Clinical Infectious Diseases

MAJOR ARTICLE

Implementation of French Recommendations for the Prevention and the Treatment of Hospital-acquired Pneumonia: A Cluster-randomized Trial

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(See the Editorial Commentary by Rello and Waterer on pages e1611–2.)

Background. We determined whether an audit on the adherence to guidelines for hospital-acquired pneumonia (HAP) can improve the outcomes of patients in intensive care units (ICUs).

Methods. This study was conducted at 35 ICUs in 30 hospitals. We included consecutive, adult patients hospitalized in ICUs for 3 days or more. After a 3-month baseline period followed by the dissemination of recommendations, an audit on the compliance to recommendations (audit period) was followed by a 3-month cluster-randomized trial. We randomly assigned ICUs to either receive audit and feedback (intervention group) or participate in a national registry (control group). The primary outcome was the duration of ICU stay.

Results. Among 1856 patients enrolled, 602, 669, and 585 were recruited in the baseline, audit, and intervention periods, respectively. The composite measures of compliance were 47% (interquartile range [IQR], 38–56%) in the intervention group and 42% (IQR, 25–53%) in the control group ($P = .001$). As compared to the baseline period, the ICU lengths of stay were reduced by 3.2 days in the intervention period ($P = .07$) and by 2.8 days in the control period ($P = .02$). The durations of ICU stay were 7 days (IQR, 5–14 days) in the control group and 9 days (IQR, 5–20 days) in the intervention group ($P = .10$). After adjustment for unbalanced baseline characteristics, the hazard ratio for being discharged alive from the ICU in the control group was 1.17 (95% confidence interval, .69–2.01; $P = .10$).

Conclusions. The publication of French guidelines for HAP was associated with a reduction of the ICU length of stay. However, the realization of an audit to improve their application did not further improve outcomes.

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Between 2016 and 2017, 3 recommendations for the prevention, diagnosis, and treatment of hospital-acquired pneumonia (HAP) were published in America, [1] Europe [2], and France [3]. The simultaneous dissemination of recommendations underlines the clinical relevance of improving the management of HAP in intensive care units (ICUs). Compliance with newly published guidelines is a slow process, possibly requiring years before reaching 90% application of a single intervention in clinical practice [4]. For instance, the proportion of brain-injured patients receiving protective mechanical ventilation did not exceed 20% at 4 months after a quality improvement program [5], whereas overall compliance with the recommendations of the Surviving Sepsis Campaign ranged from 19% to 36% at 8 years after they were first disseminated [6].

Improving methods for implementing guidelines in a short period after dissemination is thus urgently needed, most notably for the treatment of infectious diseases, because control of the pandemic requires a rapid and coordinated response from caregivers. Payment for performance has limited effects on patient outcomes [7, 8], and a national educational intervention recently failed to increase the percentage of septic patients receiving antibiotics within the first hour in Germany [9]. The conduct of a clinical audit with feedback is recommended to improve adherence to guidelines [10], yet the rates of audit completion are low in most clinical medicine areas [11].

We hypothesized that audits with feedback on the adherence to guidelines for HAP could enhance the outcomes of patients. We thus designed the PneumoCare Study (clinicaltrials.gov number NCT03348579) to show, in a nationwide, cluster-randomized clinical trial, the effects of an audit of compliance with guidelines for the prevention, diagnosis, and treatment of HAP on the duration of ICU hospitalization.

METHODS

Ethics Statement

The Ethical Committee of the Société Française d'Anesthésie Réanimation (SFAR) approved the study protocol (Comité d'Ethique de la Recherche en Anesthésie Réanimation Institutional Review Board 00010254–2017–020, Paris, France). Patients and relatives were informed of the trial and had the option to refuse the collection of their medical data. Consent was waived according to French law because the trial was a collaborative, institutional quality improvement initiative applied to all patients [12].

Population and Setting

The study was conducted in 35 ICUs of 30 hospitals in France. We collected and analyzed data from all adult (>17 years old) patients admitted to ICUs for a minimal duration of 3 days with a Simplified Acute Physiology Score (SAPS) II of 15 or more. Exclusion criteria were hospitalization in the ICU for community-acquired pneumonia, the decision to withdraw care or to restrict treatment during the first 24 hours after ICU admission, pregnancy, and legal trusteeship.

Study Design

We used a cluster-randomized design with 2 preliminary periods: Period 1 (baseline) was used as a baseline to measure the rates of adherence before the publication of the French recommendations, Period 2 (audit) was used to perform the audit, and the effect of training based on an audit with feedback was assessed during Period 3 (intervention).

Study Timeline

Period 1 (baseline) consisted of 3 months (July–September 2017), during which data were retrospectively recorded for all patients admitted to the participating ICUs who met the inclusion criteria. Between 1 October and 15 January 2018 (between phases), the recommendations for the prevention and treatment of HAP were publicly released at the SFAR Congress (September 2017) and at the Société de Réanimation de Langue Française (SRLF) Congress (January 2018). The full texts were published in November 2017 [3]. During this time period, on-site coordinators were responsible for the dissemination of guidelines to the clinicians, medical students, nurses, and physiotherapists. The audit period (Phase 2) ran from 15 January to 15 April 2018, during which time data prospectively collected from all consecutive patients admitted to participating ICUs were analyzed for an audit of the rates of compliance with the recommendations. At the end of the audit period, we randomized the ICUs into 2 groups (intervention group vs control group).

In the intervention group, a trained physician acting as a quality coordinator was informed of the local and national rates of application of the recommendations (an example of an audit is in Supplementary Figure E1). The local coordinators were thus encouraged to select interventions with local rates of application lower than those observed at the nationwide level. They were also responsible for further training of other caregivers (doctors and nurses) in the application of the selected recommendations. In the control group, the local coordinators were kept blinded to the rates of application measured during the audit and were encouraged to participate in a national registry. Period 3 consisted of a 3-month period (15 July–15 September 2018), during which data were prospectively recorded for all patients admitted to the participating ICUs after the intervention.

Cluster Randomization

ICU clusters were randomized at the end of Period 2 either to specific training that was based on the audit feedback (intervention group) or to participate in a national registry (control

group), using a randomly generated number from SAS software (1:1 ratio; SAS Institute; version 9.3).

Data Collection and Quality Control

Instructions for the data collection, along with outcome definitions, were made available to all investigators before data collection started. Data were collected by residents or clinicians using a specific online tool on a dedicated platform for clinical research (RedCap). The uniformity and completeness of data were electronically checked for quality assurance purposes. Queries for errors or incomplete fields were returned to centers for correction.

Outcomes

Because our interventions sought to improve the prevention, diagnosis, and treatment of HAP, we decided not to use either the rate of HAP or the treatment response for the primary outcome, which would not have addressed the application of all of the guidelines. *A priori*, the primary outcome was the mean number of ICU-free days at Day 28 during Period 3. The number of ICU-free days, defined as the number of days between Days 1 and 28 for which a living patient is outside the ICU, is provided as a secondary outcome. Dead patients were ascribed 0 invasive ventilation–free days. During the study, our group has demonstrated that the use of ventilator-free days has many methodological drawbacks [13]. We thus, *a posteriori*, decided to use the duration of ICU stay in the intervention and control groups during Period 3 as the primary outcome, taking into account the clustering effect and death as a competing risk. The analyses were intended to evaluate, in a hierarchical fashion, (1) the efficacy on the primary outcome of the intervention (intervention group vs control group); and (2) whether the effectiveness of the audit demonstrated, as measured by the primary outcome, the efficacy of the implementation of the guidelines independently of the audit (baseline vs audit group).

The main secondary outcomes included compliance with the recommendations, survival at Day 90, rates of HAP at Day 28, and rates of cure at the end of treatment.

Definitions

HAP was identified based on the appearance of a new infiltrate or changes in an existing infiltrate on chest X-ray associated with any 2 of the following clinical signs: body temperature >38°C, leukocytosis >12 000/ml, or leukopenia <4000/ml; and purulent pulmonary secretions that were associated with a positive quantitative or semi-quantitative bacteriological culture of a respiratory tract sample. HAP was defined as pneumonia that occurred 48 hours after admission, and could be acquired outside of the ICU. Ventilator-associated pneumonia (VAP) was considered when HAP developed in patients who had been invasively mechanically ventilated for at least 48 hours [2]. HAP cure was defined as the resolution of signs and symptoms present at diagnosis, with improvement or lack of progression of radiological signs [14, 15].

Definitions of compliance with recommendations are provided in Supplementary Table E1. Inadequate empirical antimicrobial therapy was defined as when therapy was not compliant with recommendations. De-escalation was defined as the reduction of the spectrum of antibiotics after bacterial identification. The composite measure of compliance was defined as the total number of performed actions, divided by the total number of interventions for which each patient was eligible [16]. Optimal compliance was considered in patients with a composite measure of compliance above 50%.

Statistical Analyses

The mean duration of ICU stays with a SAPS II of 15 or above was estimated to be 12 ± 7 days in the baseline period [17]. We designed the PneumoCare Study to detect a decrease from a mean duration of 12 ± 7 days at baseline to 10 ± 7 days in the intervention period. We assumed an intracluster correlation coefficient of 0.02 [16] and a cluster size of 20 with a power of 80% and a Type I error of 5% (2-sided). This required the inclusion of 532 patients (266 in the intervention group and 266 in the control group). To achieve this number, and based on *a priori* expected rates of inclusion per center, we calculated that a period of 3 months and the participation of at least 30 ICUs were required.

Continuous data were expressed as means ± standard deviations or medians (25th to 75th percentiles; interquartile ranges [IQR]) for skewed distributions. Categorical data were expressed as numbers and percentages. All data were compared between baseline and audit, and between the intervention or control groups within Period 3. Student *t* tests or Wilcoxon tests were used for comparing continuous data and chi-square or Fisher's exact tests were used for comparing categorical data.

The primary endpoint was analyzed using a Wilcoxon test and a competing risk survival model (cause-specific hazard regression) to take into account death as a competing event, with adjustments for characteristics at baseline, as well as a clustering effect. Several exploratory subgroup analyses were performed using the same competing risk survival model (optimal vs nonoptimal compliance, medical vs surgical patients, admission severity, early onset vs late onset, presence or absence of severe hypoxemia, presence or absence of drug-resistant bacteria, bronchoalveolar lavage vs tracheal sputum sampling, and VAP vs non–ventilator associated HAP). We also conducted time-series analyses to evaluate the impact of the successive recommendation periods quantitatively (see Supplementary Methods) [18, 19].

The survival distributions were estimated using Kaplan–Meier estimates, and they were compared using Cox models, considering death and HAP, with a cause-specific hazard regression for the latter (taking into account the clustering effect by a random effect). A P value <.05 was considered statistically significant. Statistical analyses were performed using SAS statistical software (SAS 9.4, SAS Institute, Cary, NC).

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Table 1. Demographic Characteristics

	Period 1 baseline		Period 2 audit			Period 3				
						Entire		Intervention	Control	
	n = 602	Number with data	n = 669	Number with data	*P* values[a]	n = 585	Number with data	n = 301	n = 284	*P* values[b]
Age, years, median (25–75th percentile)	63 (49–73)	596	66 (54–75)	667	<.001	63 (49–72)	580	61 (45–72)	66 (53–74)	.001
Male, n (%)	396 (66)	601	436 (65)	667	.85	383 (66)	585	197 (66)	186 (66)	.99
Diagnosis on admission, n (%)										
Medical	179 (30)	600	281 (42)	667	<.001	193 (33)	584	100 (33)	93 (33)	.02
Surgical	324 (54)	…	308 (46)	…		283 (49)	…	133 (44)	150 (53)	
Trauma	97 (16)	…	78 (12)	…		108 (19)	…	68 (23)	40 (14)	
SAPS-II, median (25–75th percentile)	43 (31–55)	578	45 (32–57)	633	.03	41 (28–55)	549	40 (27–55)	43 (29–56)	.23
SOFA, median (25–75th percentile)	6 (4–9)	580	6 (4–9)	645	.50	6 (3–8)	551	5 (3–8)	6 (4–8)	.21
Individual risk factors, n (%)										
Chronic hemodialysis	11 (2)	598	9 (2)	664	.49	10 (2)	583	6 (2)	4 (1)	.75
Chronic skin lesion	5 (1)	594	17 (3)	666	.02	14 (2)	584	10 (3)	4 (1)	.13
Immunosuppression	29 (5)	600	50 (8)	666	.05	41 (7)	582	25 (8)	16 (6)	.21
Chronic obstructive pulmonary disease	49 (8)	597	72 (11)	667	.12	63 (11)	582	36 (12)	27 (10)	.32
Colonized by resistant GNB	13 (2)	594	23 (4)	664	.18	15 (3)	577	9 (3)	6 (3)	.48
Colonized by MRSA	2 (.3)	599	6 (.9)	666	.29	3 (.5)	582	1 (.3)	2 (.7)	.61
Oversea hospitalization < 12 months	3 (.5)	599	9 (1)	668	.12	8 (1)	575	6 (2)	2 (.7)	.29
Intensive care unit bacterial ecology										
GNB with ESBL > 10%, n (%)	156 (26)	601	188 (28)	665	.36	128 (22)	582	80 (27)	48 (17)	.004
MRSA > 5%, n (%)	43 (7)	601	48 (7)	665	.99	41 (7)	584	41 (14)	0 (0)	<.001

Abbreviations: ESBL, extended-spectrum beta-lactamase; GNB, Gram-negative bacteria; MRSA, methicillin-resistant *Staphylococcus aureus*; SAPS-II, simplified acute physiology score; SOFA, sequential organ failure assessment.

[a]*P* values for comparison between baseline versus audit periods.

[b]*P* values for comparison between intervention versus control group.

Table 2. Compliance With Guidelines

Number of patients	Period 1 Baseline n = 602	Period 1 Baseline Number with data	Period 2 Audit n = 669	Period 2 Audit Number with data	*P* values[a]	Period 3 Entire n = 585	Period 3 Entire Number with data	Period 3 Intervention n = 301	Period 3 Control n = 284	*P*-values[b]
Prevention-related guidelines, n (%)	8 (1)	601	8 (1)	665	.84	8 (1)	579	8 (3)	0 (0)	.008
Selective digestive decontamination	579 (96)	601	612 (92)	666	.001	540 (93)	580	278 (93)	262 (93)	.86
Multifaced prevention	…	576[c]	…	612[c]		…	539[c]	…	…	
Noninvasive mechanical ventilation[c]										
Yes	122 (21)	…	163 (27)	…	.02	151 (28)	…	86 (31)	65 (25)	<.001
No	274 (48)	…	246 (40)	…		182 (34)	…	70 (25)	112 (43)	
Nonapplicable	180 (31)	…	203 (33)	…		206 (38)	…	122 (44)	84 (32)	
Early enteral nutrition[c]	238 (41)	578[c]	236 (39)	611[c]	.52	186 (35)	537[c]	128 (47)	58 (22)	<.001
Daily subglottic suctioning[c]										
Yes	149 (26)	579[c]	179 (29)	612[c]	.03	177 (33)	536[c]	110 (40)	67 (26)	.002
No	355 (61)	…	331 (54)	…		255 (48)	…	115 (42)	140 (54)	
Nonapplicable	75 (13)	…	102 (17)	…		104 (19)	…	50 (18)	54 (21)	
Control of tracheal cuff pressure[c]										
Yes	462 (80)	579[c]	490 (80)	610[c]	.01	394 (73)	537[c]	212 (77)	182 (70)	.10
No	38 (7)	…	19 (3)	…		40 (8)	…	15 (5)	25 (10)	
Nonapplicable	79 (14)	…	101 (17)	…		103 (19)	…	49 (18)	54 (21)	
Recommendations against the use of[c]:										
Selective oropharyngeal decontamination	360 (62)	579[c]	423 (69)	610[c]	.009	314 (59)	537[c]	138 (50)	176 (67)	<.001
Probiotics/symbiotics	10 (2)	579[c]	13 (2)	612[c]	.62	0 (0)	538[c]	0 (0)	0 (0)	1.00
Closed suctioning system, yes	143 (25)	577[c]	161 (26)	611[c]	.23	128 (24)	535[c]	90 (33)	38 (15)	<.001
Frequent respiratory circuit change	162 (28)	575[c]	125 (21)	608[c]	.009	113 (21)	538[c]	52 (19)	61 (24)	.15
Number of patients	174	…	188	…		149	…	92	57	
Diagnosis-related guidelines, n (%)										
Dosage of procalcitonin	46 (27)	170	49 (26)	187	.85	28 (19)	149	25 (27)	3 (5)	<.001
Chest X-ray	165 (95)	174	162 (87)	187	.01	131 (89)	148	88 (97)	43 (75)	<.001
Microbiological analysis, respiratory	163 (94)	174	166 (89)	187	.10	139 (93)	149	91 (99)	48 (84)	.001
Quantitative or semi-quantitative analysis	155 (96)	161	151 (93)	162	.22	132 (96)	147	90 (99)	42 (91)	.04
Treatment-related guidelines										
Monotherapy for empirical treatment in the absence of risk for bacterial resistance, n (%)	36 (57)	63	42 (60)	70	.74	32 (56)	57	17 (53)	15 (60)	.60
De-escalation of empirical antibiotherapy, n (%)	87 (51)	171	96 (51)	188	.97	72 (49)	148	47 (52)	25 (44)	.36
Number of days with antibiotics, mean (SD)	7 (6–8)	173	7 (5–8)	186	.81[d]	8 (4)	146	7 (2)	8 (4)	.02[d]
Composite measure of compliance, %, median (25–75th percentile)	42 (33–50)	592	42 (33–53)	665	.51[d]	42 (33–56)	583	47 (38–56)	42 (25–53)	.001

Abbreviations: ICU, intensive care unit; SD, standard deviation.

[a] *P* values for comparison of baseline versus audit periods.

[b] *P* values for comparison of intervention versus control group.

[c] Only assessed in ICU with a multifaceted program to prevent pneumonia (n = 579 in Period 1; n = 612 in Period 2; and n = 540 in Period 3).

[d] Wilcoxon test.

Table 3. Outcomes

	Period 1		Period 2			Period 3				
	Baseline, n = 602	Number with data	Audit, n = 669	Number with data	*P* value[a]	Entire, n = 585	Number with data	Intervention, n = 301	Control, n = 284	*P* value[b]
Duration of hospitalization in ICU, days										
Median (25–75th percentile)	9 (5–18)	601	8 (5–16)	662	.21[c]	8 (5–16)	580	9 (5–20)	7 (5–14)	.10[c]
Mean ± SD	15 (18)	…	13 (14)	…	.87[c]	13 (12)	…	14 (13)	12 (11)	
ICU-free days at Day 28, median (25–75th percentile)	18 (0–22)	…	18 (0–22)	…		18 (2–23)	…	17 (0–23)	20 (7–23)	.21[c]
Hospital-acquired pneumonia at Day 28, n (%)	164 (28)	597	183 (28)	663	.96	146 (25)	580	89 (30)	57 (20)	.006
Ventilator-associated pneumonia	48 (30)	158	61 (34)	180		46 (32)	145	26 (30)	20 (35)	
Hospital-acquired pneumonia, not associated with mechanical ventilation	110 (70)	158	119 (66)	180		99 (68)	145	62 (70)	37 (65)	
Empirical treatment failure,[d] n (%)	25 (17)	148	20 (13)	157	.31	13 (10)	133	9 (11)	4 (8)	.77
Hospital-acquired pneumonia evolution, n (%)										
Clinical cure at the end of treatment	99 (66)	591	117 (75)	650	.16	99 (72)	573	61 (71)	38 (75)	.63
Relapse with same pathogens	26 (17)	…	17 (11)	…		14 (10)	…	8 (9)	6 (12)	
Recurrence with other pathogens	26 (17)	…	22 (14)	…		24 (18)	…	17 (20)	7 (14)	
Duration of invasive mechanical ventilation, days, mean ± SD	7.5 ± 12.7	595	7.5 ± 11.8	657	.65	6.3 ± 10.6	578	6.9 ± 11.6	5.6 ± 9.3	.29
Duration of noninvasive mechanical ventilation, days, mean ± SD	1.7 ± 3.8	591	1.8 ± 3.9	650	.11	1.6 ± 3.6	575	1.8 ± 4.1	1.4 ± 3.0	.54
Death at Day 90, n (%)	102 (17)	600	113 (17)	659	.94	88 (15)	575	48 (16)	40 (14)	.46

Abbreviations: ICU, intensive care unit; SD, standard deviation.

[a]*P* values for comparison between baseline versus audit periods.

[b]*P* values for comparison between intervention versus control group.

[c]Wilcoxon test.

[d]Defined as 1 or more bacteria not susceptible to empirical antibiotherapy.

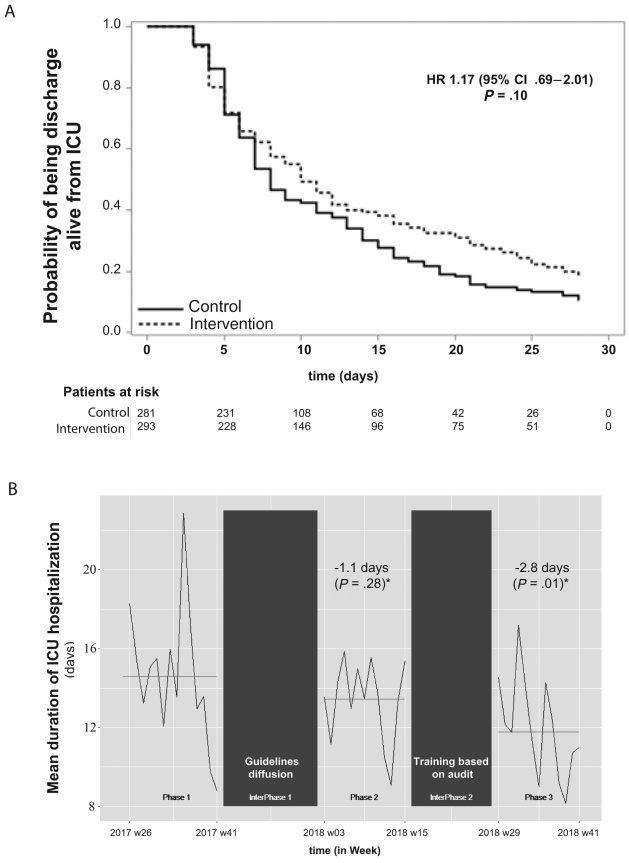

Figure 1. Duration of ICU hospitalizations. *A*, Cumulative incidence curves for the probability of being discharged alive from ICU during Period 3 of the intervention and the control groups. *B*, Time series analysis of the duration of ICU hospitalization (y-axis) by weeks (x-axis) during the baseline, audit, and intervention periods. **P* values for the comparison with the mean duration of ICU hospitalization observed during Phase 1 (baseline). Abbreviations: CI, confidence interval; HR, hazard ratio; ICU, intensive care unit.

report; or in the decision to submit the paper for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

Population

We included a total of 1856 patients (602 in the baseline period, 669 in the audit period, and 585 in the intervention period; see Supplementary Figure E2). The randomization process allocated 18 ICUs to the intervention group (representing 301 patients) and 17 ICUs to the control group (representing 284 patients). The demographic features at ICU admission are listed in Table 1.

Compliance With French Guidelines

Table 2 shows the rates of compliance with guidelines. The composite measures of compliance were 47% (IQR, 38–56%) in the intervention group and 42% (IQR, 25–53%) in the control group ($P = .001$). The rates of compliance were not associated with the level of evidence of recommendations (Supplementary Figure E3), and varied among centers (Supplementary Figure E4).

Primary Outcome

The durations of ICU stay were 7 days (IQR, 5–14 days) in the control group and 9 days (IQR, 5–20 days) in the intervention group ($P = .10$; Table 3). When we considered death at Day 28 as a competing risk, and after adjustment for characteristics at baseline (age, cause of hospitalization, immunosuppression, and chronic obstructive pulmonary disease), the hazard ratio in the control group for being discharged alive from ICU was 1.17 (95% confidence interval [CI], .69–2.01; $P = .10$; Figure 1A). The numbers of ICU-free days at Day 28 were 17 (IQR, 0–23 days) in the intervention group and 20 (IQR, 7–23 days) in the control group ($P = .21$).

Evolution of the Median ICU Length of Stay

Given the hierarchical procedure planned *a priori*, the comparison of the ICU lengths of stay between the baseline and other periods should be considered exploratory. As compared to baseline, the ICU lengths of stay were reduced by 1.1 days ($P = .28$) during the audit period and by 2.8 days ($P = .01$) during the intervention period (Figure 1B). However, as compared to baseline, we observed a nonsignificant reduction in the intervention group (−3.2 days; $P = .07$), and a significant decrease in the control group (−2.8 days; $P = .02$; Supplementary Figure E5).

Subgroup Analyses

The intervention did not alter the risk of the primary outcome in the exploratory subgroups: optimal versus nonoptimal compliance, medical versus surgical patients, admission severity (SAPS II < 28 versus > 28), early versus late-onset, presence versus absence of severe hypoxemia ([partial pressure of arterial oxygen] PaO_2: [fraction of inspired oxygen] FiO_2 < 200 mmHg), presence versus absence of multidrug-resistant bacteria, bronchoalveolar lavage versus tracheal sputum sampling, and VAP versus non–ventilator associated HAP (Figure 2).

Secondary Outcomes

Survival at Day 90

During the baseline period, 102 (17.0%) patients were nonsurvivors, as compared to 113 (17.2%) during the audit period ($P = .94$; Supplementary Figure E6*A*; Table 3). After adjustments for age and cause of hospitalization, the hazard ratio for death at Day 90 was 0.79 (95% CI, .47–1.32; $P = .25$) in the control group as compared to the intervention group (Figure 3A).

HAP at Day 28

The diagnosis criteria and the pathogens responsible for HAP are shown in Supplementary Tables E2 and E3. The rates of HAP were similar between the baseline and the audit period (28% vs 28%, respectively; $P = .96$; Supplementary Figure E6*B*). Out of the 146 episodes of HAP recorded in Phase 3, 46 (32%) were non–ventilator

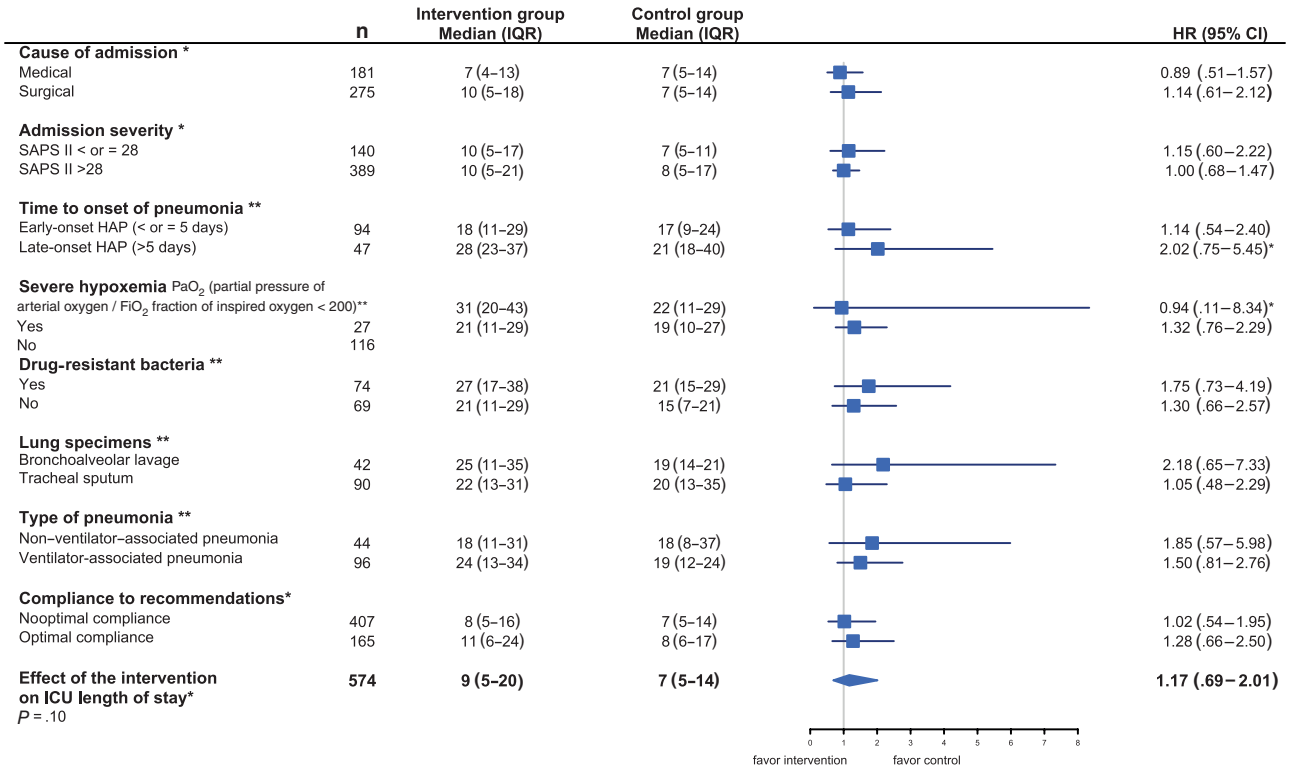

Figure 2. Subgroup analyses. HR of the primary outcome in a posteriori–defined subgroups. The square represents the HR and the horizontal bars represent 95% CIs. *Calculated in the full population. **Calculated only in patients with hospital-acquired pneumonia. Abbreviations: CI, confidence interval; FiO_2, fraction of inspired oxygen; HAP, hospital-acquired pneumonia; HR, hazard ratio; ICU, intensive care unit; IQR, interquartile range; PaO_2, partial pressure of arterial oxygen; SAPS, Simplified Acute Physiology Score.

associated pneumonia and 99 (68%) were VAP (Table 3). HAP was diagnosed in 89 (30%) patients in the intervention group versus 57 (20%) patients in the control group ($P = .01$; Figure 3B).

Adequate Antibiotic Prescription

The rate of empirical treatment failure was 17% at baseline and decreased to 11% and 8% during Phase 3 in the intervention group and the control group, respectively (Table 3). The ICU lengths of stay were 20 days (IQR, 11–29 days) in the 120 patients with an adequate antibiotic prescription and 31 days (IQR, 17–36 days) in the 13 patients with inadequate treatment ($P = .07$). Supplementary Table E4 describes the outcomes of patients receiving adequate versus inadequate treatment.

DISCUSSION

An audit aimed at locally adapting the training of caregivers to national guidelines for the prevention, diagnosis, and treatment of HAP did not significantly enhance the outcomes of ICU patients, most notably the durations of ICU stays, when compared to participation in a national registry. However, the rates of compliance to recommendations increased after the training of caregivers was adapted to the results of the audit, when the duration of ICU stay decreased with the dissemination of the recommendations.

The successful implementation of guidelines is a slow process that depends on several factors, including the methods of developing, disseminating, and implementing those recommendations. We did not observe an association between the rates of application and the degree of evidence of guidelines, which suggests that the grading of recommendations is not used by clinicians to prioritize their interventions. The observation that clinicians can rapidly implement recommendations with a low level of evidence is meaningful when the world is facing a pandemic for which the efficiency of no intervention is well demonstrated.

Several monocenter studies have demonstrated a positive role for local champions in the prevention of HAP [20, 21]. In a multicenter before-and-after study, the implementation of recommendations by local ICU improvement teams composed of medical leaders and nurse managers was associated with low compliance to guidelines. Yet, a reduction in the duration of ICU lengths of stay was observed [22]. Our study completed these results by showing that a nationwide audit with feedback to local champions increased compliance with guidelines. We thus proposed that the combination of training by local champions with the performance of an audit to prioritize interventions has the potential to accelerate the implementation of guidelines into daily practice.

The rate of ICU patients developing HAP remained close to 20%, which is similar to that reported in the EU-VAP survey

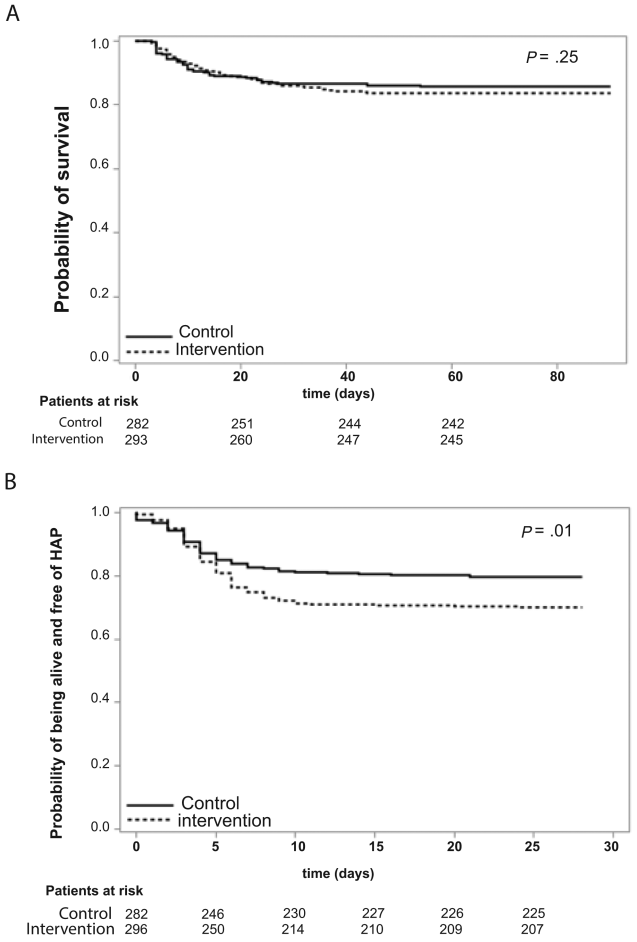

Figure 3. Probability of survival and HAP. *A*, Probability of survival during Period 3 in the control and intervention groups. *B*, Cumulative incidence curves for the probability of HAP during Period 3 in the intervention and the control groups. Abbreviation: HAP, hospital-acquired pneumonia.

performed 10 years ago [17]. The probability of treatment failure still exceeded 25%. This absence of improvement in HAP outcomes may indicate that the current strategies used for the diagnosis and treatment of HAP have reached their limits. Because no adjunctive therapies to antibiotics are currently recommended, new, ground-breaking approaches must be explored. New methods based on the modulation of the microbiome and immunotherapies have recently been proposed, but their efficacy still needs to be clinically demonstrated [23–25].

The rate of HAP diagnosis was even higher in the intervention group than in the control group. However, the nationwide implementation of a comprehensive, evidence-based bundle of measures for prevention without changes to the criteria for diagnosis reduced the risk of VAP in Spain [26]. This discrepancy further underlines the question of the accuracy of the diagnosis of HAP in the ICU. One can suggest that the local coordinator invited the team to pay more attention to the diagnosis of HAP. Indeed, the interobserver variability for the diagnosis of HAP in the ICU is high [27], and the clinical suspicions of VAP are frequently inaccurate when compared to autopsy findings [28]. Thus, the intervention could have increased the ability of clinicians to diagnose HAP, which would be beneficial by reducing the risk of delayed treatment. However, the absence of improvement in patient outcomes suggests, instead, that compliance with the recommended strategy has increased the number of false-positive diagnoses of HAP, potentially prompting the unnecessary prescription of antibiotics.

Our study has several limitations. First, an imbalance between the ICU groups remains possible in a cluster-randomized trial. However, the results remained unchanged after adjustment for the baseline differences. Second, no recommendation was made by the French experts to measure biomarkers, such as procalcitonin, to guide the treatment of HAP, which possibly limited the effects of the intervention on the de-escalation of empirical antimicrobial treatment. Third, the use of the duration of ICU stay as a primary outcome may have hidden other effects on patient outcomes. The delays to improvement of oxygenation and recovery of organ failure are associated with mortality and ICU length of stay, and could thus have been interesting alternative criteria [29]. Still, there is no international consensus for the use of these criteria in trials evaluating the treatment of HAP [15].

In conclusion, a center-scaled audit after the dissemination of national guidelines increased compliance with recommendations in daily practice, but effects on patient outcomes remained to be demonstrated.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. A. Roquilly was the principal investigator who oversaw the study conduct; helped develop all study materials, including the trial protocol; assisted with participant recruitment and data collection at the Nantes site; participated in data analysis and interpretation of the results; and drafted and revised the manuscript. M. L. provided oversight on the trial design; helped develop study materials, including the trial protocol; provided oversight on trial conduct; participated in data analysis and the interpretation of the results; and revised the manuscript. F. F. and V. S. were the trial statisticians and provided advice and input related to all statistical issues; completed the final data analysis and interpretation of results; and revised the manuscript. G. C., S. L., A. F., B. F., H. D. C., M. D. d.D., C. G., J.-M. C., K. Lagarde, M. H., A. S., C. M., A. O., J. B., C. I., P.-F. P., K. Lakhal, A. R., K. A., P. G., A. T. D., B. C., A. C., C. D.-F., R. B., J. A. D., A. M., J. M., and G. B. were the principal investigators at research sites and assisted with the development of the protocol and other study materials; referred or actively recruited participants at sites; assessed participant eligibility; and delivered formal training. Study collaborators were Alban Jaouen (MD, Angers Hospital), Pr Marc Gainnier (MD, PhD, La Timone Hospital, Marseille), and Stéphanie Ruiz (MD, PhD, Rangueil Hospital, Toulouse).

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Potential conflicts of interest. A. R. has served as a consultant for BioMérieux and Merck Sharp and Dohme (MSD) and has received grants from BioMérieux. C. M. received speaker honoraria from BioMérieux. S. L. received speaking fees from MASIMO, Vifor Pharma, and Pfizer. M. L. received fees as a lecturer for MSD, Pfizer, Octapharma, Aspen, 3M, and Orion; received fees as a consultant for Amomed and Aguettant; and received grants from Amomed. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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