6
	CAZ+AMI	7
	CEFE+CIP	3
	CAZ+MOXI	2
	CEFE+FLU	1
	CIP+AMOXIclav	2
	LEVO+AMOXIclav	3
	LEVO+AMOXIclav+CLA	1
LEVO+AMI	1	
CIP+OXA	1	

	OXA+AZT	1
MRSA (n=1)	VAN	1
Non-MDR pathogens or <i>P. aeruginosa</i> (n=51)	AMOXIclav	32
	AMOXIclav+metronidazol	1
	CEF	7
	MOXI	1
	CTX	1
	CTX+metronidazol	3
	CEF+CLA	1
	temocillin	3
	OXA	2
No empiric therapy (n=1)		1

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
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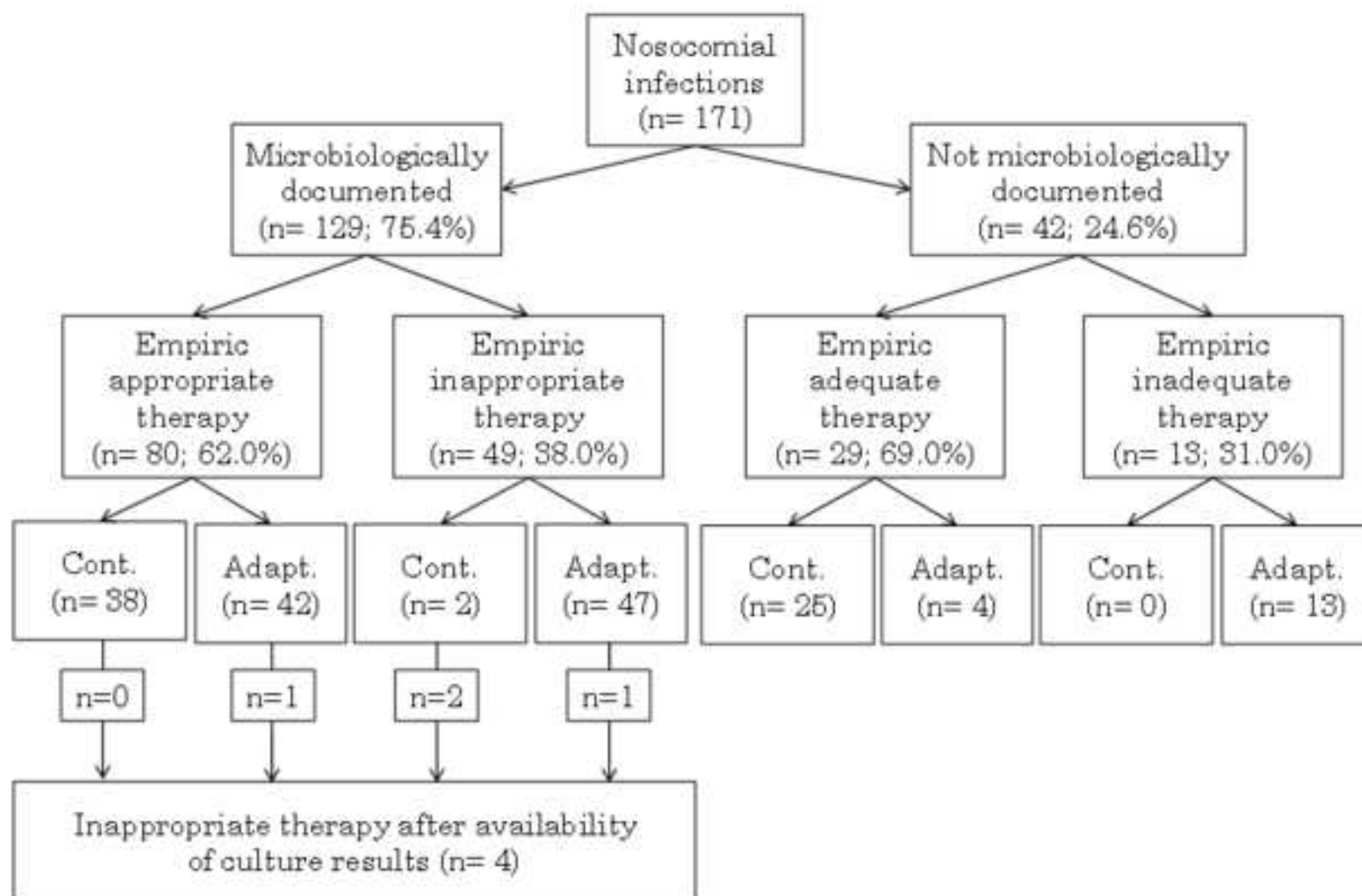
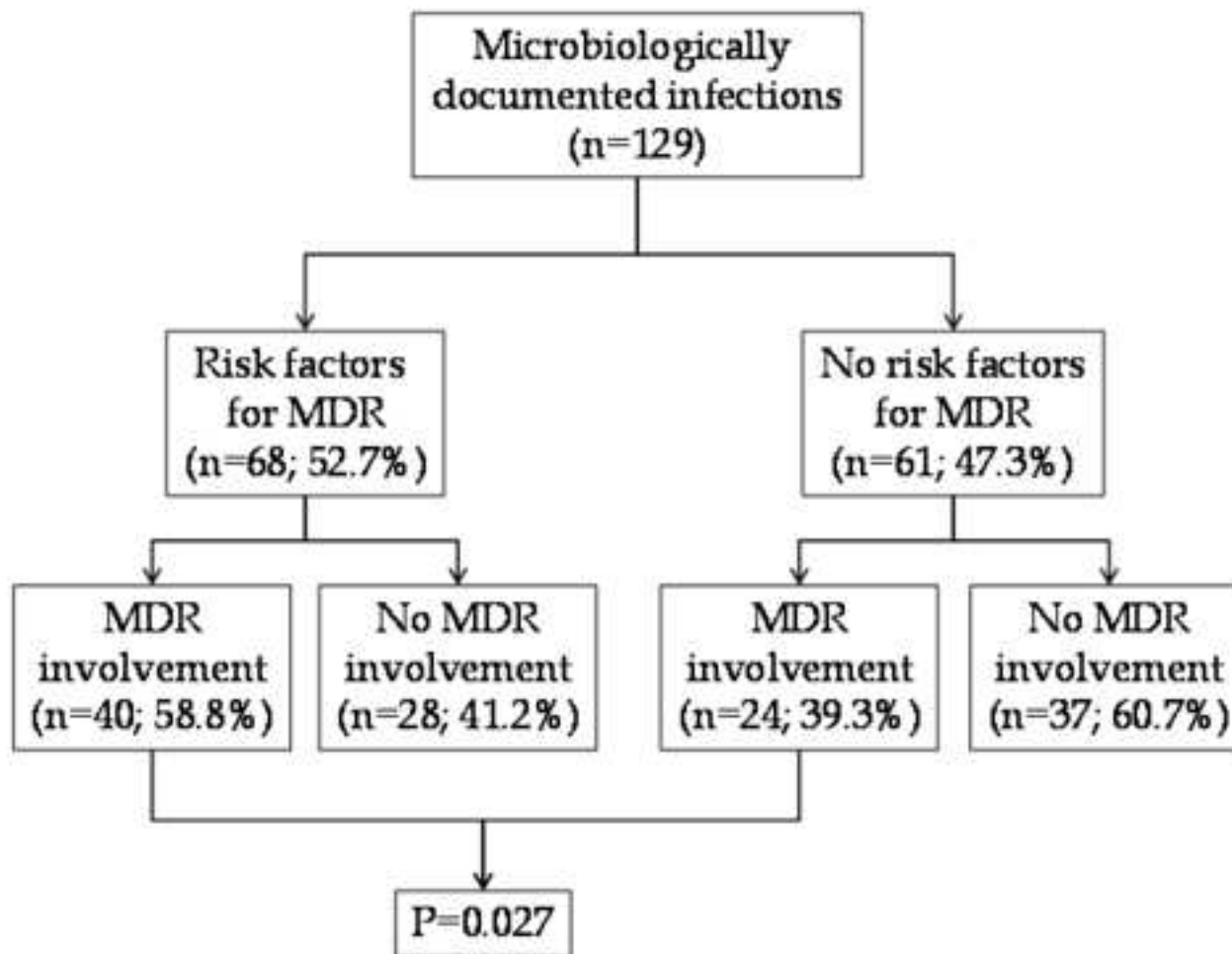


Figure 3
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33 **Abstract**

34 This prospective, observational multicenter (n=24) study investigated relationships
35 between antimicrobial choices and rates of empiric appropriate or adequate therapy,
36 and subsequent modification of therapy in 171 ICU patients with severe nosocomial
37 infections. Appropriate antibiotic therapy was defined as in-vitro susceptibility of the
38 causative pathogen and clinical response to the agent administered. In non-
39 microbiologically documented infections, therapy was considered adequate in the
40 case of favorable clinical response <5 days. Patients had pneumonia (n=127; 66
41 ventilator-associated), intra-abdominal infection (n=23), and bloodstream infection
42 (n=21). Predominant pathogens were *Pseudomonas aeruginosa* (n=29) *Escherichia coli*
43 (n=26), *Staphylococcus aureus* (n=22), and *Enterobacter aerogenes* (n=21). In 49.6% of
44 infections multidrug resistant (MDR) bacteria were involved, mostly extended-
45 spectrum Beta-lactamase producing Enterobacteriaceae and MDR non-fermenting
46 Gram-negative bacteria. Prior antibiotic exposure and hospitalization in a general
47 ward prior to ICU admission were risk factors for MDR. Empiric therapy was
48 appropriate/adequate in 63.7% of cases. Empiric schemes were classified according
49 to coverage of (i) ESBL-producing Enterobacteriaceae and non-fermenting Gram-
50 negative bacteria (“meropenem-based”), (ii) non-fermenting Gram-negative bacteria
51 (schemes with an antipseudomonal agent), and (iii) first-line agents not covering
52 ESBL-Enterobacteriaceae nor non-fermenting Gram-negative bacteria. Meropenem-
53 based schemes allowed for significantly higher rates of appropriate/adequate
54 therapy ($p<0.001$). This benefit remained when only patients without risk factors for
55 MDR were considered ($p=0.021$). In 106 patients (61%) empiric therapy was

56 modified: in 60 cases following initial inappropriate/inadequate therapy, in 46
57 patients in order to refine empiric therapy. In this study which reflects real-life
58 practice, first-line use of meropenem provided significantly higher rates of the
59 appropriate/adequate therapy, irrespective of presence of risk factors for MDR.

60

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

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63 Introduction

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

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

83 In order to achieve this goal, two main strategies have been proposed. In the
84 surveillance-assisted strategy, the empiric regimen is selected mainly based on the

85 presence or absence of MDR pathogens in routine surveillance cultures. The strength
86 of this approach is the high negative predictive value of surveillance cultures to
87 predict MDR involvement in subsequent infection. If cultures are taken at least twice
88 weekly, this strategy is capable to combine high rates of empiric appropriate therapy
89 with reduced consumption of antibiotics in pneumonia and bacteremia [27-33]. The
90 cost-effectiveness of this approach, however, remains unclear. Another approach is
91 the 'de-escalation strategy' which, if there are risk factors for MDR, recommends an
92 empiric start with a regimen which covers most potential MDR pathogens such as
93 extended-spectrum beta-lactamase producing (ESBL) Enterobacteriaceae, non-
94 fermenting Gram-negative bacteria, and meticillin-resistant *Staphylococcus aureus*
95 (MRSA) [34-36]. Once culture results are available, and if feasible, narrowing the
96 antimicrobial spectrum is advised. This concept, often referred to as 'de-escalation', is
97 widely used and advocated [37-40]. This strategy has been shown to be successful
98 and safe, and may also reduce antibiotic use and hence limit the emergence of MDR
99 [36, 41].

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

108

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110 **Methods**

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

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

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

131 secondary to other sources than pneumonia or intra-abdominal infection were
132 classified as secondary bloodstream infection.

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

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

144 Severity of disease was assessed by means of the acute physiology and chronic health
145 evaluation (APACHE) II score [46]. The following co-morbid conditions were
146 recorded: respiratory disease (chronic restrictive, obstructive or pulmonary vascular
147 disease resulting in severe exercise restriction), cardiac disease (New York Heart
148 Association Class IV), diabetes mellitus, hepatic disease (cirrhosis and portal
149 hypertension; episodes of past upper gastro-intestinal bleeding attributed to portal
150 hypertension or prior episodes of hepatic failure or encephalopathy), renal disease
151 (chronic glomerulonephritis, nephropathy, or chronic kidney disease), neurologic

152 disease (impairment of alertness or confusion) malignancy (haematologic or solid
153 tumor), and neutropenia (absolute neutrophil count <1500 cells/mm³).

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

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

171 *Data analyses.* For comparisons between groups of continuous variables the Mann
172 Whitney U test and Fisher Exact test or Chi-square test were used as appropriate.
173 Independent relationships with empiric appropriate or adequate therapy were

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

181

182

183 **Results**

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

199 *Risk factors for multidrug resistance (MDR).* Risk factors for MDR were assessed in
200 order to evaluate empiric antimicrobial regimens relative to their presence. No
201 specific underlying conditions appeared to predispose for MDR involvement. MDR
202 involvement was more frequent in patients with prior antibiotic exposure (74.3% vs.
203 41.3%, p=0.001; relative risk 4.26, 95% CI: 1.80-10.09). Hospitalization in another
204 ward prior to ICU admission was also recognized as significantly associated with

205 MDR involvement (59.0% vs. 40.9%, $p=0.041$; relative risk 2.08, 95% CI: 1.03-4.22).

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

208

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

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

223 *Empiric antimicrobial selection and rates of appropriate or adequate therapy.* In 12 infections
224 the causative pathogen was meticillin-resistant (10 MRSA, 2 meticillin-resistant
225 *Staphylococcus epidermidis*). Vancomycin administered empirically in 14 cases, but in
226 only was a meticillin-resistant pathogen involved. The rate of inappropriate therapy

227 in case of meticillin-resistance involvement was thus 75%. Due to the relative low
228 prevalence of meticillin-resistance and the low added value of initiating a
229 glycopeptide, the association of such an agent did not alter the study results in this
230 particular cohort. Therefore, we analyzed rates of empiric appropriate or adequate
231 therapy irrespective of the coverage of MRSA (Figure 4a). Coverage of of ESBL-
232 producing Enterobacteriaceae (by MER-based empiric schemes) allowed for
233 significantly higher rates of appropriate or adequate therapy. We hypothesized that
234 the benefit of using a MER-based empiric scheme would disappear when only
235 patients without risk factors for MDR were taken into account. However, in this
236 analysis empiric schemes covering of ESBL-producing Enterobacteriaceae remained
237 superior (Figure 4b).

238 When MER-based empiric schemes were compared with others, a difference of
239 approximately 30% in empiric appropriate or adequate therapy was observed when
240 all patients were included (89.2% vs. 56.0%; $p < 0.001$), and this distinction remained
241 when only patients without risk factors for MDR were considered (83.6% vs. 53.8%;
242 $p = 0.040$).

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

248

249 **Discussion**

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

255 Several reasons for the low rate of appropriate or adequate therapy are possible. The
256 overall prevalence of MDR in this particular cohort is high (~50%) and the rate of
257 appropriate or adequate therapy in infections caused by MDR pathogens was low
258 (35.9%). MDR is recognized as a determinant of inappropriate therapy [47-52]. The
259 involvement of MDR can be partly predicted by some typical risk factors such as
260 prior antibiotic exposure and length of ICU stay (or mechanical ventilation in case of
261 pneumonia) of >7 days [32, 53]. Other risk factors such as underlying diseases and
262 recent surgery/hospitalization can also be taken into account. However, in our
263 cohort of ICU patients with nosocomial infection some of the recognized risk factors
264 failed to predict the involvement of MDR. Also, MDR pathogens were isolated in
265 about 40% of patients in the absence of these risk factors. As a consequence, the
266 predictive value of these risk factors was low. As such, the generally accepted
267 concepts of risk for MDR involvement were not supported by this particular cohort.
268 It appears that there exists a serious problem of MDR in general wards in Belgian
269 hospitals, thereby contributing to the low rate of appropriate empiric therapy.

270 Indeed, a decade ago a higher incidence of *Enterobacter aerogenes* with an increasing
271 resistance pattern was noticed in Belgian hospitals [54, 55].

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

282
283 In 62% (n=106) of patients empiric therapy was modified. In 60 cases modification
284 followed initial inappropriate or inadequate therapy, in the other 46 patients empiric
285 therapy could be refined (true de-escalation). It is noteworthy that when only
286 microbiologically documented infections are considered, four of 129 patients
287 received inappropriate therapy even after culture results were available (Figure 1). In
288 MER-based empiric schemes (n=37) therapy was continued in 23 and modified in 14
289 patients (in four cases because of initial inappropriate therapy and in 10 to narrow
290 the spectrum). This supports the approach of empiric antibiotic coverage followed by
291 de-escalation. Likweise Baran *et al.* found that previous exposure to carbapenems

292 was 44% in patients with infections caused by imipenem-resistant *Acinetobacter*
293 *baumannii*, but only 12% in patients infected by imipenem-susceptible strains [56].
294 However multivariate analysis showed it was previous antibiotic exposure, and not
295 carbapenem exposure specifically, that was an independent risk factor for imipenem-
296 resistance. The link between exposure and specific resistance development is
297 intuitive, but such findings suggest the aim of reducing microbial selection pressure
298 is valid for all antimicrobial agents. Further, based on the Surveillance of
299 Antimicrobial Use and Antimicrobial Resistance in German ICUs (SARI project),
300 Meyer E *et al.* identified carbapenem use as an independent predictor for increased
301 incidence of *Stenotrophomonas maltophilia* [57].

302
303 This study has its limitations. Firstly, no outcome data are available since the primary
304 aim of the study was to describe antibiotic prescription patterns and how they
305 perform in terms of appropriate therapy. However, the relationship between initial
306 empiric failure to cover the causative pathogen and adverse outcomes was
307 demonstrated repeatedly, and is generally accepted as an important quality indicator
308 [58, 59]. Secondly, the cohort does not represent a consecutive series of ICU patients
309 with nosocomial infections This may have led to selection bias for more severe
310 infections, with a higher likelihood of MDR involvement, although there is no reason
311 to believe this would have changed the relationship between MDR infection and risk
312 factors.

313 In conclusion, in this prospective study, which reflects real life practice in ICU
314 patients with nosocomial infections, the rate of appropriate or adequate empiric

315 therapy was 63.7%. This study demonstrated that classic risk factors for MDR such as
316 prior antibiotic exposure and length of ICU stay, may be insufficient to predict MDR
317 involvement. As such, empiric first-line use of MER allowed for significantly higher
318 rates of appropriate or adequate therapy, irrespective of presence of these risk
319 factors, and may be recommended in settings with a high prevalence of MDR
320 pathogens. In addition, these data illustrate the necessity for strict infection
321 prevention and control.

322

323

324 **Declarations**

325 **Funding:** This study was sponsored by an unrestricted grant by AstraZeneca,
326 Belgium. Dr. Blot is supported by a grant from the European Society of Intensive
327 Care Medicine and iMDsoft Patient Safety Research Award 2008.

328 **Competing Interests:** No conflicts of interest to declare

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

331

332

333

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348

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- 506
507
508

509 **Figure Legends**

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

512 MDR, multidrug resistance or multidrug resistant

513 ESBL, extended spectrum beta-lactamase producing Enterobacteriaceae

514 MRSA, meticillin- resistant *Staphylococcus aureus*

515 MRSE, meticillin-resistant *Staphylococcus epidermidis*

516

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

519 Cont., continuation of empiric therapy

520 Modif., modification of empiric therapy

521

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

525 MDR, multidrug resistance

526

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

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

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

534 Group 1: coverage of of ESBL-producing and *Pseudomonas aeruginosa* (meropenem-based
535 schemes)

536 Group 2: coverage of *P. aeruginosa* (schemes containing an antipseudomonal agent)
537 Group 3: no coverage of of ESBL-producing, or non-fermenting, Gram-negative bacteria
538 (first line agents)
539
540

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

Coverage	Empiric regimens	n
ESBL- <i>Enterobacteriaceae</i> + <i>P. aeruginosa</i> + MRSA (n=6)	MER+VAN	5
	MER+VAN+AMI	1
ESBL- <i>Enterobacteriaceae</i> + <i>P. aeruginosa</i> (n=31)	MER	18
	MER+AMI	9
	MER+OXA	1
	MER+CIP+AMI	1
	MER+PIPtaz+AMI	2
<i>P. aeruginosa</i> + MRSA (n=7)	PIPtaz+VAN+LEVO	1
	PIPtaz+VAN	1
	CAZ+VAN	1
	CEFE+VAN	2
	CEFE+VAN+AMI	2
<i>P. aeruginosa</i> (n=74)	PIPtaz	12
	PIPtaz+AMI	12
	PIPtaz+FLU	2
	PIPtaz+AMOXIclav	1
	AMOXIclav+AMI	4
	CAZ	2
	CEFE	8
	CIP	2
	LEVO	3
	CEFE+AMI	6
	CAZ+AMI	7
	CEFE+CIP	3
	CAZ+MOXI	2
	CEFE+FLU	1
	CIP+AMOXIclav	2
	LEVO+AMOXIclav	3
	LEVO+AMOXIclav+CLA	1
	LEVO+AMI	1
	CIP+OXA	1

	OXA+AZT	1
MRSA (n=1)	VAN	1
Non-MDR pathogens or <i>P. aeruginosa</i> (n=51)	AMOXIclav	32
	AMOXIclav+metronidazole	1
	CEF	7
	MOXI	1
	CTX	1
	CTX+metronidazole	3
	CEF+CLA	1
	temocillin	3
	OXA	2
	No empiric therapy (n=1)	

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

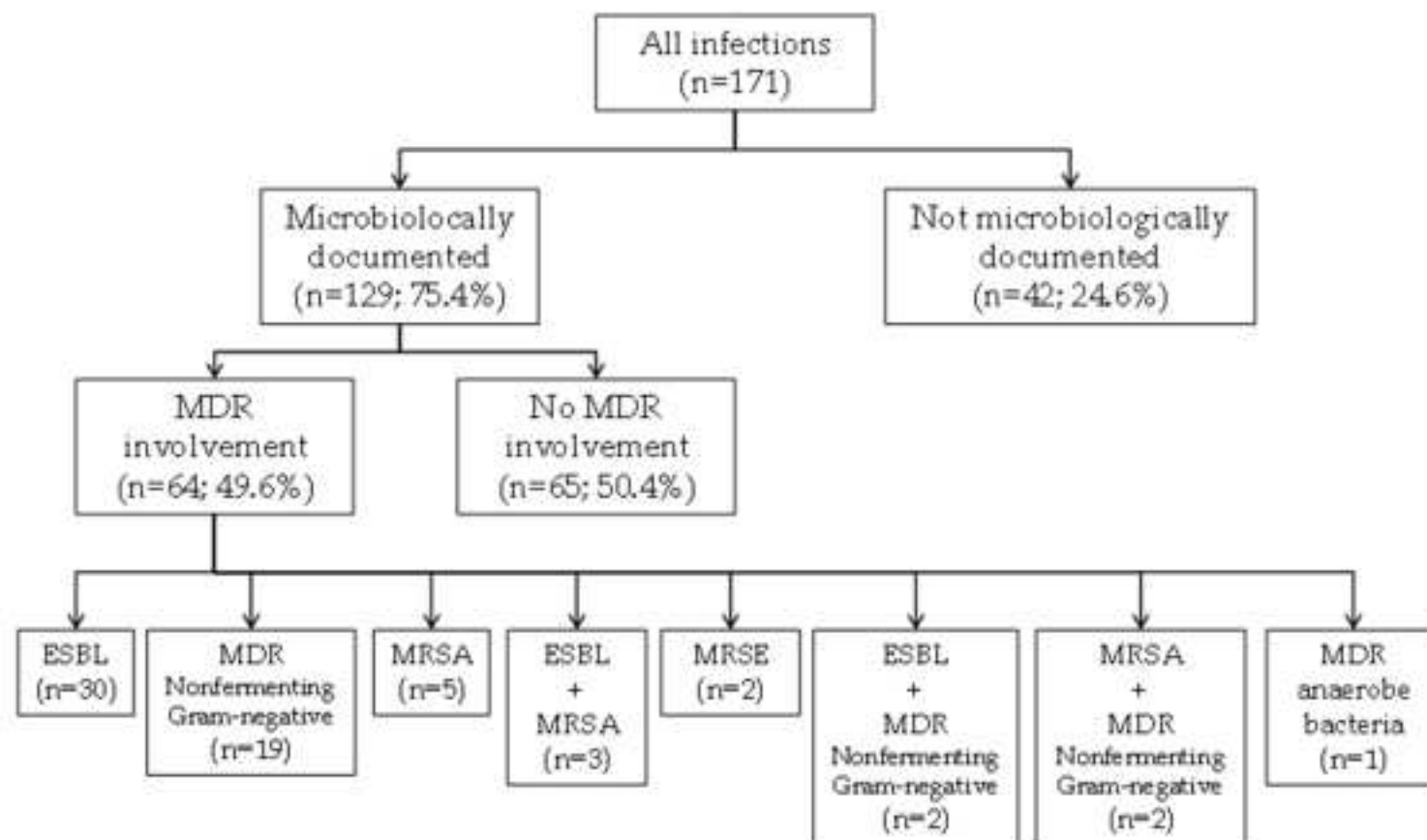
CLA, clarithromycin

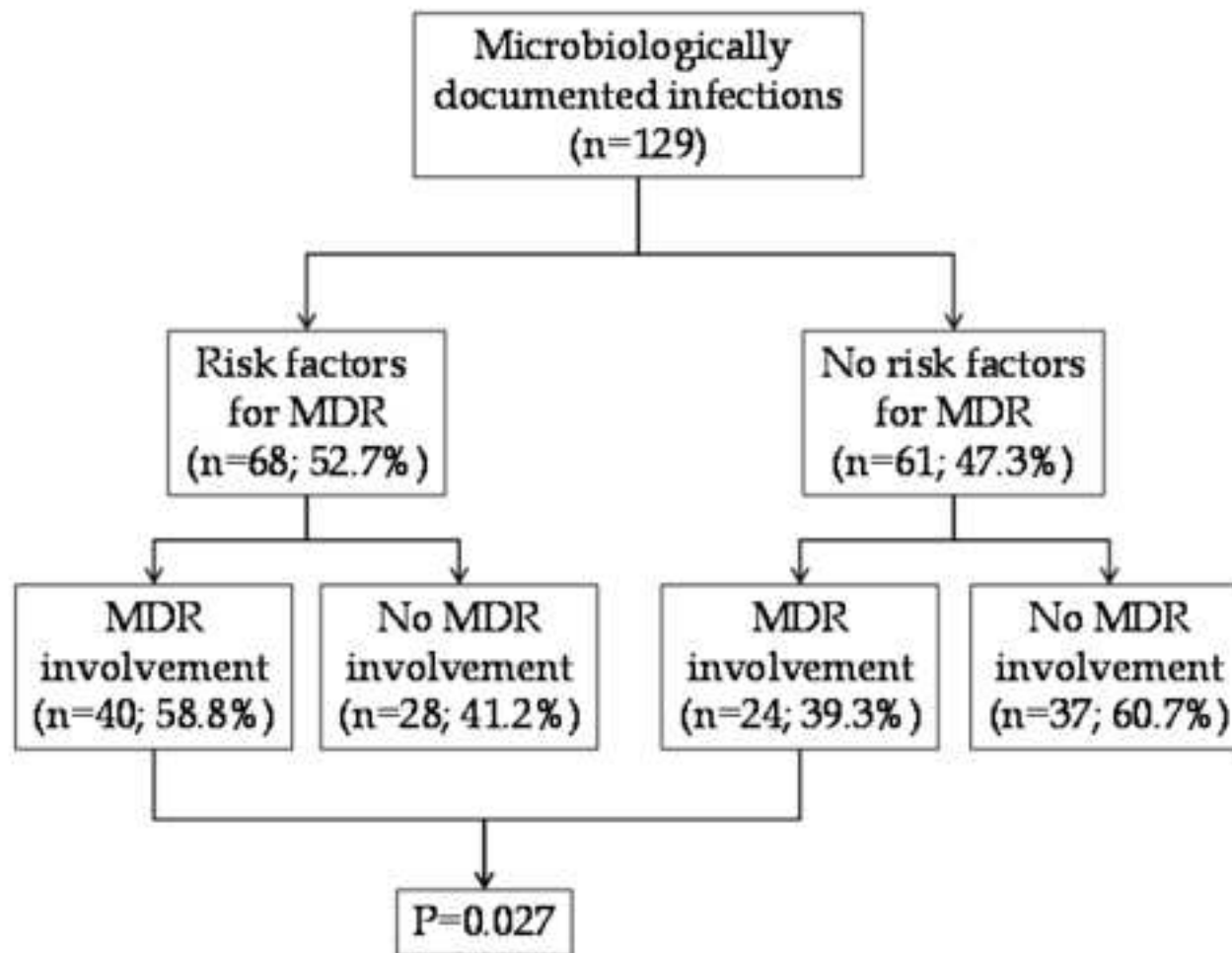
Table 2 - Characteristics of 171 ICU patients with a nosocomial infection.

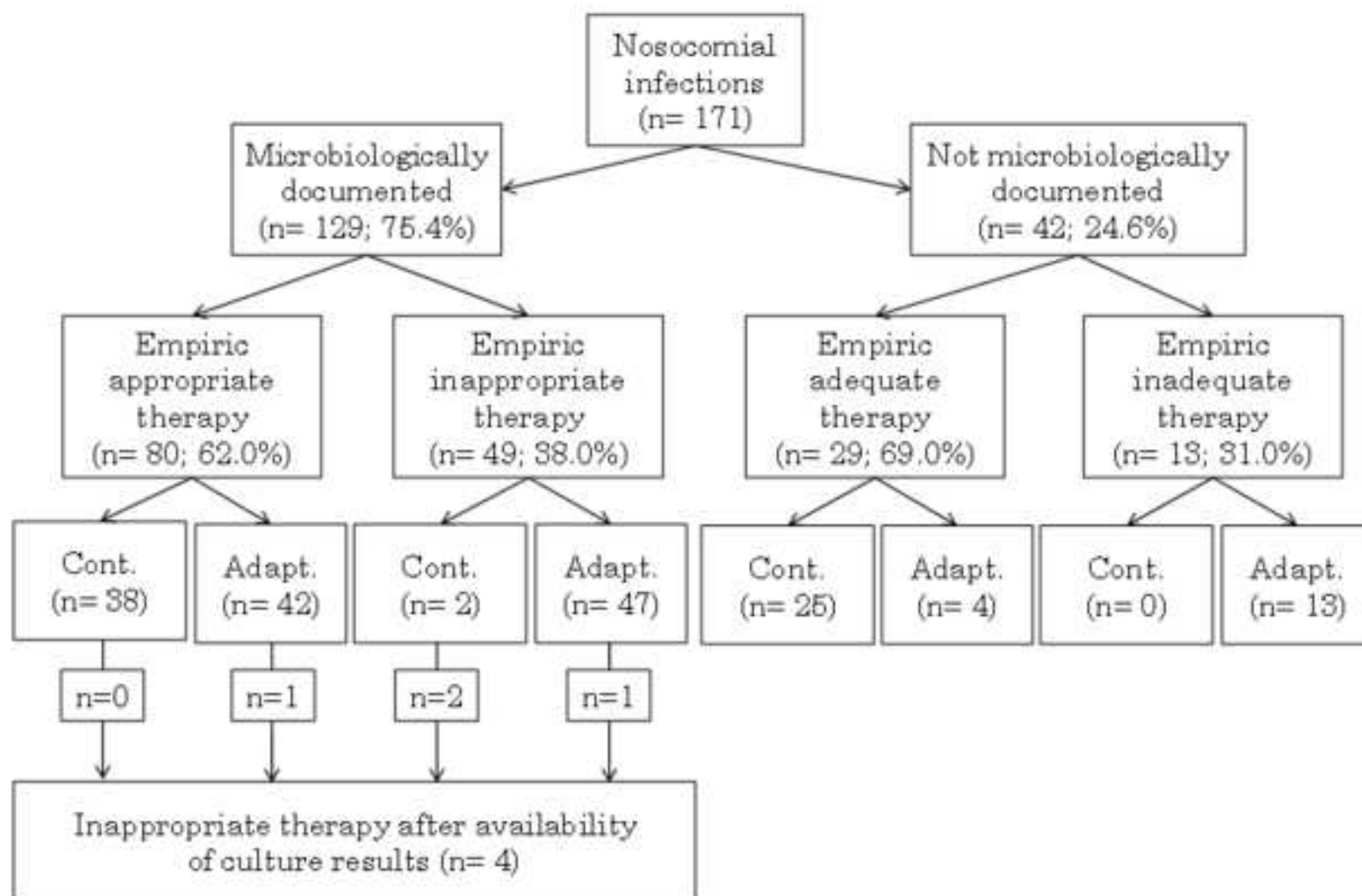
Characteristic	
Gender (male)	107 (62.0)
Age (years)	67 (55 - 76)
APACHE II score	20 (15 - 24)
Recent trauma / surgery	39 (22.8)
Co-morbidities	139 (81.3)
Respiratory disease	66 (38.6)
Cardiac disease	59 (34.5)
Neurologic disease	28 (16.4)
Diabetes mellitus	36 (21.1)
Hepatic disease	11 (6.4)
Renal disease	20 (11.7)
Malignancy	28 (16.4)
Neutropenia	1 (0.6)
Corticosteroid therapy	20 (11.7)
Prior hospitalization	51 (30.4)
Hospitalization at another ward prior to ICU admission	84 (50.0)
Prior antibiotic use	49 (28.7)
ICU-acquired infection	115 (66.7)
ICU stay before onset of infection (days)	3.8 (0 - 6)

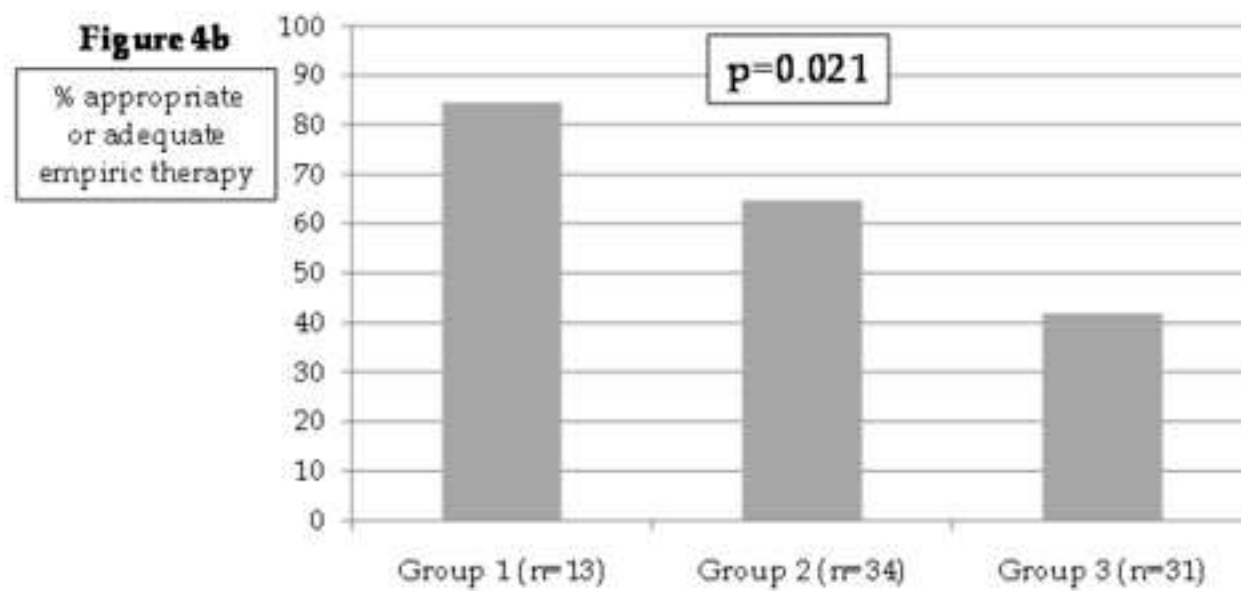
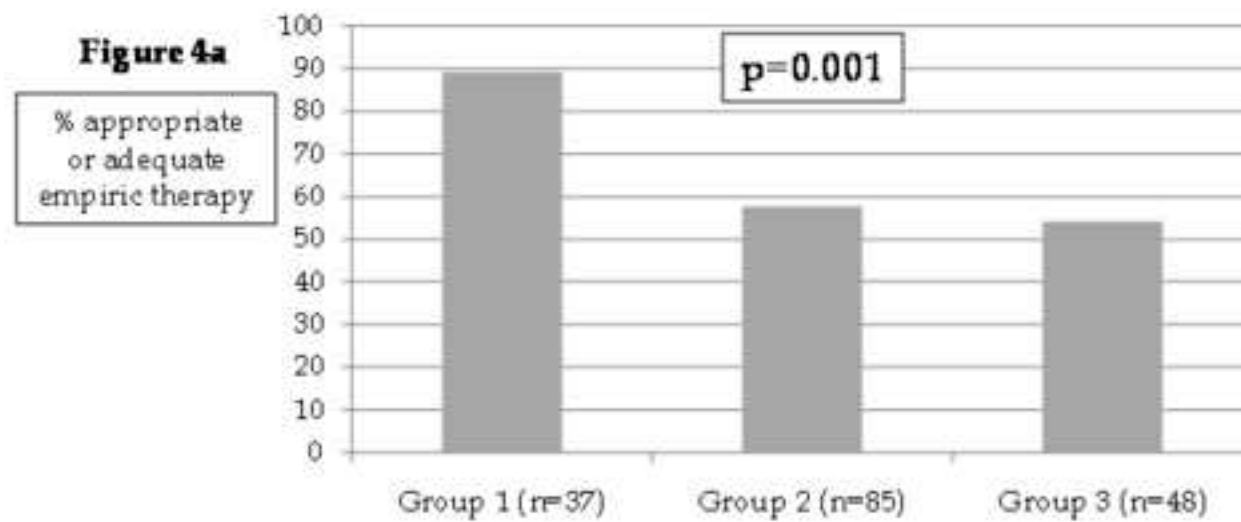
Data are described as n (%) or median (interquartile range)

Figure 1
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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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ARTICLE INFO

Article history:

Received 17 September 2009

Accepted 23 November 2009

Keywords:

Antibiotic resistance

Multidrug resistance

Intensive care

Infection

Appropriate therapy

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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.

Accepted Manuscript

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 bacteraemia [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/mm³).

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 χ^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 pneumoniae* ($n = 7$) 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.

Funding

This study was sponsored by an unrestricted grant from AstraZeneca (Belgium). SB is supported by a grant from the European Society of Intensive Care Medicine and iMDsoft Patient Safety Research Award 2008.

Competing interests

None declared.

Ethical approval

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

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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, methicillin-resistant *Staphylococcus aureus*; MRSE, methicillin-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 methicillin-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

Coverage	Empirical regimens	<i>n</i>
ESBL-producing Enterobacteriaceae + <i>Pseudomonas aeruginosa</i> + MRSA (<i>n</i> = 6)	MER+VAN	5
	MER+VAN+AMI	1
ESBL-producing Enterobacteriaceae + <i>P. aeruginosa</i> (<i>n</i> = 31)	MER	18
	MER+AMI	9
	MER+OXA	1
	MER+CIP+AMI	1
	MER+PIP/TAZ+AMI	2
<i>P. aeruginosa</i> + MRSA (<i>n</i> = 7)	PIP/TAZ+VAN+LEV	1
	PIP/TAZ+VAN	1
	CAZ+VAN	1
	CEP+VAN	2
	CEP+VAN+AMI	2
<i>P. aeruginosa</i> (<i>n</i> = 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 <i>P. aeruginosa</i> ($n = 51$)	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, methicillin-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.

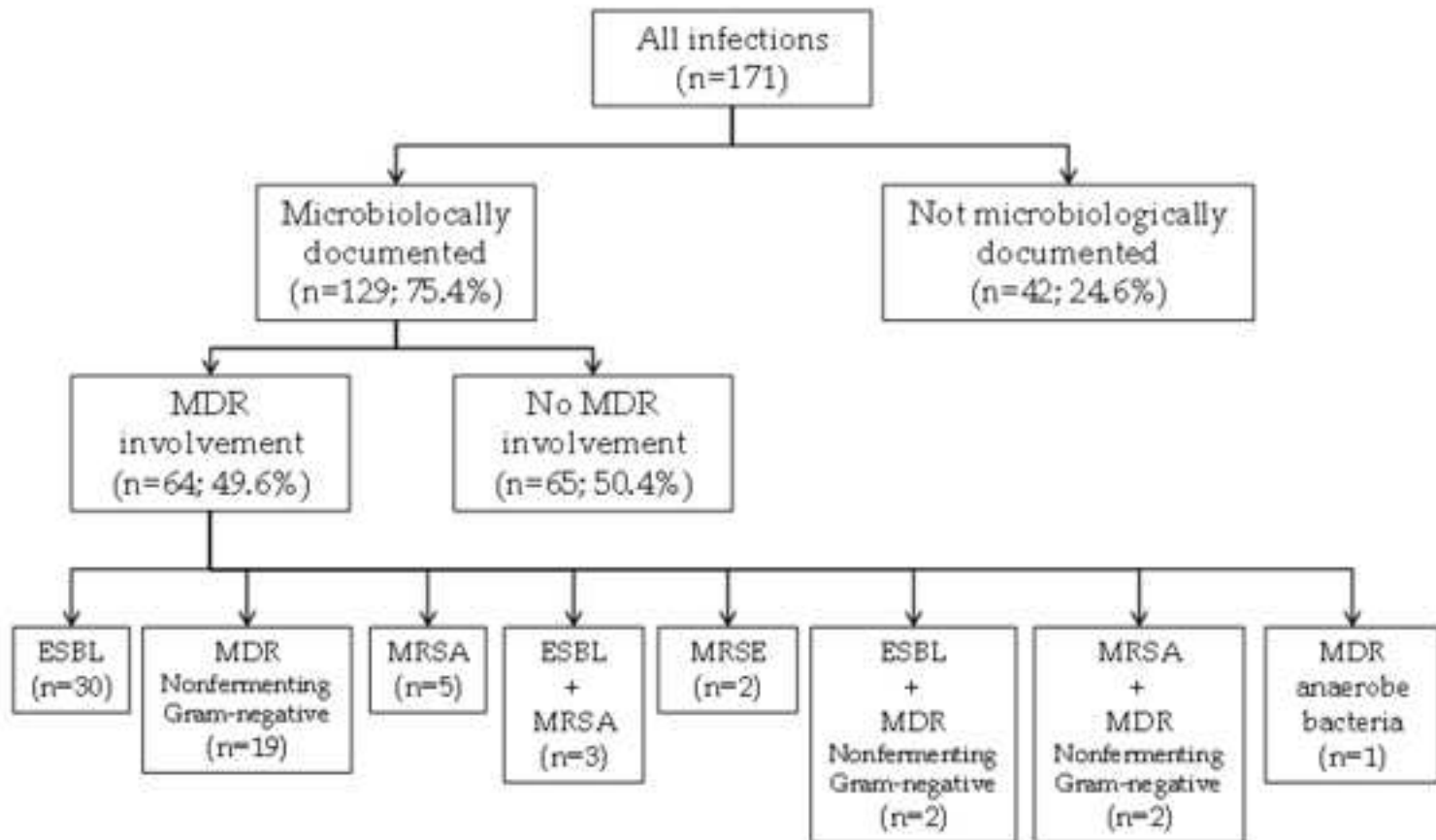
Table 2

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

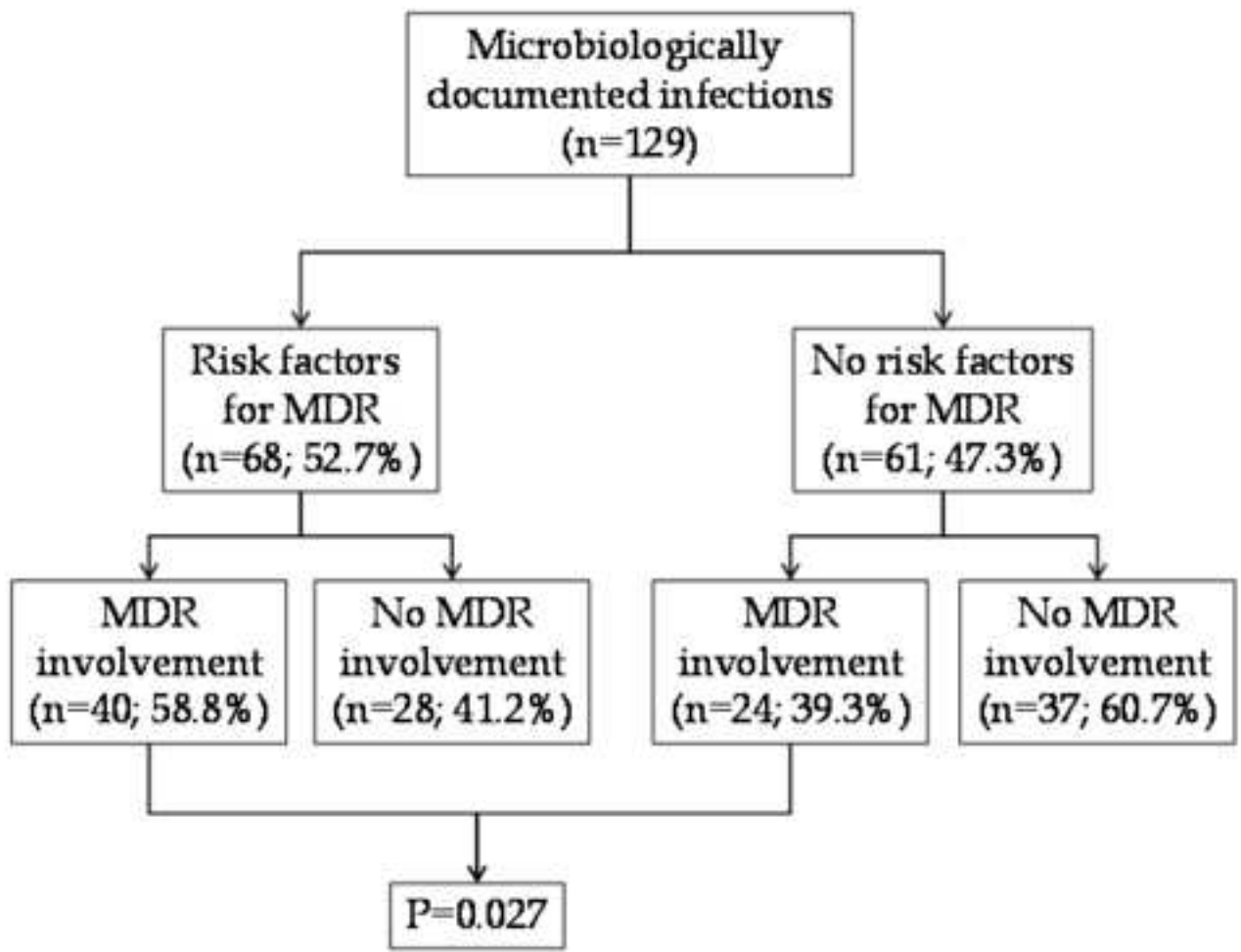
Characteristic	<i>n</i> (%) ^a
Gender (male)	107 (62.6)
Age (years) [median (IQR)]	67 (55–76)
APACHE II score [median (IQR)]	20 (15–24)
Recent trauma/surgery	39 (22.8)
Co-morbidities	139 (81.3)
Respiratory disease	66 (38.6)
Cardiac disease	59 (34.5)
Neurological disease	28 (16.4)
Diabetes mellitus	36 (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.

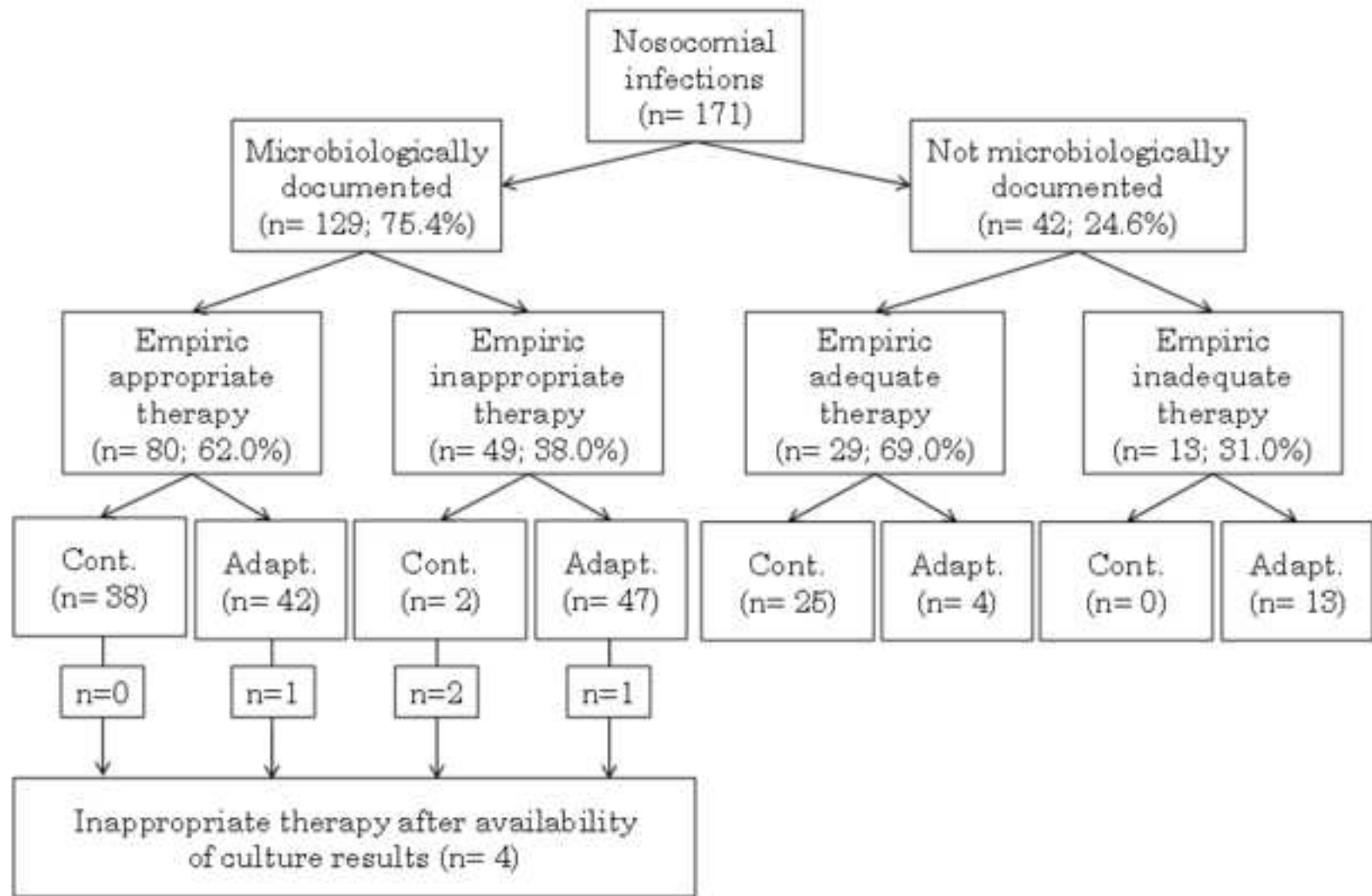
^a Data are *n* (%) unless otherwise stated.



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