ICU Acquisition Rate, Risk Factors, and Clinical Significance of Digestive Tract Colonization With Extended-Spectrum Beta-Lactamase–Producing Enterobacteriaceae: A Systematic Review and Meta-Analysis*

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Objective: To evaluate the acquisition rate, identify risk factors, and estimate the risk for subsequent infection, associated with the colonization of the digestive tract with extended-spectrum beta-lactamase–producing Enterobacteriaceae during ICU-hospitalization.

Data Sources: PubMed, EMBASE, and reference lists of all eligible articles.

Study Selection: Included studies provided data on ICU-acquired colonization with extended-spectrum beta-lactamase–producing Enterobacteriaceae in previously noncolonized and noninfected patients and used the double disk synergy test for extended-spectrum beta-lactamase–producing Enterobacteriaceae phenotypic confirmation. Studies reporting extended-spectrum beta-lactamase–producing Enterobacteriaceae outbreaks or data on pediatric population were excluded.

Data Extraction: Two authors independently assessed study eligibility and performed data extraction.

Data Synthesis: Thirteen studies (with 15,045 ICUs-patients) were evaluated using a random-effect model and a meta-regression analysis. The acquisition rate of digestive tract colonization during ICU stay was 7% (95% CI, 5–10) and it varies from 3% (95% CI, 2–4) and 4% (95% CI, 2–6) in the Americas and Europe to 21% (95% CI, 9–35) in the Western Pacific region. Previous hospitalization (risk ratio, 1.57 [95% CI, 1.07–2.31]) or antibiotic use (risk ratio, 1.65 [95% CI, 1.15–2.37]) and exposure to beta-lactams/beta-lactamase inhibitors (risk ratio, 1.78 [95% CI, 1.24–2.56]) and carbapenems (risk ratio, 2.13 [95% CI, 1.49–3.06]) during the ICU stay were independent risk factors for ICU-acquired colonization. Importantly, colonized patients were more likely to develop an extended-spectrum beta-lactamase–producing Enterobacteriaceae infection (risk ratio, 49.62 [95% CI, 20.42–120.58]). The sensitivity and specificity of prior colonization to predict subsequent extended-spectrum beta-lactamase–producing Enterobacteriaceae infection were 95.1% (95% CI, 54.7–99.7) and 89.2% (95% CI, 77.2–95.3), respectively.

Conclusions: The ICU acquisition rate of extended-spectrum beta-lactamase–producing Enterobacteriaceae ranged from 5% to 10%. Previous use of beta-lactam/beta-lactamase or carbapenems and recent hospitalization were independent risk factors for extended-spectrum beta-lactamase–producing Enterobacteriaceae colonization, and colonization was associated with significantly higher frequency of extended-spectrum beta-lactamase–producing Enterobacteriaceae subsequent infection and increased mortality. (*Crit Care Med* 2017; 45:705–714)

Key Words: colonization; extended-spectrum beta-lactamase; infection; intensive care unit; meta-analysis

*See also p. 752.

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Drs. Detsis and Mylonakis accept full responsibility for the conduct of the study, have access to the data, and have control of the decision to publish. Drs. Detsis had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs. Detsis and Karanika conceptualized and designed the study, performed the literature search, participated in data collection, extraction and interpretation, prepared tables and figures, performed the statistical analysis, wrote and drafted the initial article, approved the final article as submitted and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Dr. Mylonakis conceptualized and designed the study, interpreted the data, reviewed and revised the article, approved the final article as submitted, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Infections caused by extended-spectrum beta-lactamase–producing Enterobacteriaceae (ESBL-PE) is an emerging threat worldwide (1, 2). In the United States, the Centers for Disease Control and Prevention has characterized ESBL-PE as a serious threat involved in 26,000 healthcare-acquired infections and 1,700 deaths per year. In the same report, the excess medical cost was estimated to be $40,000 per infection (3). Infections by ESBL-PE are especially common among critically ill patients (4, 5), and outbreaks have been reported in several countries (6–8). A better understanding of patients at high risk for ESBL-PE infection may allow a more effective empiric therapy and help tailor appropriate preventive policies. In this context, colonization with ESBL-PE is suggested as a risk factor for ESBL-PE infection (9) and the purpose of this study is to assess the ICU acquisition rate of digestive tract colonization with ESBL-PE, identify the risk factors for colonization and estimate the risk for subsequent ESBL-PE infection.

MATERIALS AND METHODS

Data Sources and Searches

We performed a systematic search of PubMed and EMBASE databases for studies published up to November 2015 to identify all studies reporting data regarding the acquisition rate of digestive tract colonization with ESBL-PE throughout ICU hospitalization. Our search term was as follows: "(ESBL or [extended-spectrum beta-lactamase] or [extended-spectrum β-lactamase]) and (ICU or [intensive care unit] or [critically ill patient*] or [high-risk patient*])." Two authors (M.D., S.K.) screened independently titles and abstracts, and all potentially relevant studies were assessed in full text. We also reviewed the reference lists of all eligible studies and systematic reviews relevant to our study. Discrepancies were resolved by consensus. Abstracts from conference proceedings were not considered. In our study, we followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses and Meta-analysis Of Observational Studies in Epidemiology recommendations (**Supplementary Table 1**, Supplemental Digital Content 1, http://links.lww.com/CCM/C304; and **Supplementary Table 2**, Supplemental Digital Content 2, http://links.lww.com/CCM/C305).

Study Selection

Our primary outcome of interest was the acquisition rate of digestive tract colonization with ESBL-PE during ICU stay when the patients had been previously documented as noncolonized. We focused on the digestive tract, as it is the main reservoir of ESBL-PE (10, 11). We considered as digestive tract colonization any positive rectal, perianal, stool, or fecal culture and included studies that used the double disk synergy test for phenotypic confirmation, that, according to the National Committee for Clinical Laboratory Standards, it is the gold standard method for ESBL identification (12).

In an effort not to overestimate our outcomes of interest, we excluded from our analysis colonized patients if they were infected with an ESBL-PE strain before or concurrently with the documentation of their colonization status. For the same reason, studies which reported data during an outbreak and studies which did not differentiate results between ESBL-PE infection and colonization were also excluded. For studies that provided data before and after an intervention that aimed at decreasing ESBL-PE colonization, only the data prior the intervention were included in our analysis. Studies that did not study explicitly the acquisition in the ICU were excluded and restrictions for English language and adult population were imposed.

Data Extraction and Quality Assessment

We defined the acquisition rate as the number of patients who had a negative sample of digestive tract on ICU admission and became positive during their stay, divided by the number of patients who were negative at their admission having at least one more sample during their ICU stay. As secondary outcomes, we estimated the time between admission and ESBL-PE colonization and between ESBL-PE colonization to ESBL-PE infection. We were also interested in studying the risk for subsequent ESBL-PE infection and estimated the mortality among patients colonized with ESBL-PE bacteria (either at admission or acquired), compared with noncolonized patients. Additionally, we assessed the impact of potential risk factors (**Supplementary Table 3**, Supplemental Digital Content 3, http://links.lww.com/CCM/C306) on acquisition rate of ESBL-PE colonization throughout ICU stay and calculated the prevalence of colonization with ESBL-PE at admission in ICU. Also, we extracted the individual characteristics of each study.

We used the Newcastle-Ottawa Scale (NOS) to assess the quality of eligible studies (13). As our primary outcome of interest was the acquisition rate of digestive tract colonization with ESBL-PE during ICU stay when the patients had been previously documented as noncolonized, we excluded from our assessment three fields of the NOS, namely "selection of the nonexposed cohort," "demonstration that the outcome of interest was not present at the start of the study," and "comparability between cohorts," which were not applicable for our analysis. Studies that were awarded four or more (out of five maximum) stars were considered to be of high quality (**Supplementary Table 4**, Supplemental Digital Content 4, http://links.lww.com/CCM/C307).

Data Synthesis and Analysis

We carried out a random-effects meta-analysis to estimate the pooled prevalence and the 95% CIs using the DerSimonian and Laird approach (14). The Freeman Tukey arcsine method was used to address stabilizing variance (15). We used the Egger's test (ET) to explore publication bias due to small study effect (16). We selected a random and not a fixed-effects model, because we assumed that the effects are heterogeneous due to factors such as differences in study designs and infection control measures. The heterogeneity among studies was estimated using the τ -square statistic (14, 17). We grouped studies according to World Health Organization (WHO) regions (18). For time trends, we determined as index year of each

eligible study the median year of the study. Then, the estimated coefficients were transformed to rates and fitted values plotted against the index year (19). Meta-regression analysis was implemented to account for potential sources of heterogeneity and confounding. The effect of ESBL-PE prevalence at admission and the geographic distribution of ESBL-PE acquisition in the different WHO regions were explored through univariate and multivariate random-effects meta-regression using the Knapp and Hartung modification (20).

In a secondary analysis, which included only studies providing data on risk factors for ESBL-PE colonization during the ICU stay, we calculated the association with ESBL-PE colonization with the potential risk factors listed in Supplementary Table 3 (Supplemental Digital Content 3, http://links.lww.com/CCM/C306). Pooled relative effects (including mortality and risk factors) were measured using random-effects meta-analysis, and they were reported as unadjusted risk ratio (RR) estimates and 95% CIs. The heterogeneity was measured by Cochran Q.

To assess the effect of ESBL-PE colonization on infection with ESBL-PE, we performed a diagnostic accuracy meta-analysis. The bivariate random-effects model, accounting for correlation between studies, was used to estimate pairs of logit-transformed sensitivity and specificity and their 95% CI (21, 22). We also determined the positive likelihood ratio (LR+), negative likelihood ratio (LR–), diagnostic odds ratio (DOR), and their 95% CI.

The effect of ESBL-PE colonization on the length of stay, the time of admission to colonization and the time of ESBL-PE colonization to ESBL-PE infection were evaluated using random-effects meta-analysis and reported as mean in days and 95% CI. Median values and their interquartile ranges extracted from included studies were transformed to means and SDs (23). *p* value per study was used to calculate 95% CI and SE and vice versa (24, 25). The Stata v14 software package (StataCorp, College Station, TX) and the Excel were used to perform the statistical analysis. The statistical significance threshold was set at 0.05.

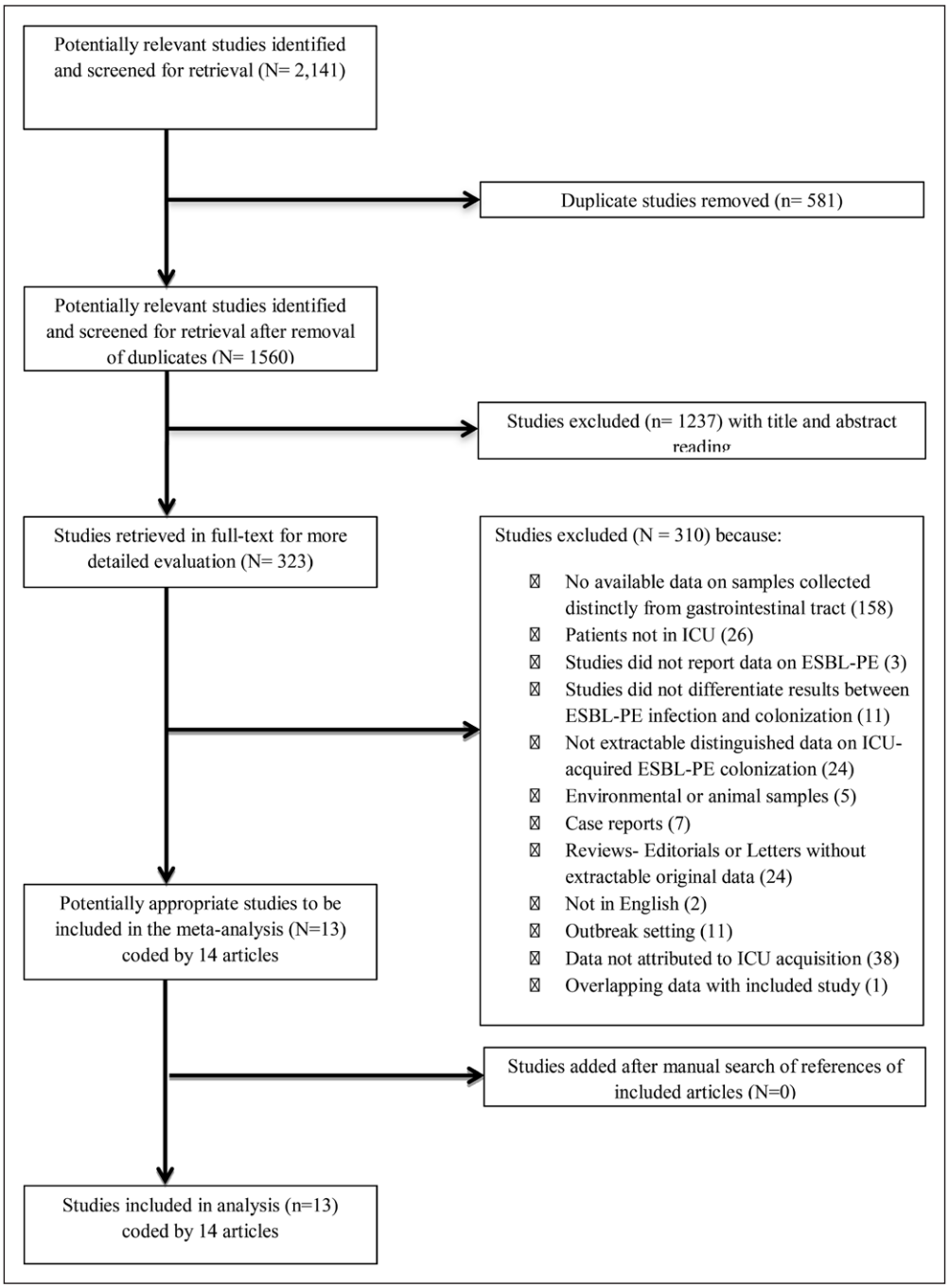

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of meta-analysis.

RESULTS

Our initial search yielded 1,560 nonduplicate potentially relevant citations. After title and abstract screening, 323 studies were identified as eligible for full text review. Of these, 310 articles were excluded from the final analysis and the selection process is detailed in **Figure 1**. We also excluded reported data on two ICUs of one multicenter study included 10 ICUs due to an ESBL-PE outbreak during the study period (26). At the end, 13 studies (26–38) coded from 14 articles (26–39)

TABLE 1. Characteristics of Included Studies

Author Mid-Year	Country	Patients Screened at Admission	No. of Colonized at Admission (%)	Patients at Risk for ICU Acquired Colonization	No. of ICU Colonization (%)	Sample Bacteria	Sampling Time After Admission	Age Sex Male	ICU Type (Beds) Hospital (No. of Participated)
Americas									
Harris et al (38, 39), 2005	USA	1,806	113 (6.3%)	1,693	56 (3.3%)	Perianal *Escherichia coli*, *Klebsiella pneumonia*	Weekly/ discharge	55.7[a] 54%	Medical/surgical (NR) University (1)
Ajao et al (37), 2005	USA	NR	NR	9,371	236 (2.5%)	Perianal *E. coli*, *K. pneumonia*, other Enterobacteriae	Weekly/ discharge	55.7 (15.6)[a] 55%	Medical/surgical (29–48) University (1)
Martins et al (35), 2000	Brazil	231	5 (2.2%)	226	13 (5.8%)	Rectal, other nonsterile *K. pneumonia*	One sample after of 72 hr	49 (8–95)[b] 51%	General (10) University affiliated (1)
European									
Bruyère et al (34), 2009	France	587	22 (3.8%)	565	18 (3.2%)	Rectal *E. coli*, *K. pneumonia*, other Enterobacteriae	Weekly	63.1 (14.7)[a] 68.3%	Medical (NR) NR
Grohs et al (33), 2011	France	269	38 (14.2%)	231	10 (4.3%)	Rectal *E. coli*, *K. pneumonia*, other Enterobacteriae	Daily/ discharge	64.2 (18.3)[a] 58.7%	Medical-surgical (NR) Teaching (1)
Nseir et al (30), 2007	France	NR	NR	469	8 (1.7%)	Rectal *E. coli*, *K. pneumonia*, other Enterobacteriae	Weekly	60 (12)[a] 64%	Medical/surgical (30) University (1)
Thiébaut et al (26), 2005	France	598	24 (4.0%)	574	20 (3.5%)	Rectal *E. coli*, *K. pneumonia*, other Enterobacteriae	Twice a week/ discharge	59 (47–72)[b] 58.9%	Medical/surgical (147) Multicenter (8)
Troché et al (29), 1998	France	1,059	27 (2.6%)	1,032	39 (3.8%)	Rectal NR	Weekly/ discharge	NR NR	Surgical (NR) NR
Razazi et al (28), 2011	France	531	82 (15.4%)	212	28 (13.2%)	Rectal *E. coli*, *K. pneumonia*, other Enterobacteriae	Twice a week	64 (50–75)[b] NR	Medical (24) University affiliated (1)
Western Pacific									
Lan et al (32), 2001	Taiwan	NR	NR	48	20 (41.7%)	Rectal *E. coli*, *K. pneumonia*	48 hr, weekly, discharge	> 18 NR	Medical (NR) Regional
Kim et al (36), 2012	Korea	347	98 (28.2%)	91	11 (12.1%)	Rectal *E. coli*, *K. pneumonia*, other Enterobacteriae	weekly, discharge	Adults NR	Medical/surgical (NR) Teaching (1)
Ma et al (31), 2009	China	686	224 (32.7%)	462	69 (14.9%)	Rectal	Weekly/ discharge	66 (9–101)[b] 59%	Medical/surgical (10–49) Multicenter (8)

(Continued)

TABLE 1. *(Continued).* Individual Studies

Author Mid-Year	Country	Patients Screened at Admission	No. of Colonized at Admission (%)	Patients at Risk for ICU Acquired Colonization	No. of ICU Colonization (%)	Sample Bacteria	Sampling Time After Admission	Age Sex Male	ICU Type (Beds) Hospital (No. of Participated)
Eastern Mediterranean									
Moustaoui et al (27), 1996	Morocco	85	9 (10.6%)	76	16 (21.1%)	Rectal *E. coli*, *K. pneumonia*, other Enterobacteriae	Weekly/ discharge	NR NR	Surgical (NR) University (1)-

n = number, NR = not reported.

[a]Mean (SD).

[b]Median (range).

Characteristics of 13 studies: mid-year country and World Health Organization region of study conduction, number of patients evaluated and screened at admission and during ICU stay, number of patients colonized at admission and acquired, sampling site and bacteria included in screening policy, sampling time after admission, patients demographics and size and type of ICU and hospital.

were included in our meta-analysis. The main characteristics of included studies are summarized in **Table 1**.

Overall, the 13 included studies provided data on 15,045 ICU patients. Two studies were retrospective (34, 37) and 11 (84.6%) were prospective (26–33, 35, 36, 38). The majority of the studies were conducted in Europe (6/13, all in France) (26, 28–30, 33, 34). From the remaining seven studies, three were conducted in the Western Pacific region (China, Taiwan, and Korea) (31, 32, 36), three in the Americas (two in the United States and one in Brazil) (35, 37, 38), and one in the Eastern Mediterranean region (Morocco) (27).

Among the 15,045 patients who were documented as noncolonized at admission, the pooled acquisition rate of digestive tract colonization with ESBL-PE during the ICU stay was 7% ([95% CI, 5–10] [$\tau^2 < 0.001$] [ET = 1.32; $P_{ET} = 0.006$]) (26–38) (**Fig. 2**). In the analysis of time trend plot, we found a stable trend in ESBL-PE acquisition among ICU patients (annual rate = – 0.5%; $p = 0.730$) (26–38) (**Supplementary Fig. 1**, Supplemental Digital Content 5, http://links.lww.com/CCM/C308). The acquisition in the Americas region was 3% ([95% CI, 2–4] [$\tau^2 < 0.001$] [ET = 0.57; $P_{ET} = 0.006$]) (35, 37, 38) (in the United States 3% [95% CI, 2–3]) (37, 38) and in Europe (France) was 4% ([95% CI, 2–6] [$\tau^2 = 0.01$] [ET = 1.27; $p = 0.250$]) (26, 28–30, 33, 34), whereas in the Western Pacific, it was 21% ([95% CI, 9–35] [$\tau^2 = 0.07$] [ET = 1.56; $p = 0.542$]) (31, 32, 36). Due to evidence of small study effect in the estimation of the pooled acquisition rate ($P_{ET} = 0.006$), we re-estimated the pooled acquisition rate of digestive tract colonization with ESBL-PE during the ICU stay only in larger studies. In this analysis, we included studies with more than 463 patients at risk (this value was the median among the initial included studies). This analysis included four studies from France and two studies from United States (26, 29, 30, 34, 37, 38), and even after this restriction, the combined estimate for acquisition rate was 3% (95% CI, 2–4%). This finding was similar with the estimation of the fixed-effects model (**Supplementary Fig. 2**, Supplemental Digital Content 6, http://links.lww.com/CCM/C309).

The pooled prevalence of digestive tract ESBL-PE colonization at admission in the ICU (based on 10 studies with 6,199 patients) was 10% ([95% CI, 5–17] [$\tau^2 = 0.10$] [ET = 1.79; $p = 0.476$]) (26–29, 31, 33–36, 38) and the geographic distribution was similar with the distribution of acquisition rate (**Supplementary Fig. 3**, Supplemental Digital Content 7, http://links.lww.com/CCM/C310). In the univariate meta-regression analysis, we found that the acquisition rate is associated with ESBL-PE burden at admission (coefficient = 0.46, $p = 0.019$, based on 10/13 included studies) and with the WHO region (coefficient = 0.21, $p = 0.004$, based on all included studies), but this association was not seen in the multivariate analysis testing the combination of these two factors ($p = 0.360$ and $p = 0.476$, respectively). As a result, the prevalence of ESBL-PE colonization at admission and the geographic region does not appear to independently predict the acquisition rate.

Three studies provided data regarding the time between admission and ESBL-PE acquisition. The estimated pooled mean length of ICU stay before the digestive tract colonization was 11.4 days ([95% CI, 9.7–13.1] [$\tau^2 < 0.001$]). It should be noted that the three studies with relevant data had only 57 patients, but there was no small-study effect (ET = –0.44; $P_{ET} = 0.430$) (26, 28, 35).

We assessed the potential risk factors for ESBL-PE colonization during the ICU stay, if three or more studies provided data on the same factor (**Table 2**) (Supplementary Table 3, Supplemental Digital Content 3, http://links.lww.com/CCM/C306). The pooled mean difference in length of ICU stay between colonized and noncolonized patients, based on three studies with 513 patients, was 8.94 days longer (95% CI, 1.30–16.6) ($p = 0.022$) for colonized patients (27, 28, 35). Based on three studies that included 900 patients (28, 31, 35), patients who had received beta-lactam/beta-lactamase inhibitors or carbapenems during their hospitalization in ICU were significantly more likely to be colonized with ESBL-PE (RR, 1.78 [95% CI, 1.24–2.56] [$Q = 0.60$; $P_Q = 0.74$] [ET = 1.01; $P_{ET} = 0.38$] and RR, 2.13 [95% CI, 1.49–3.06] [$Q = 1.69$; $P_Q = 0.43$] [ET = 1.13; $P_{ET} = 0.68$], respectively). Additionally, we calculated that patients who had received antibiotic treatment within the previous year (3 studies with 749 patients [27,

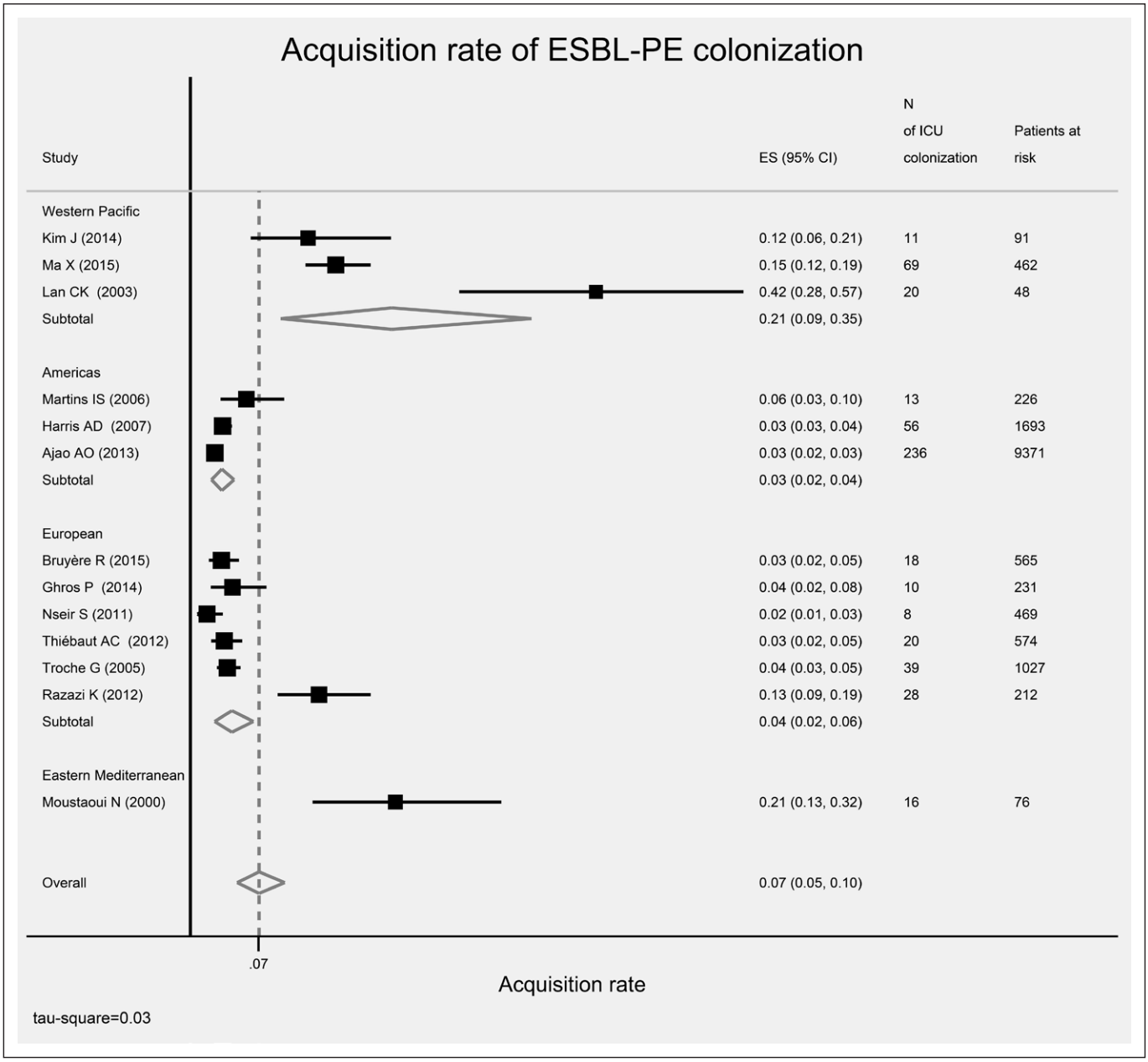

Figure 2. Forest plot of included studies stratified by World Health Organization regions and areas. Individuals and combined estimates of extended-spectrum beta-lactamase–producing Enterobacteriaceae (ESBL-PE) colonization. ES = effect size.

28, 31]) or had been hospitalized within the previous 6 months (3 studies with 763 patients [27, 31, 35]), were at higher risk for ESBL-PE colonization during ICU stay (RR, 1.65 [95% CI, 1.15–2.37] [$Q = 1.25$; $P_Q = 0.54$] [ET = –1.10; $P_{ET} = 0.46$] and RR, 1.57 [95% CI, 1.07–2.31] [$Q = 1.08$; $P_Q = 0.58$] [ET = –0.83; $P_{ET} = 0.57$], respectively). Unfortunately, the studies (with the exemption of [28]) did not report any further details on the type of antimicrobial agents, route of administration, or the duration of treatment.

Four studies with 1,359 patients reported extractable data on the manifestation of ESBL-PE infection among colonized (either at admission or acquired) and noncolonized patients (27, 28, 34, 35). All studies followed up patients until death or discharge from ICU and colonized patients were 49.62 ([95% CI, 20.42–120.58] [$Q = 2.01$; $P_Q = 0.570$] [ET = –1.88; $P_{ET} = 0.074$]) times more likely to develop an ESBL-PE infection, compared with noncolonized patients (**Fig. 3**). The combined sensitivity and specificity of screening for ESBL-PE colonization as a predictive tool for ESBL-PE infection were 95.1% (95% CI, 54.7–99.7) and 89.2% (95% CI, 77.2–95.3), respectively. Positive and negative LRs were 8.80 (95% CI, 4.15–18.67) and 0.055 (95% CI, 0.004–0.75), respectively, and the DOR was 160.9 (95% CI, 12.3–2099.8). Based on the LR+ (42), a positive screening culture increased by 40% the probability for infection. The estimated time between ESBL-PE colonization to infection (based on two studies with only 10 patients) was 5.9 days (95% CI, 4.0–7.9) ($\tau^2 = 0.948$) (28, 35). Based on four studies with 1,487 patients, we

TABLE 2. Pooled and Per Included Study Estimations on Significant Risk Factors for Digestive Tract Colonization During ICU Stay

Risk Factors				
During ICU Stay				
Exposure to beta lactam/ beta-lactam inhibitor	**No. of patients with digestive tract colonization during ICU stay, among those with history of exposure to beta-lactam inhibitor**	**No. of patients with digestive tract colonization during ICU stay, among those without history of exposure to beta-lactam inhibitors**	**RR (95% CI)**	**Time**
Martins et al (35)	5/54 (9.3%)	8/172 (4.7%)	1.99 (0.68–5.83)	NR
Razazi et al (28)	21/120 (20.0%)	7/92 (7.6%)	2.30 (1.02–5.18)	NR
Ma et al (31)	27/131 (20.6%)	42/331 (12.7%)	1.62 (1.05–2.52)	NR
Pooled RR			1.78 (1.24–2.56)	
Exposure to carbapenems	**No. of patients with digestive tract colonization during ICU stay, among those with history of exposure to carbapenems**	**No. of patients with digestive tract colonization during ICU stay, among those without history of exposure to carbapenems**		
Martins et al (35)	4/38 (10.5%)	9/188 (4.8%)	2.20 (0.71–6.77)	NR
Razazi et al (28)	11/37 (29.7%)	17/175 (9.7%)	3.06 (1.57–5.98)	NR
Ma et al (31)	20/86 (23.3%)	49/376 (13.0%)	1.78 (1.12–2.84)	NR
Pooled RR			2.13 (1.49–3.06)	
Factors Prior to ICU Admission				
Prior any antibiotic treatment before ICU admission	**No. of patients with digestive tract colonization during ICU stay, among those with history of prior antibiotic treatment**	**No. of patients with digestive tract colonization during ICU stay, among those without history of prior antibiotic treatment**		
Moustaoui et al (27)	1/4 (25.0%)	16/71 (22.5%)	1.11 (0.19–6.39)	NR
Razazi et al (28)	16/110 (14.6%)	12/102 (11.8%)	1.24 (0.62–2.49)	Previous year
Ma et al (31)	37/175 (21.1%)	32/287 (11.2%)	1.90 (1.23–2.93)	Last 3 mo
Pooled RR			1.65 (1.15–2.37)	
Previous hospitalization	**No. of patients with digestive tract colonization during ICU stay, among those with history of prior hospitalization**	**No. of patients with digestive tract colonization during ICU stay, among those without history of prior hospitalization**		
Moustaoui et al (27)	13/62 (21.0%)	3/13 (23.1%)	0.91 (0.30–2.74)	NR
Martins et al (35)	3/34 (8.8%)	10/192 (5.2%)	1.69 (0.49–5.84)	6 mo prior ICU admission
Ma et al (31)	36/181 (19.9%)	33/281 (11.7%)	1.69 (1.10–2.61)	6 mo prior ICU admission
Pooled RR			1.57 (1.07–2.31)	

NR = not reported, RR = relative risk.

also found that the pooled relative risk for overall mortality among colonized (either at admission or acquired) and noncolonized patients was 1.57 ([95% CI, 1.25–1.98] [$Q = 2.96$; $P_Q = 0.397$] [ET = –0.70; $P_{ET} = 0.607$]) (28, 31, 34, 35). Unfortunately, there were no extractable data on baseline characteristics and comorbidities among colonized and noncolonized patients for further analysis.

DISCUSSION

This analysis demonstrates that during their ICU hospitalization, patients have a significant risk to become colonized with ESBL-PE. The acquisition rate varies between different geographic areas, but it is significant even in the United States and Europe and, in the Western Pacific, it can be as high as 21%. Risk factors for ICU-acquired colonization can be related to medical

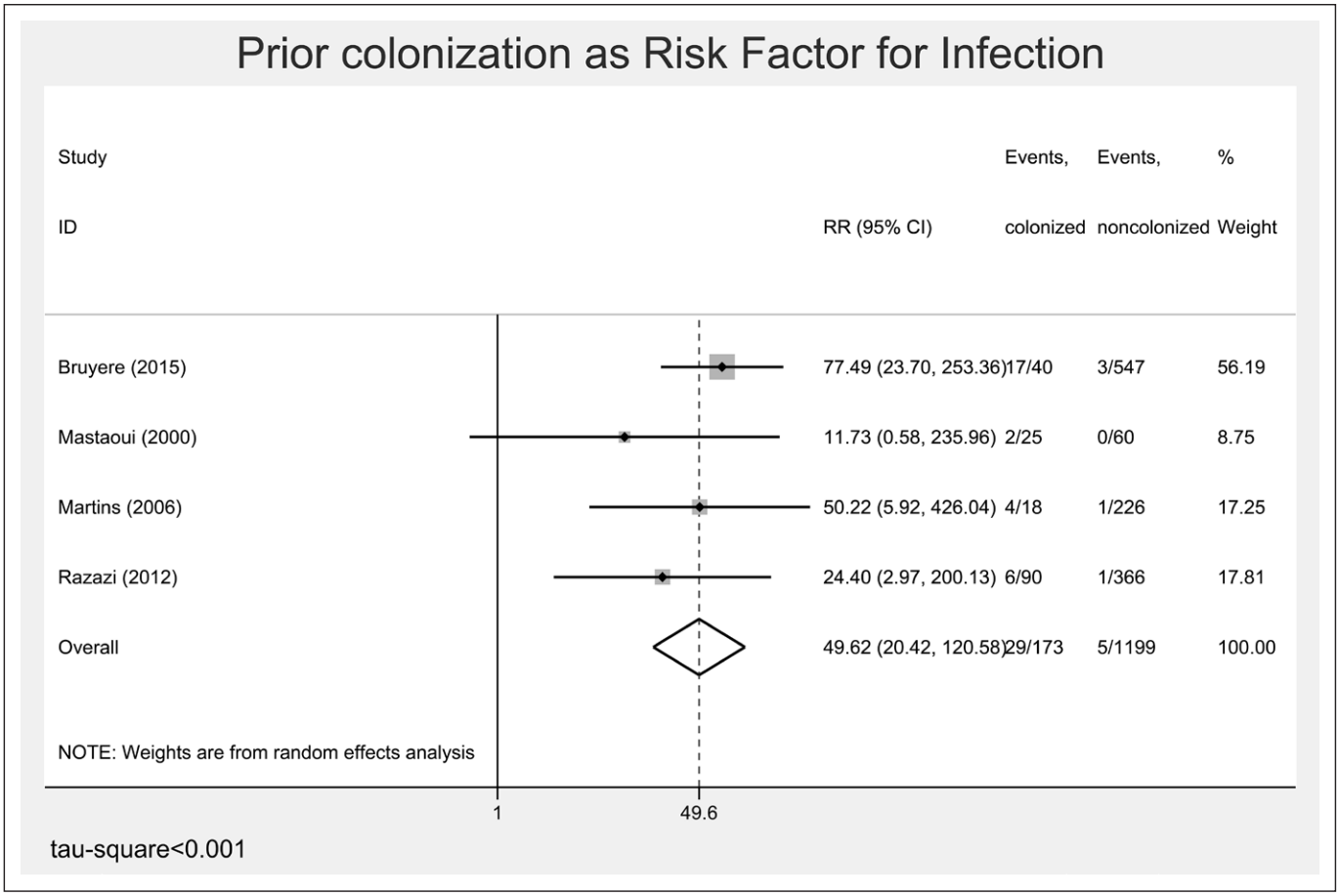

Figure 3. Forest plot of included studies. Relative risk (RR) estimates of extended-spectrum beta-lactamase–producing Enterobacteriaceae infection among colonized and noncolonized individuals.

history (such as previous hospitalization or antimicrobial use), or to the management during the ICU stay (such as beta-lactam/beta-lactamase inhibitor agents or carbapenems). Remarkably, the risk for ESBL-PE subsequent infection among colonized patients was almost 50 times higher than in noncolonized patients, and colonization of the digestive tract with ESBL-PE can be a useful tool to predict infection by ESBL-PE.

Notably, we found that overall one out of 10 patients were already colonized with ESBL-PE at admission to the ICU. This finding could be associated with the high reported rates of community-acquired colonization that in a recent meta-analysis was estimated to be as high as 14% (40). However, by performing sensitivity analysis on the factors which may affect the acquisition of ESBL-PE during ICU hospitalization, we found that the prevalence of ESBL-PE colonization at admission does not predict the acquisition rate. This finding confirms the established knowledge that patient-to-patient transmission and environmental contamination are not as important for the acquisition of ESBL-PE in the ICU setting (30, 37, 38) and that other factors (discussed in the next paragraphs) are more important for ESBL-PE colonization.

Our analysis confirms previous reports that antibiotic exposure and previous contact with the healthcare system are independent risk factors for ESBL-PE colonization (26, 41, 42). It is reasonable to assume that at least some of these patients may be colonized at admission. One explanation could be the failure of admission surveillance samples to identify some of the colonized patients. Indeed, a study which compared different screening policies for ESBL-PE identification carriage showed that sampling at admission, weekly, and at discharge identifies 89.6% of colonized patients compared with sampling at admission or discharge only which identifies 77.1% and 79.2%, respectively, suggesting that multiple screening samples increase sensitivity (33).

Carbapenems are the treatment of choice in ESBL-PE infections (43) and, at the same time, we found that carbapenems and beta-lactams/beta-lactamase inhibitors increase the risk of colonization in ICU. This can be explained by the fact that ESBL-PE genes are also associated with transfer of genetic material that confers resistance to beta-lactams (including oxyimino-beta-lactams) (44) or other antibacterial agents (45). Thus, empirical treatment provided in ICU patients should be selected cautiously.

ESBL-PE infections can lead to serious complications including death (46), and we found that colonized patients have approximately 50 times higher risk in developing ESBL-PE infection compared with the noncolonized. The combined sensitivity and specificity of screening for ESBL-PE colonization as a predictive tool for ESBL-PE infection were 95.1% and 89.2%, respectively, and a positive screening culture increases by 40%

the probability for infection (47). These findings confirm further the necessity for evaluation and potential implementation of surveillance screening strategies during ICU hospitalization, especially in patients meeting certain risk factors. However, this strategy should be tested, because the results of published studies on decolonization measures are still controversial and inconclusive (48, 49). Another potential benefit of surveillance screening is that it allows monitoring of colonized patients and carbapenems might be considered as empirical therapy in case of infection among colonized patients. This strategy should also be evaluated and monitored by a stewardship team in order not to lead to abuse of carbapenems that in turn can also increase the incidence of ESBL-PE bacteria.

Regarding the limitations in our study, the publication bias on the pooled prevalence estimate is significant (although it does not apply to all geographic areas and does not seem to affect our estimates). Also, it should be noted that studies are disproportionally distributed between countries, with France accounting for half of the studies. Finally, the risk factor and the risk for infection analyses were performed in a small proportion of included studies. This fact, in combination with the different definition for ESBL infection, might have impacted the results on the incidence of subsequent infection and the risk factor analyses. However, since we applied strict criteria on our definitions and excluded outbreaks from our estimations, our findings are more likely to underestimate, rather than overestimate, the actual prevalence.

In conclusion, ICU patients are at high risk for becoming colonized with ESBL-PE and colonization is associated with significantly higher incidence of subsequent infection. Early identification of colonization may help the selection of appropriate empiric treatment and future studies should focus on the evaluation of protocols that monitor for colonization, and the development of preventive measures that may halt spread of ESBL-PE in this setting.

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