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Infectious Disease Practice

Empirical antibiotic therapy improves outcomes in mechanically ventilated patients with COVID-19: An emulated targeted trial within a prospective, multicentre cohort study

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SUMMARY

Background: Bacterial pulmonary superinfections develop in a substantial proportion of mechanically ventilated COVID-19 patients and are associated with prolonged mechanical ventilation requirements and increased mortality. Albeit recommended, evidence supporting the use of empirical antibiotics at intubation is weak and of low quality. The aim of this study was to elucidate the effect of empirical antibiotics, administered within 24 h of endotracheal intubation, on superinfections, duration of mechanical ventilation, and mortality in mechanically ventilated patients with COVID-19.

Methods: Emulated targeted trial by means of a propensity score-matched analysis of a prospective multicentre cohort study of consecutive mechanically ventilated patients admitted to 62 Spanish intensive care units suffering from COVID-19 between March 2020 and February 2021.

Results: Overall, 8532 critically ill COVID-19 patients were included, of which 2580 mechanically ventilated patients remained after matching. Empirical antibiotics were prescribed to 1665 (64%) at intubation. Pulmonary superinfections developed in 39% and 47% of patients treated with and without empirical antibiotics, respectively ($p < 0.01$). Patients treated with empirical antibiotics had a shorter duration of mechanical ventilation (incidence risk ratio: 0.85 [95% confidence interval (CI), 0.78 – 0.94], $p < 0.01$) and a reduced stay in the intensive care unit (incidence risk ratio: 0.89 [95% CI, 0.82 – 0.97] days, $p < 0.01$). Mortality 28 days after endotracheal intubation was 28% in patients treated with empirical antibiotics as opposed to 32% in patients treated without (odds ratio: 0.76 [95% CI, 0.61 – 0.94], $p < 0.01$).

Conclusion: The administration of empirical antibiotics at intubation in mechanically ventilated COVID-19 patients was associated with a reduced incidence of pulmonary superinfections, a shorter duration of mechanical ventilation and intensive care unit stay, and a lower mortality rate. Notwithstanding these benefits, the applicability of these findings to other viral pneumonias and beyond the pandemic context remains uncertain.

Registration: www.clinicaltrials.gov (NCT04457505).

Introduction

Antibiotics are an ineffective treatment for viral syndromes. Nevertheless, during the pandemic, secondary bacterial pulmonary infections (superinfections) developed in approximately 50% of all mechanically ventilated patients suffering from COVID-19 and were associated with prolonged mechanical ventilation requirements and increased mortality.[1–5] Extrapolating from the similar occurrence of

coinfections in Influenza A pneumonia,[6–8] the administration of empirical antibiotics at intubation was recommended for mechanically ventilated COVID-19 patients in most clinical guidelines.[9–11] However, this recommendation was not supported by robust, high-quality evidence.

In accordance with the aforementioned guidelines, during the pandemic, most mechanically ventilated COVID-19 patients were treated with empirical antibiotics in clinical practice.[4] Yet, the indiscriminate use of empirical antibiotics has recently been criticised, arguing that empirical therapy is only warranted in case of suspected or proven bacterial superinfection.[12–16] Moreover, the early and inappropriate use of broad-spectrum antibiotics has been associated with increased mortality in patients with pneumonia,[17] a finding that is especially relevant given that antimicrobial-resistant pathogens are emerging as one of the leading health threats of the 21st century.[18]

Given the ubiquitous uncertainty surrounding the role of empirical antibiotic therapy at endotracheal intubation for mechanically ventilated patients with COVID-19, the purpose of the present analysis was to determine whether administration of empirical antibiotics at intubation could reduce pulmonary superinfections, shorten the duration of mechanical ventilation, and reduce mortality.

Methods

Study design

The CIBERESUCICOVID study was a prospective, observational, multicentre cohort study comprised of all consecutive patients admitted to 62 Spanish intensive care units (ICU) for COVID-19 between March 2020 and February 2021[19] (e-Appendix 1). The study (ClinicalTrials.gov Identifier: NCT04457505) was approved by the ethics committee of the Hospital Clinic of Barcelona (HCB/2020/0370) and the local ethics committees at each participating centre. The study complies with the tenets of the Declaration of Helsinki, the Guidelines on Good Clinical Practice issued by the European Medicines Agency, and all applicable Spanish laws and regulatory requirements. This manuscript was prepared in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines for observational studies.

Inclusion and exclusion criteria

Inclusion criteria for the CIBERESUCICOVID study were (I) a laboratory-confirmed SARS-CoV-2 infection, (II) at least 18 years of age, and (III) a critical manifestation of COVID-19 requiring treatment in an ICU.

Additional inclusion criteria for this ancillary analysis were (i) a requirement for invasive mechanical ventilation during the ICU stay, (ii) endotracheal intubation performed after ICU admission and (iii) a survival of at least 48 h after intubation. Exclusion criteria were (i) a requirement for extracorporeal membrane-oxygenation (ECMO) support, (ii) a proven infection or administration of antibiotics before endotracheal intubation, and (iii) missing antibiotic or microbiological data.

Data collection

A standardised dataset was prospectively collected during the ongoing COVID-19 pandemic for all critically ill COVID-19 patients admitted to the participating centres. Data collection was performed through an anonymized electronic case report form managed by the Research Electronic Data Capture (REDCap) tool hosted on a secure server by trained local researchers. Data were collected daily and included patient sociodemographic characteristics, vital parameters, arterial blood gas analyses, laboratory values, treatment modalities, and organ support therapies. Comprehensive data on microbiological sampling and the administered antibiotic therapies were also collected. Three independent, experienced data collectors trained in critical care reviewed the data before the statistical analyses were performed. If the data collectors detected any anomalies or had any questions, site investigators were contacted for resolution. Missing analyses were performed and site investigators were approached to obtain missing data whenever possible. Patients with a percentage of missing data > 20% on relevant data, including important baseline and outcome variables, were not cleared for analysis by the data quality team.

Intervention and clinical definitions

Patients who received antibiotics within 24 h of endotracheal intubation were classified as having received empirical antibiotic therapy. If antibiotic therapy was initiated more than 24 h after intubation, the patients were classified as not having received empirical antibiotic therapy.

Clinically relevant pulmonary superinfection was defined as the presence of microorganisms with known pulmonary pathogenicity detected by quantitative culture in either tracheobronchial aspirates or bronchoalveolar lavage specimens, or as the presence of *Streptococcus pneumoniae* or *Legionella pneumophila* antigens in a urine specimen, in accordance with the literature.[20] No distinction was made between ventilator-associated pneumonia and ventilator associated tracheobronchitis, as traditional diagnostic criteria overlap with the presentation of COVID-19 pneumonia in critically ill patients.[21] Bacterial coinfections were defined as clinically-relevant pulmonary superinfections arising within 48 h of endotracheal intubation.[12] Microorganisms were considered antimicrobial-resistant if they were “difficult-to-treat” by susceptibility testing or were “potentially drug-resistant” bacteria (e-Appendix 2).[22,23] Broad-spectrum antibiotics were defined as antibacterial agents with activity against methicillin-resistant *Staphylococcus aureus* or *Pseudomonas aeruginosa*, such as glycopeptides, amingoglycosides or antipneumococcal, antipseudomonal β-lactams.[24] Septic shock was defined according to the Sepsis-3 definition.[25]

Primary, secondary and infection-related outcomes

The primary outcome measure was the absolute 28-day mortality after endotracheal intubation. Secondary outcome measures included ICU and hospital mortality, duration of mechanical ventilation including the cumulative number of ventilator-free days in the 28 days following intubation (the ventilator-free count in patients who died before day 28 was set at 0), as well as length of ICU and hospital stay in surviving patients. Infection related secondary outcome measures included the incidence of clinically-relevant pulmonary or blood stream infections, causative antimicrobial-resistant microorganisms and septic shock.

Missing data and multiple imputation

The median fraction of missing information of variables with missing data was 26 [17–29] %. To account for missing data (e-Table 1) multivariate imputation by chained equations under fully conditional specification with predictive mean matching, considering five candidate donors, under the missing at random assumption and a hierarchical structure considering a random centre clustering effect was performed.[26] A total of 105 parallel imputation models with 1000 iterations each were run. Further details regarding the imputation methodology are provided in e-Appendix 3.

Statistical analysis

This study was designed to emulate a pragmatic, per-protocol, randomised controlled trial, in order to enable causal inference of the

average treatment effect associated with empirical antibiotic treatment (e-Appendix 4).[27] Propensity score matching on a large set of 50 relevant confounders at ICU admission and at endotracheal intubation was performed to ensure identical baseline conditions at the start of the emulated intervention (e-Table 2).[28] A causal diagram was proposed before any formal analysis was undertaken (e-Figure 1).[29] Matching was performed with a treatment-to-control ratio of 2 to 1–without replacement–employing a calliper of 0.1 standard deviations of the logit propensity score. Matching was performed independently on all 105 previously imputed data sets and the results for all analyses were pooled together in order to obtain the final reported estimates by means of Rubin's rules.[30] To ensure ideal matching of treatment and control, six distinct matching algorithms were compared to each other and assessed based on a standardised mean deviation < 0.1, a variance ratio < 2 and a Kolmogorov-Smirnov statistic < 0.5, as described elsewhere.[31–33] The sensitivity analyses involved inversed probability of treatment weighting and full case analyses (including only variables with a missing rate < 20% and the SOFA score at intubation). The matching methodology used in this study is described in detail in e-Appendix 5.

Population characteristics were compared with the Mann-Whitney-U test for continuous variables and the chi-squared test for categorical variables. Univariable and multivariable (double-adjusted [34]) binomial logistic regressions, adjusting for the full set of matching variables, were used to analyse all binary outcome effects, which are reported as odds ratios (OR) with their 95% confidence intervals (CI). Analogously, continuous effects were analysed by univariable and multivariable negative binomial regression, employing a zero-inflated term in the analysis of ventilator free days to account for binomial overdispersion. All analyses accounted for centre clustering through random effects terms.

Statistical analysis was performed through a fully scripted data management pathway using the R environment for statistical computing version 4.4.1. The employed packages are listed in e-Appendix 6. A two-sided $p < 0.05$ was considered statistically significant. Values are given as medians [interquartile ranges] or counts (percentages) as appropriate.

Results

Population and matching

A total of 8532 patients with a critical manifestation of COVID-19 were admitted to 62 participating Spanish ICUs between March 2020 and February 2021 (Fig. 1). Complete datasets were available for 4098 patients intubated in the ICU. After excluding patients who met the exclusion criteria, a total of 3712 mechanically ventilated patients were included into the final analysis.

Empirical antibiotic therapy within 24 h of endotracheal intubation was prescribed to 2773 (75%) patients, whereas 939 (25%) did not receive empirical antibiotic therapy. Overall, patients who received empirical antibiotics were more severely ill than patients who did not receive empirical antibiotics (Table 1).

In light of this disbalance between groups, patients were matched by means of the *nearest neighbour propensity matching with*

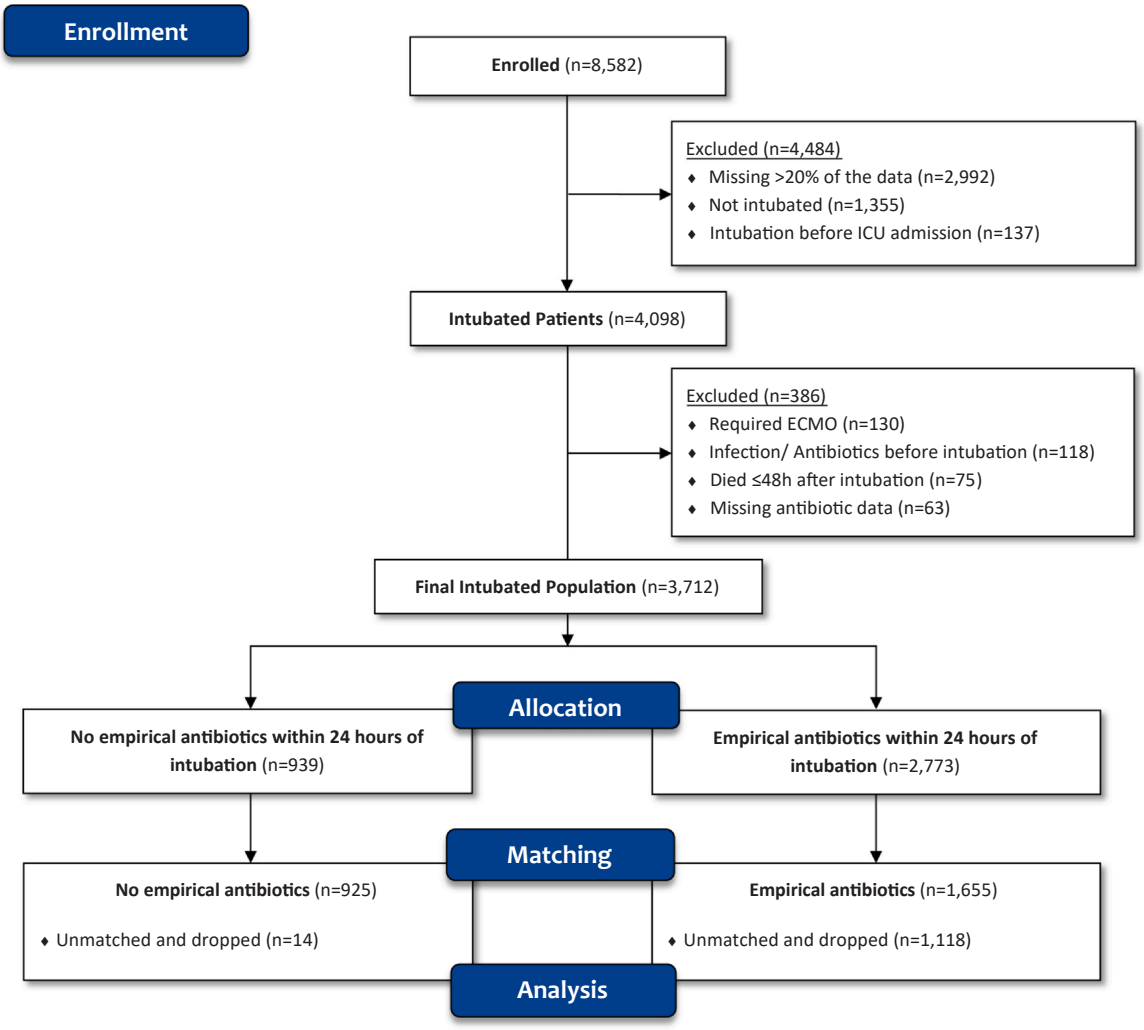


Fig. 1. Study flow chart.

calliper algorithm, which offered the best covariate balancing characteristics among the tested matching algorithms while matching the highest number of patients (Table 1, e-Figure 2).

Characteristics of the matched population

A total of 2580 patients remained after applying the matching algorithm. Of these 1655 (64%) had received empirical antibiotics within 24 h of endotracheal intubation and 925 (36%) had not. All baseline characteristics were balanced between the groups, suggesting excellent matching robustness (Table 1, Fig. 2, e-Figure 2).

Antibiotic therapy

In the empirical antibiotic group, the median duration of antibiotic therapy was 6 [4–8] days, with a minimum duration of two days (Fig. 2). Empirical antibiotic therapy was prescribed as monotherapy in 41%, dual-therapy in 50% and triple-therapy in 9% of the patients. The most commonly employed antibiotics were third-

Table 1
Baseline characteristics at admission to the intensive care unit and at intubation.

	Unmatched				Matched			
	No Empirical Antibiotics	Empirical Antibiotics	*p*	SMD[a]	No Empirical Antibiotics	Empirical Antibiotics	*p*	SMD[a]
n	939	2773			925	1655		
Characteristics at intensive care unit admission								
Age, years	65 [57–72]	65 [56–71]	0.35	0.03	65 [57–72]	65 [57–72]	0.85	< 0.01
Sex, male	654 (70)	1962 (71)	0.58	0.02	281 (30)	485 (29)	0.62	< 0.01
Body mass index, kg/m^2	29 [26–32]	29 [26–32]	0.44	0.02	29 [26–32]	29 [26–32]	0.83	< 0.01
Time from symptom onset until hospital admission, days	7 [5–9]	7 [4–9]	0.84	0.02	7 [5–9]	7 [4–9]	0.87	< 0.01
Time from hospital admission until ICU admission, days	2 [0 – 5]	1 [0 – 3]	< 0.01	0.21	2 [0 – 5]	2 [0 – 4]	0.12	< 0.01
APACHE II score at ICU admission	12 [9–17]	13 [10–17]	0.68	0.08	12 [10–17]	13 [9–17]	0.90	< 0.01
SOFA score at ICU admission	5 [4–7]	6 [4–8]	< 0.01	0.31	5 [4–7]	5 [4–7]	0.42	< 0.01
Comorbidities								
Arterial hypertension	503 (54)	1455 (52)	0.57	0.02	491 (53)	862 (52)	0.69	< 0.01
Diabetes mellitus	254 (27)	709 (26)	0.40	0.03	245 (27)	410 (25)	0.38	< 0.01
Chronic heart disease	116 (12)	354 (13)	0.78	0.01	115 (12)	211 (13)	0.85	< 0.01
Chronic pulmonary disease	86 (9)	264 (10)	0.79	0.01	84 (9)	157 (10)	0.77	< 0.01
Chronic kidney disease (moderate to severe)	53 (6)	189 (7)	0.24	0.05	50 (5)	87 (5)	0.96	< 0.01
Chronic liver disease (moderate to severe)	8 (1)	30 (1)	0.68	0.02	8 (1)	18 (1)	0.73	< 0.01
Chronic rheumatologic disease	47 (5)	121 (4)	0.47	0.03	45 (5)	79 (5)	1.0	< 0.01
Malignant neoplasm	38 (4)	87 (3)	0.22	0.05	35 (4)	65 (4)	0.93	< 0.01
Solid organ transplant	9 (1)	49 (2)	0.12	0.07	9 (1)	15 (1)	1.0	< 0.01
Bone marrow transplant	1 (0)	3 (0)	1.00	0.01	1 (0)	2 (0)	1.0	< 0.01
Acquired immune deficiency syndrome	4 (0)	14 (1)	0.98	0.01	4 (0)	8 (0)	1.0	< 0.01
Other forms of immunosuppression	17 (2)	57 (2)	0.74	0.02	17 (2)	30 (2)	1.0	< 0.01
Characteristics at intubation								
Time from ICU admission until intubation, days	0 [0 – 1]	0 [0 – 1]	< 0.01	0.23	0 [0 – 1]	0 [0 – 1]	0.09	< 0.01
Respiratory support before intubation								
Conventional oxygen therapy	340 (36)	1159 (42)	< 0.01	0.12	340 (37)	648 (39)	0.23	< 0.01
High-flow oxygen therapy	381 (41)	1071 (39)	0.33	0.04	376 (41)	656 (40)	0.68	< 0.01
Non-invasive ventilation	181 (19)	355 (13)	< 0.01	0.18	173 (19)	277 (17)	0.24	< 0.01
SOFA score at intubation	7 [4–8]	7 [4–8]	0.01	0.14	7 [4–8]	7 [4–8]	0.80	< 0.01
PaO_2/ FiO_2 Ratio, mmHg	114 [82 – 164]	118 [84 – 169]	0.32	0.08	114 [83 – 163]	119 [83 – 169]	0.22	< 0.01
Positive end-expiratory pressure, cmH_2O	12 [10–14]	12 [10–14]	< 0.01	0.17	12 [10–14]	12 [10–14]	0.92	< 0.01
Static respiratory system compliance, ml/cmH_2O	34 [27–41]	35 [28–44]	0.08	0.14	34 [27–45]	34 [27–46]	0.52	< 0.01
Ventilatory ratio	1.7 [1.4 – 2.1]	1.7 [1.3 – 2.1]	0.75	< 0.01	1.7 [1.3 – 2.2]	1.7 [1.3 – 2.1]	0.89	< 0.01
Mean arterial blood pressure, mmHg	83 [72–98]	86 [72–99]	0.32	0.05	83 [72–98]	83 [71–98]	0.77	< 0.01
Norepinephrine dose, µg/kg/min	0 [0 – 0.6]	0.2 [0 – 1.0]	< 0.01	0.17	0 [0 – 0.6]	0 [0 – 0.6]	0.22	0.02
pH	7.4 [7.3 – 7.4]	7.4 [7.3 – 7.4]	< 0.01	0.11	7.4 [7.3 – 7.4]	7.4 [7.3 – 7.4]	0.79	< 0.01
Arterial lactate, mmol/l	1.4 [1.1 – 1.9]	1.5 [1.1 – 1.9]	0.42	0.04	1.4 [1.1 – 1.9]	1.5 [1.1 – 1.9]	0.87	< 0.01
Haemoglobin, g/dl	13 [12–14]	13 [12–14]	0.95	0.01	13 [12–14]	13 [12–14]	0.85	< 0.01
Thrombocyte count, 10^9/l	239 [189 – 317]	235 [178 – 307]	0.12	0.05	238 [185 – 316]	242 [185 – 319]	0.62	< 0.01
Leukocyte count, 10^9/l	10 [7–13]	9 [7–13]	0.18	0.05	10 [7–13]	10 [7–13]	0.92	< 0.01
Neutrophil count, 10^9/l	8 [6–12]	8 [6–12]	0.42	0.02	8 [6–12]	8 [6–12]	0.61	< 0.01
Lymphocyte count, 10^9/l	0.7 [0.5 – 1.0]	0.7 [0.4 – 0.9]	0.08	0.08	0.7 [0.5 – 1]	0.7 [0.5 – 1]	0.52	0.01
C-reactive protein, mg/l	105 [36 – 193]	148 [70 – 243]	< 0.01	0.33	109 [41 – 202]	114 [50 – 212]	0.10	0.01
Procalcitonin, µg/l	0.2 [0.1 – 0.4]	0.3 [0.1 – 0.7]	< 0.01	0.32	0.2 [0.1 – 0.5]	0.2 [0.1 – 0.5]	0.14	< 0.01
Interleukin-6, ng/l	62 [27 – 143]	90 [39 – 173]	< 0.01	0.27	78 [37 – 156]	84 [38 – 168]	0.35	< 0.01
Ferritin, µg/l	1300 [699 – 2121]	1246 [677 – 2054]	0.63	0.06	1293 [699 – 2076]	1216 [681 – 2082]	0.49	< 0.01
D-dimer, mg/l	1360 [691 – 4200]	1201 [626 – 3620]	0.13	0.03	1300 [670 – 4096]	1295 [662 – 3940]	0.69	< 0.01
Lactate dehydrogenase, U/l	495 [376 – 662]	536 [408 – 724]	< 0.01	0.20	512 [388 – 687]	508 [388 – 675]	0.89	0.01
Creatinine, µmol/l	71 [53–88]	71 [62–88]	< 0.01	0.25	71 [53–88]	71 [62–88]	0.11	< 0.01
Bilirubin (total), µmol/l	10 [7–15]	10 [7–15]	0.48	0.03	10 [7–15]	10 [7–15]	0.42	< 0.01
International normalised ratio	1.1 [1.0 – 1.3]	1.2 [1.1 – 1.3]	< 0.01	0.20	1.1 [1.1 – 1.3]	1.1 [1.1 – 1.3]	0.49	< 0.01
Drug therapies received								
Corticosteroids	820 (87)	2308 (83)	< 0.01	0.12	807 (87)	1413 (86)	0.27	< 0.01
Remdesivir	188 (20)	301 (11)	< 0.01	0.26	178 (19)	281 (17)	0.05	< 0.01
Tocilizumab	401 (43)	1107 (40)	0.14	0.09	394 (42)	662 (40)	0.23	0.01

Quantitative data are expressed as medians [interquartile range] or counts (percentages), as appropriate.
Abbreviations: APACHE – Acute Physiology and Chronic Health disease Classification System; FiO_2 – Fraction of Inspired Oxygen; ICU – Intensive Care Unit; PaO_2 – Partial pressure of arterial oxygen; SMD – Standardised Mean Difference; SOFA – Sequential Organ Failure Assessment.
[a] A standardised mean difference < 0.1 indicates a negligible difference between the means of two distributions.

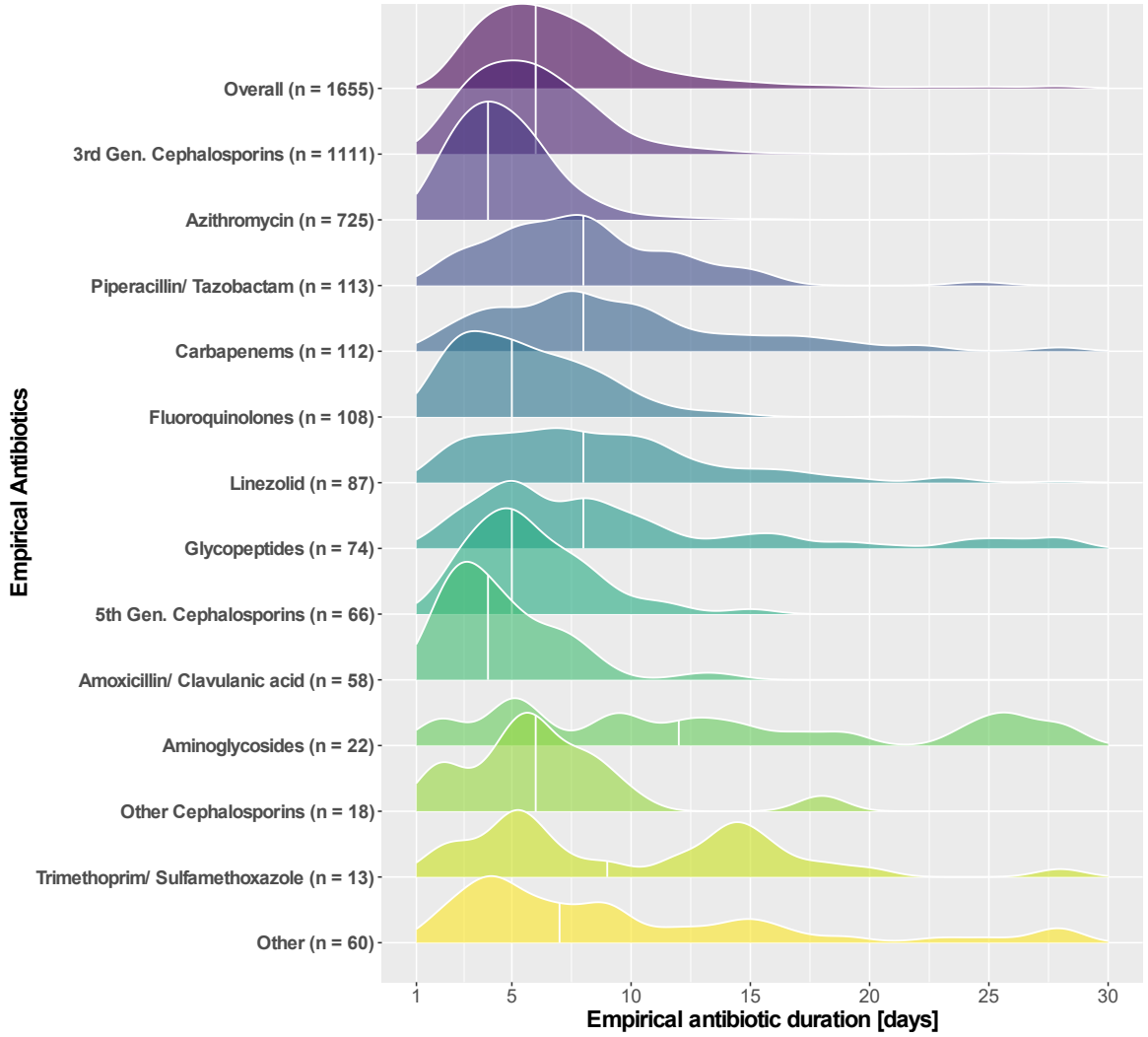


Fig. 2. Empirical antibiotics administered at intubation and duration thereof. Density plots presenting the distribution of individual antibiotic therapy durations. The white bar defines the median of the distribution.

generation cephalosporins (30%), or cephalosporins combined with azithromycin (36%), and 12% of the patients received carbapenem, glycopeptide, or aminoglycoside coverage (e-Table 3).

In the 925 patients not treated with empirical antibiotics, a total of 536 (58%) patients received antibiotics starting a median of 6 [2–6] days after intubation with a median duration of antibiotic therapy of 13 [7–25] days (Fig. 3).

Bacterial superinfections

A total of 1087 (42%) patients experienced a clinically relevant pulmonary superinfection episode during their ICU stay. The infection rate was lower in the empirical antibiotic group (39%) than in the group that did not receive empirical antibiotics (47%) (Adjusted OR: 0.72 [95% CI, 0.59 – 0.86], p < 0.01) (Table 2). Patients treated with empirical antibiotics also presented a lower incidence of septic shock (13% vs. 18%) (Adjusted OR: 0.62 [95% CI, 0.48 – 0.81], p < 0.01).

Early bacterial coinfection was detected in pulmonary microbiological samples drawn at endotracheal intubation in 40 (2%) patients and did not differ between patients that received (n=25, 2%) or did not receive (n=15, 2%) empirical antibiotics at the initiation of mechanical ventilation (Fig. 4). Within 48 h, the number of patients with bacterial coinfections increased to 105 (7%). Of these, 57 (3%) occurred in patients treated with empirical antibiotics and 48 (5%) in patients treated without empirical antibiotics. The two most common causative pathogens of pulmonary coinfection within 48 h of intubation were methicillin-susceptible *Staphylococcus aureus* (30%) and *Enterobacterales* (17%).

The median time to first pulmonary superinfection was 9 [5–15] days in patients treated with empirical antibiotics and 6 [3–11] days in those treated without (p < 0.01). Susceptible pathogens appeared a median of 8 [4–13] days, and antimicrobial-resistant pathogens a median of 13 [7–24] days, after endotracheal intubation (p < 0.01). The cumulative rate of pulmonary superinfections with susceptible pathogens was lower in patients treated with empirical antibiotics as opposed to patients treated without them (≤6 days: −17 [95% CI, −19 – −15], 6–15 days: −4 [95% CI, −5 – −3] superinfections per 1000 patients/ day) (p < 0.01) (Fig. 4**C**). After 15 days, there were no between-group differences in superinfection rates. The cumulative incidence of antimicrobial-resistant pathogens in both groups was comparable throughout the study period (p=0.87).

The causative pathogens responsible for most pulmonary superinfections were *Enterobacterales* (37%), *Pseudomonas aeruginosa* (24%), and methicillin-susceptible *Staphylococcus aureus* (20%) (e-Table 4). Overall, 11% of the antimicrobial-resistant pulmonary superinfections were caused by *Acinetobacter baumannii*, *Stenotrophomonas maltophilia*, methicillin-resistant *Staphylococcus aureus* and extended-spectrum beta-lactamase producing *Enterobacterales*.

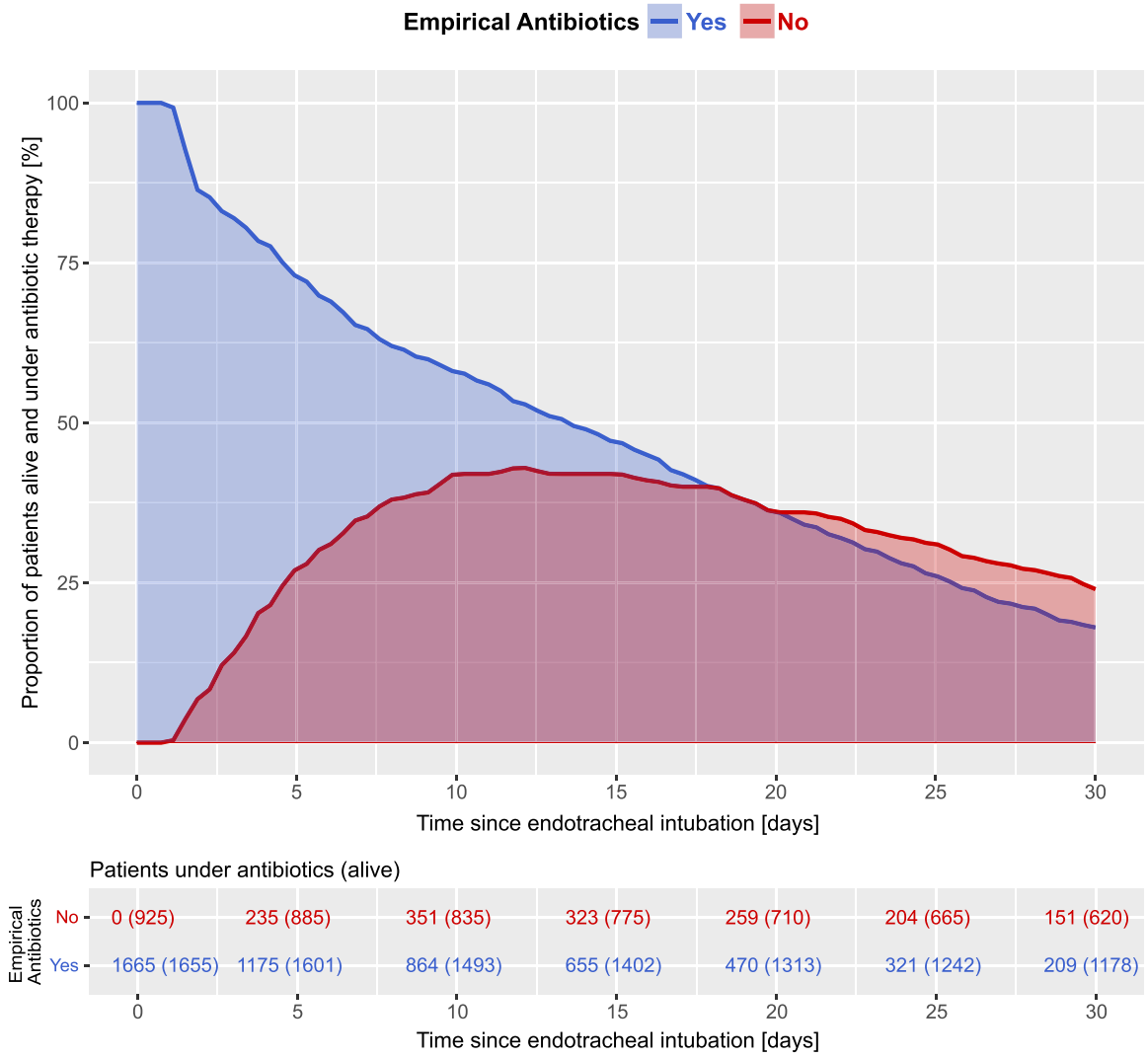


Fig. 3. Proportion of patients alive and under antibiotic therapy. Cumulative distribution plots displaying the proportion of patients alive and receiving antibiotic therapy stratified by the prescription of empirical antibiotics (blue) or the lack thereof (red) at endotracheal intubation. The underlying table presents the absolute number of patients under antibiotic therapy per time point with the number of alive patients given in parentheses.

Primary and secondary outcomes

Twenty-eight days following endotracheal intubation, 467 (28%) patients treated with empirical antibiotics, as opposed to 300 (32%) patients not treated with empirical antibiotics, had died (Adjusted OR: 0.76 [95% CI, 0.61 – 0.94], $p < 0.01$) (Table 2). These results were consistent for ICU and hospital mortality (Table 2).

At 28 days post-intubation, the median number of ventilator-free days in the empirical antibiotic group was 2 [0 – 17], whereas it was 0 [0 – 16] in the untreated group ($p < 0.01$). Overall, patients treated with empirical antibiotics presented a shorter duration of mechanical ventilation (Adjusted incidence risk ratio: 0.85 [95% CI, 0.78 – 0.94] days, $p < 0.01$), a shorter ICU length of stay (Adjusted incidence risk ratio: 0.89 [95% CI, 0.82 – 0.97] days, $p < 0.01$) and a shorter total hospital length of stay (Adjusted incidence risk ratio: 0.92 [95% CI, −0.86 – 0.98] days, $p < 0.02$).

Sensitivity analyses

To ensure the robustness of the primary and secondary analyses, multiple sensitivity analyses—including inverse probability weighting and full case analyses—were performed. Overall, the primary and secondary outcomes were consistent across all analyses, including the full case scenario (e-Appendix 7–10).

Furthermore, to reject temporality or specific centres as a cause of bias, we investigated the effect of the phases of the pandemic (e-Figure 3) and of individual centres (e-Figure 4) on the effect estimate of empirical antibiotics on 28-day mortality. The results were consistent with the main analysis.

VanderWeele's method was used to explore the robustness of the main analysis to unmeasured confounding. For the main analysis to lose significance, an unmeasured confounder associated with a 2-fold [95% CI, 1.3 – 2.7] increase in both empirical antibiotics and survival would have had to have been overlooked during the analysis. By comparison, the two strongest predictors of mortality were age (1.06 [95% CI, 1.05 – 1.07]) and corticosteroid use (0.63 [95% CI, 0.46 – 0.87]). Thus, to explain away the effect of empirical antibiotics, an unmeasured confounder akin to a 12-year decrease in age or exclusive corticosteroids use among patients treated with empirical antibiotics would be required.

Exploratory analyses

An essential consideration in prescribing empirical antibiotics is the ability to identify specific subpopulations that may benefit from

Table 2
Primary, secondary and infection-related outcomes.

	No Empirical Antibiotics	Empirical Antibiotics	Odds Ratio [95% CI]	p-value	Adjusted Odds Ratio [95% CI]	p-value
n	925	1655				
Primary outcome						
28-day mortality	300 (32)	467 (28)	0.82 [0.67 – 0.97]	0.02	0.76 [0.61 – 0.94]	< 0.01
Secondary outcomes						
ICU mortality	357 (39)	574 (35)	0.83 [0.70 – 0.97]	0.02	0.81 [0.68 – 0.97]	0.02
Hospital mortality	376 (41)	593 (36)	0.80 [0.67 – 0.97]	0.02	0.76 [0.62 – 0.95]	0.01
Ventilator free days in 28 days[a,b]	0 [0 – 16]	2 [0 – 17]	0.97 [0.91 – 1.03] 0.71 [0.6 – 0.84]	0.33 < 0.01	0.98 [0.92 – 1.04] 0.65 [0.54 – 0.79]	0.53 < 0.01
Length of mechanical ventilation in survivors, days	17 [9–34]	15 [8–29]	0.85 [0.78 – 0.94]	< 0.01	0.85 [0.78 – 0.94]	< 0.01
Length of ICU stay in survivors, days	21 [11–39]	20 [11–35]	0.88 [0.82 – 0.96]	< 0.01	0.89 [0.82 – 0.97]	< 0.01
Length of hospital stay in survivors, days	33 [20–53]	32 [21–49]	0.92 [0.86 – 0.98]	0.02	0.92 [0.86 – 0.98]	0.02
Infection-related outcomes						
Relevant pulmonary superinfection[c]	435 (47)	652 (39)	0.73 [0.62 – 0.87]	< 0.01	0.72 [0.59 – 0.86]	< 0.01
Antimicrobial-resistant	145 (16)	256 (15)	0.98 [0.77 – 1.25]	0.89	0.98 [0.76 – 1.25]	0.85
Positive blood cultures	326 (35)	545 (33)	0.89 [0.75 – 1.08]	0.26	0.89 [0.74 – 1.08]	0.23
Antimicrobial-resistant	42 (5)	58 (4)	0.77 [0.49 – 1.22]	0.27	0.74 [0.46 – 1.19]	0.22
Septic shock	162 (18)	207 (13)	0.67 [0.53 – 0.86]	< 0.01	0.62 [0.48 – 0.81]	< 0.01

Quantitative data are expressed as median [interquartile range] or counts (percentages) as appropriate.
Binary outcomes are modelled by means of logistic (Odds Ratios) and continuous outcomes by means of negative binomial regressions (Incidence Risk Ratios).
Adjusted models account for the full set of matching variables.
Abbreviations: CI – Confidence Interval; ICU – Intensive Care Unit.
[a] Ventilator free days were calculated at day 28 after endotracheal intubation, patients who died before day 28 were assigned a value of 0.
[b] Ventilator free days were modelled by means of a zero-inflated negative binomial model. (Left) Incidence Risk Ratios for negative binomial component and (right) Odds Ratio for logistic component.
[c] Defined as superinfections caused by microorganisms with relevant lower-respiratory tract pathogenicity in accordance with the criteria defined by Chastre et. al.[20]

this treatment. For this reason, we investigated the predictive capacity of a range of variables (age, paO2/FiO2 ratio, C-reactive protein, procalcitonin, and the presence of multi-organ dysfunction or septic shock) on the association between empirical antibiotics and mortality (e-Figure 5). The interaction analysis unveiled that lower levels of C-reactive protein (< 100 mg/l) and procalcitonin (0.25 μg/l), along with the absence of multi-organ dysfunction and septic shock, were independent predictors of improved survival with empirical antibiotic use ($p < 0.01$).

To evaluate the separation between groups, we analysed the effect of receiving antibiotics at a later stage and never receiving antibiotics (e-Figure 6). Our analysis indicated an increased incidence of pulmonary superinfections with a later initiation of antibiotics. Additionally, there was an observed increase in mortality depending on the chosen antibiotic strategy, with mortality rates rising from early antibiotic administration at intubation to delayed initiation, and peaking among those patients who never received antibiotics.

Finally, we conducted a subgroup analysis to determine the risk-benefit profile of empirical broad-spectrum antibiotics versus narrow-spectrum antibiotics. Overall, empirical treatment with broad-spectrum antibiotics did neither reduce 28-day mortality (OR: 1.1 [95% CI, 0.84 – 1.47], p=0.450), nor did it decrease the number of ventilator-free days at day 28 when compared to empirical treatment with narrow-spectrum antibiotics (Incidence risk ratio: 0.99 [95% CI, 0.93 – 1.04] days, p=0.728). Similarly, empirical treatment with broad-spectrum antibiotics did not alter the incidence of superinfections with antimicrobial-resistant pathogens when compared to empirical treatment with narrow-spectrum antibiotics (OR: 1.02 [95% CI, 0.70 – 1.49], p=0.910).

Discussion

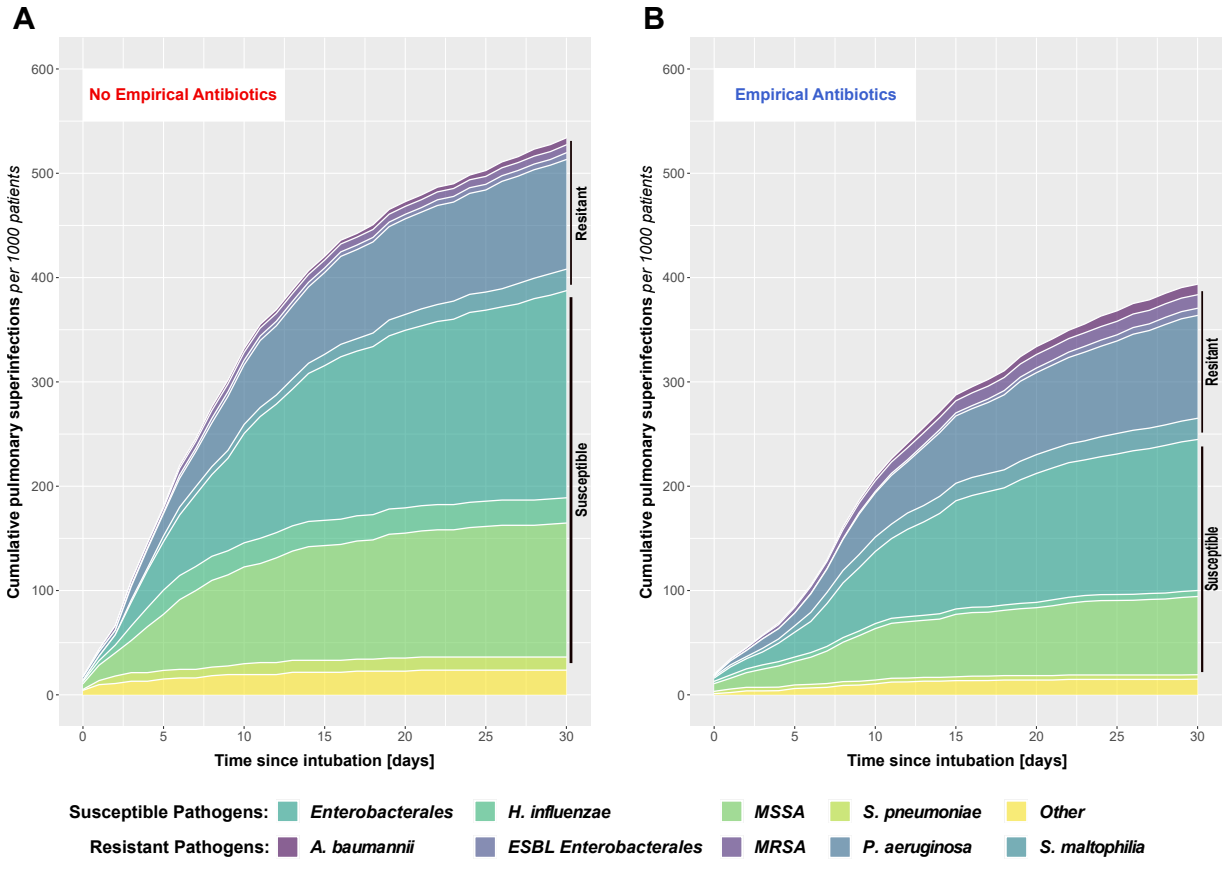
In the present matched analysis of patients from a multicentre cohort study, administration of empirical antibiotics within 24 h of endotracheal intubation was associated with a reduction in 28-day mortality. This effect was accompanied by a lower rate of clinically-relevant pulmonary superinfections and septic shock, fewer days on mechanical ventilation and a shorter ICU and hospital stay. No increased incidence in antimicrobial-resistant pathogens was observed in patients treated with empirical antibiotics.

The decision of whether to administer empirical antibiotics after endotracheal intubation in critically ill COVID-19 patients remains a daily and critical question for practicing clinicians. Viral pneumonias are associated with an elevated risk of complicating bacterial pulmonary superinfections,[35] which are one of the main independent causes of mortality in these patients.[1,6,7,12] The aetiology of these pulmonary superinfections can be traced back to community-acquired coinfections, already present at intubation, which are then followed by nosocomial superinfections that develop during mechanical ventilation.

During the 2009 Influenza A pandemic, the incidence of pulmonary coinfections in critically ill patients oscillated between 15% and 30%.[6,7] Similar rates have been reported in COVID-19 patients, ranging from 10% to 20%.[2,12] The clinical signs and symptoms of these early bacterial coinfections largely overlap with the presentation of COVID-19 pneumonia in mechanically ventilated COVID-19 patients, which can hinder accurate clinical diagnosis.[2,21] This has prompted a number of clinicians to administer empirical antibiotics for 48 to 72 h until proof of negative lower respiratory tract microbiological involvement is available.[36] However, due to the thick and difficult-to-aspirate secretions characteristic of COVID-19 patients, which may lead to an initial underreporting of early bacterial coinfections as probably occurred in our study (5%), this practice might sometimes be inadequate.[37] Hence, some specialised centres have chosen to withhold empirical antibiotic therapy altogether, advocating for a watchful approach based on early sampling of patients by bronchoscopy combined with fast eubacterial polymerase-chain reaction techniques.[2]

Following coinfection, the cumulative incidence of bacterial superinfections in mechanically ventilated COVID-19 patients is generally reported to be 50%,[1,2,12] a finding that is consistent with our data (42%). These nosocomial superinfections stem from pathogens that have colonised the oropharynx and translocate to the lung either during endotracheal intubation, or subsequently by continuous pooling and leaking of secretions around the endotracheal tube.[20]

Thus, effectively, clinicians are not only faced with the decision to administer empirical antibiotics in order to treat suspected coinfections



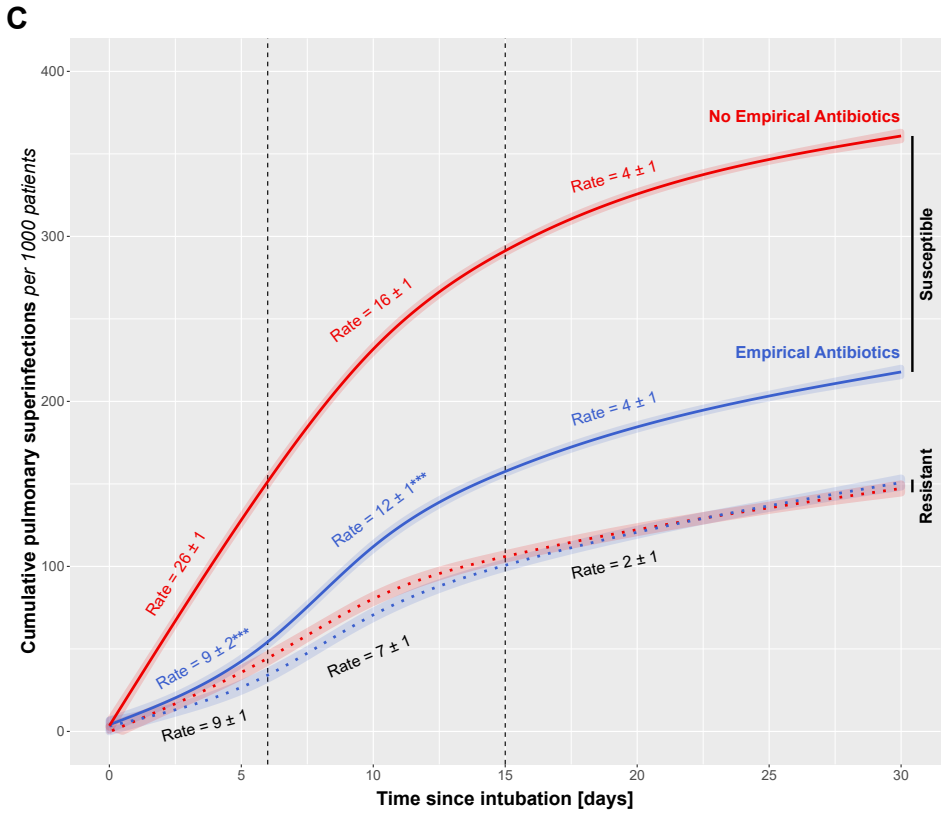


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Fig. 4. Cumulative pulmonary superinfections and causative microorganisms in patients having received (A) no empirical antibiotic therapy and (B) empirical antibiotic therapy at intubation. (C) Rate of pulmonary superinfections. (A, B) Individual patients could account for more than one pulmonary superinfection, however persistance of the same pathogen in consecutive samples could not. Pathogens were defined as resistant if they were multi-drug resistant by susceptibility testing or belonged to the category of "potentially drug-resistant" bacteria. *A. baumannii* – *Acinetobacter baumannii*; ESBL – Extended-spectrum beta-lactamase; *H. influenzae* – *Haemophilus influenzae*; MRSA – Methicillin-resistant *Staphylococcus aureus;* MSSA – Methicillin-susceptible *Staphylococcus aureus; P. aeruginosa* – *Pseudomonas aeruginosa; S. maltophilia* – *Stenotrophomonas maltophilia*; *S. pneumoniae* – *Streptococcus pneumoniae.* (C) Cubic spline regression model estimating the incidence rate of pulmonary superinfections (stratified by susceptibility of the causative pathogen) in patients treated with and without empirical antibiotics. Vertical dotted lines represent spline knots, p-values assess differences in piecewise slopes between patients treated with and without empirical antibiotics, ***$p < 0.001$.

present at the moment of intubation, but also have to consider possibly arising superinfections shortly thereafter. This is especially relevant given that patients with COVID-19 have an increased predisposition towards developing superinfections due to the treatments used (e.g., deep sedation, corticosteroids, and other immunomodulators), together with pandemic-related factors such as lower nurse-to-patient ratios and less compliance with preventive measures.[38,39]

Within this context, our data robustly supports the efficacy of initiating empirical antibiotic therapy upon intubation suggesting a 4% decrease in 28-day mortality rates. Notably, this protective effect coincided with a tangible reduction in both the duration of mechanical ventilation and length of ICU stay, which were reduced by three and two days, respectively, in our patient cohort. Although the explicit mechanism underpinning the protective effect of empirical antibiotics remains subject to debate, emerging evidence—including data from our study as well as other recent studies—seems to indicate a twofold effect. First, empirical antibiotics may resolve any undiagnosed bacterial coinfections that are already present at intubation, which is crucial given the propensity for bacterial co-infections to develop in viral pneumonias. Second, early antibiotic administration could serve prophylactically, potentially averting early-onset VAPs. Concretely, our findings suggest that empirical antibiotics lead to a three-fold reduction in the incidence of superinfections within the initial 6 days post-intubation, with a sustained reduction in superinfection rates for up to 15 days thereafter. Empirical antibiotic coverage exerted its most significant impact on mitigating the occurrence of methicillin-susceptible *Staphyloccocus aureus*, *Streptococcus pneumonia* and *Haemophilus influenza.* These pathogens, predominantly sourced from the oral and upper respiratory flora, are commonly held responsible for coinfections and superinfections arising within the first days of intubation in mechanically ventilated patients.[20]

Despite lingering skepticism, the hypothesis that empirical antibiotics can act prophylactically garners increasing support from trials spanning diverse patient cohorts including comatose[40,41] and cardiac arrest patients,[42] as well as in investigations exploring inhaled antibiotics in intubated general ICU populations.[43] Collectively, these trials have demonstrated a consistent decrease in the occurrence of early-onset VAPs, although not late-onset ones. Moreover, these findings resonate with the favourable outcomes associated with selective digestive decontamination, predominantly attributed to the brief course of intravenous antibiotics.[44,45] Highlighting this reduction in early-onset VAPs is crucial as it may provide insight into the mortality benefit seen with empirical antibiotics in COVID-19 patients, where increased pulmonary bacterial burden and VAPs are linked to prolonged ventilation and heightened mortality rates.[5,46] This notion is further strengthened by the explorative result that patients without signs of superinfection, such as low C-reactive protein and procalcitonin levels, responded best to empirical antibiotics.

In the present study, empirical antibiotics were not associated with a higher rate of antimicrobial-resistant pathogens, which are generally associated with an increased morbidity and mortality in mechanically ventilated patients.[47] Chronologically, antimicrobial-resistant infections emerged a median of 4 days after infections caused by antimicrobial-susceptible pathogens—7 days after empirical antibiotic coverage was ceased—and may thus have been unaffected by the choice of the empirical antibiotic.

This study has several limitations. *First,* the ideal study design to answer the investigated question in order to fully exclude residual confounding is a randomised, double-blind, placebo-controlled trial. However, given the relatively small effect size, such a study would require a major effort in time and resources. Additionally, to date, there is strong evidence supporting the validity of emulated targeted trials,[48–50] which is reflected in the robustness of the main analyses across a variety of sensitivity analyses including inversed probability weighting and full case scenarios. *Second,* in the context of the pandemic and due to the study design, a systematic longitudinal microbiological sampling of all patients at regular intervals was not performed. Consequently, the incidence of superinfections, including anti-microbial resistant pathogens such as *Clostridium difficile*, may have been underestimated in this study. *Third*, the use of selective digestive track decontamination was not explicitly investigated. *Fourth,* the underlying cohort study was performed in the setting of the COVID-19 pandemic, which may have hindered the implementation of preventive measures for bacterial superinfections during mechanical ventilation. In fact, the incidence of bacterial superinfections was decidedly higher in this population compared to other viral pneumonias requiring critical care.[3] It remains thus unclear if these results can be extrapolated to COVID-19 cases outside of pandemic settings, or even further, to other viral pneumonias requiring mechanical ventilation. *Fifth,* the long-term effect of empirical antibiotic coverage on the microbiological ecology of ICUs was not studied and remains unknown.

Despite the limitations described above, this study has several important strengths, most notably the large, multicentre patient cohort and the comprehensive data that were collected and analysed. Furthermore, the matching methodology employed was rigorously implemented, considered most observable confounders and limited the biasing effect of missing data through the use of multiple imputation with 105 independently fitted and pooled models. Additionally, all results were robust and consistent with the notion of a protective effect associated with the administration of empirical antibiotics.

Conclusion

The administration of empirical antibiotics at intubation in mechanically ventilated COVID-19 patients was associated with a reduced incidence of pulmonary superinfections, a shorter duration of mechanical ventilation and intensive care unit stay, and a lower mortality rate. Notwithstanding these benefits, the applicability of these findings to other viral pneumonias and beyond the pandemic context remains uncertain.

Ethical approval and consent to participate

The study was approved by the ethics committee of the Hospital Clinic of Barcelona (HCB/2020/0370) and the local ethics committees at each participating centre. The study complies with the tenets of the Declaration of Helsinki, the Guidelines on Good Clinical Practice issued by the European Medicines Agency, and all applicable Spanish laws and regulatory requirements. Requirement for informed consent was waived due to the observational nature of the study.

Role of the funder

None of the funding sources had a role in the design or conduct of the study; collection, management, analysis, or interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

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Author contributions

AC, AM, RF, LF, JR, RM, OP, JAL, RA, AG, DdGC, FB and AT initiated and managed the prospective cohort. PDWG and FRC conceived and designed the present study. All authors were involved in data acquisition. PDWG performed statistical analysis. PDWG and FRC analysed and interpreted the data. PDWG and FRC drafted the first version of the manuscript and subsequent revisions thereof. All authors reviewed and revised the manuscript for important intellectual content. All authors approved submission of the final manuscript. PDWG and FRC had full access to the study data and take full responsibility for the contents of the manuscript including the integrity and accuracy of the data analysis.

Data availability

The corresponding author may provide specified analyses or fully de-identified parts of the dataset upon reasonable request.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jinf.2025.106411.

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