Cohort Study

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Postoperative pneumonia after lung resection: a prospective double-blind comparative study of bronchial colonization and antibiotic prophylaxis

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Background: Postoperative pneumonia (POP) remains a major cause of morbidity after lung cancer surgery. The role of perioperative antibiotic prophylaxis (PAP), particularly the choice of antibiotics and their adjustment to bronchial colonization, is still debated.

Methods: We conducted a prospective, double-blind, comparative study including 200 patients with primary lung malignancy undergoing lung resection. Patients received either cefazolin or amoxicillin–clavulanic acid as PAP. Preoperative bronchial colonization was assessed before surgery. The primary outcomes were the incidence of POP according to the antibiotic regimen and colonization status.

Results: The cohort comprised 200 patients (median age 68 years, range 44–83; 48.5% women). POP occurred in 47 patients (23.5%). Of these, 23 (21.5%) had received cefazolin and 24 (25.8%) amoxicillin–clavulanic acid, with no significant difference between regimens. Colonization was detected in 178 patients (89.0%), including 36 (20.2%) with potentially pathogenic microorganisms (PPMs). POP incidence was similar in non-colonized (22.7%), colonized (23.6%), and PPM-colonized patients (25.0%) (all $P \geq 0.51$). Only one patient (0.5%) died within 30 days, unrelated to pneumonia.

Conclusions: In this prospective comparative study, POP after lung cancer surgery did not significantly differ according to the prophylactic antibiotic regimen or colonization status. However, given the relatively small number of patients with PPM colonization and the single-center design, these findings should be interpreted cautiously. Standard perioperative prophylaxis with cefazolin appears appropriate, while routine preoperative colonization screening may not be necessary. Further studies are needed to better define risk-adapted preventive strategies.

Keywords: airway colonization, antibiotic prophylaxis, lung resection, postoperative pneumonia

Introduction

Postoperative pneumonia (POP) represents a major infectious challenge following lung cancer surgery, typically occurring 48–72 hours after the procedure[1–6]. Its reported incidence after anatomical lung resections ranges from 1.5 to 25%[5–8]. The development of POP significantly worsens patient outcomes, being associated with increased requirements for intensive care unit admission, prolonged hospitalization, greater antibiotic use, and elevated in-hospital mortality[1–3,9].

Anatomical lung resections are classified as *clean-contaminated* surgical procedures due to the transection of the airways during surgery[5,10–12]. This interruption of airway integrity substantially increases the risk of microbial entry into the otherwise sterile thoracic cavity. Consequently, the pathogens responsible for POP are not limited to skin flora but frequently include microorganisms that typically colonize the upper respiratory tract[12–15].

HIGHLIGHTS

- Postoperative pneumonia remains common after lung cancer surgery.
- Amoxicillin–clavulanic acid and cefazolin showed similar outcomes.
- Cefazolin remains a valid choice for perioperative prophylaxis in lung cancer surgery.
- Future multicenter trials are warranted to validate risk-based prophylaxis strategies and to establish unified international guidelines.

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Perioperative antibiotic prophylaxis (PAP) is widely recognized as an evidence-based measure to reduce the risk of surgical site infections[1,11,16]. However, the optimal antibiotic agent, dosing regimen, and duration of prophylaxis in lung resections remain subjects of debate. The absence of standardized international guidelines for PAP in non-cardiac thoracic procedures contributes to considerable variability in clinical practice among institutions and countries[4,5,7,9–12].

Achieving adequate serum and tissue concentrations of the chosen antibiotic during surgery is crucial for effective prevention, ensuring coverage of the most likely pathogens[2,4,7,11,13]. Nevertheless, despite the routine administration of PAP, POP continues to represent a substantial source of morbidity and mortality, underscoring the need for novel preventive strategies[5,7,13,17].

With the growing concern of antimicrobial resistance and increasing evidence of respiratory tract colonization in patients with lung cancer, there is a pressing question of whether PAP should be individualized and tailored to each patient's microbiological status[13]. Recent advances in artificial intelligence and large language models have also begun to influence clinical research and scientific communication in medicine, including thoracic surgery and infectious disease research[18]. The objective of our study was, therefore, to compare the occurrence of pneumonia between two different antibiotic regimens and investigate whether the incidence of pneumonia differs in patients colonized with potentially pathogenic microorganisms (PPMs). The comparison between cefazolin and amoxicillin–clavulanic acid was selected because these two antibiotics are widely used in thoracic surgery and yet had not previously been evaluated in a prospective comparative design to determine if one provides superior protection against POP.

Patients and methods

This prospective, double-blind comparative study included 200 consecutive patients with histologically confirmed non-small cell lung cancer (NSCLC) or typical and atypical carcinoid tumors, treated between January 2023 and March 2025. Patients were admitted to the University Clinic for Respiratory and Allergic Diseases in Golnik, and surgical procedures were performed at Surgery Bitenc d.o.o. A flow diagram of patient enrollment and study design is presented in Figure 1.

Eligibility

Patients were eligible if they were at least 18 years old, had primary NSCLC (adenocarcinoma, squamous cell carcinoma, adenosquamous cell carcinoma, large-cell carcinoma, or large-cell neuroendocrine carcinoma) staged IA–IIIA (eighth/ninth TNM classification) or IIIB and IV after neoadjuvant treatment, or typical and atypical carcinoid, and were assessed as fit for radical resection (World Health Organisation [WHO] performance status 0–1). Exclusion criteria included a WHO performance status of more than 1, uncontrolled chronic or infectious disease, recent antibiotic use (within the last 14 days), allergy to β-lactam antibiotics, or administration of non-study antibiotics during hospitalization. All participants provided written informed consent. The study was approved by the National Medical Ethics Committee of the Republic of Slovenia (no. 0120-163/2021/3).

Study protocol

Patients were allocated sequentially to receive either amoxicillin–clavulanic acid or cefazolin. The study was conducted in a double-blind manner, such that neither the patients, the operating

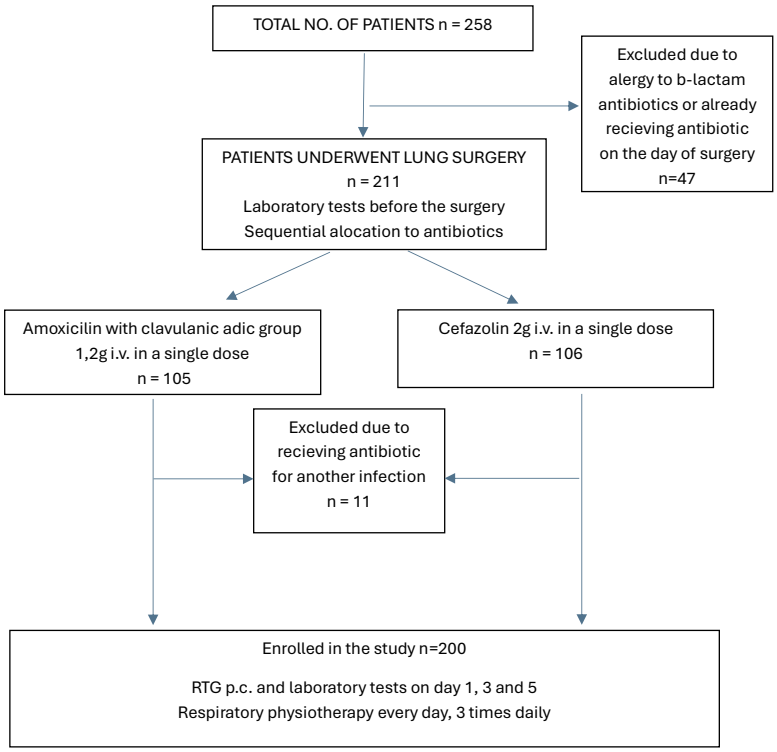

Figure 1. Consort flow diagram.

surgeons, nor the investigators were aware of which antibiotic was administered.

All patients with suspected primary lung cancer underwent diagnostic evaluation and treatment according to current guidelines. Patients with radiologically suspected malignancy on computed tomography (CT) underwent bronchoscopy and positron emission tomography-computed tomography scans. During bronchoscopy, tumor samples were collected when feasible, and additional specimens of bronchial mucosa were obtained using a protected sterile catheter for microbiological analysis. When the lesion was inaccessible via bronchoscopy, a CT-guided needle biopsy was performed for histopathological verification. After the diagnostic work-up, cases with confirmed NSCLC or typical and atypical carcinoid were reviewed by the thoracic oncology board. Patients deemed suitable for surgery underwent anatomical lung resection (lobectomy, bilobectomy, pneumonectomy, or segmentectomy) within 7–21 days after board approval. Postoperatively, patients were admitted to the surgical department, where infectious complications were closely monitored.

Bronchoscopy

Bronchoscopy was conducted under moderate sedation, with a strict no-suction policy before reaching the carina. Upon entering the trachea, topical anesthesia using lidocaine was administered to the main and upper lobar bronchi. To detect bacterial colonization, we collected sterile brushes (OLYMPUS disposable cytology brush BC-202D-210) from the bronchi of the targeted lobe containing the tumor before diagnostic sampling. Each sample was preserved in 1 mL of sterile saline solution and subsequently sent to the microbiology laboratory. Peripheral tumor sampling was performed using various bronchoscopic techniques to determine the histological types of tumors.

Microbiological analysis

Protected sterile brush samples were promptly processed in the microbiology laboratory, beginning with vortexing and slide preparation before dilution and plating. Gram staining and microscopic examination assessed specimen quality, bacterial morphology, and abundance. Samples were diluted to a final dilution of 10^{-3} and inoculated on various solid and liquid media [blood agar, chocolate agar, Brucella blood agar, CHROMagar^{TM} Orientation (CHROMagar, France), and thioglycollate broth]. Plates were incubated aerobically and anaerobically at 35°C, with growth evaluation at 24, 48, and 72 hours. Liquid medium subculturing onto the same solid media plates confirmed bacterial morphotypes and their colony-forming units per milliliter (CFU/mL). A cutoff of ≥10^3 10^3 CFU/mL defined positive culture results. Identification and antimicrobial susceptibility testing were conducted using the MALDI Biotyper® (Bruker Daltonics GmbH & Co., Germany) and the standardized EUCAST disc diffusion method. Bacteria were classified as PPMs (e.g., *Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, Staphylococcus aureus, Pseudomonas aeruginosa*, and Enterobacterales) or non-PPMs (e.g., *Streptococcus viridans* group, *Neisseria* spp., *Corynebacterium* spp., and coagulase-negative staphylococci)[19].

Surgery and postoperative management

Surgery was performed 7–21 days after board approval. Preoperative anesthesiology assessment included documentation of demographic and clinical data. Procedures were performed under general anesthesia, either via open thoracotomy or video-assisted thoracic surgery (VATS). All patients had blood samples taken before they received PAP after induction of anesthesia.

Patients were, as previously described, allocated sequentially to two groups before surgery.

- **Group 1** received the standard prophylaxis regimen: cefazolin 2 g IV in a single dose (administered immediately after intubation, 45 minutes prior to the incision).
- **Group 2** received amoxicillin with clavulanic acid 1.2 g IV in a single dose (administered immediately after intubation, 45 minutes prior to the incision).

Postoperatively, patients were admitted to the surgical ward. Hourly measurements of body temperature were recorded. A chest X-ray and blood inflammatory markers were obtained on postoperative days 1, 3, and 5. All patients initiated respiratory physiotherapy, and during encouraged coughing, the presence of purulent sputum was assessed. POP was diagnosed if there was a presence of a new pulmonary infiltrate on chest radiography together with at least one clinical sign (elevated C-reactive protein, leukocytosis >12 × 10^9/L, purulent sputum, or fever >38°C); cases of atelectasis with these findings were also classified as pneumonia[17,20].

Statistical analysis

The differences between groups were assessed using the Mann–Whitney *U* test or the Wilcoxon test, as appropriate. The response to different antibiotic regimens and the incidence of pneumonia in various subgroups were evaluated using Fisher's exact test. All reported *P*-values are two-tailed. All statistical analyses were carried out using IBM SPSS (version 28, Chicago, IL, USA).

Results

Patient characteristics

A total of 200 consecutive patients were enrolled in the study. The cohort included 103 men (51.5%) and 97 women (48.5%), with a median age of 68 years (range: 44–83 years). One hundred patients (50.0%) were current or former smokers. Chronic obstructive pulmonary disease was present in 50 patients (25.0%), while 19 patients (9.5%) had type 2 diabetes mellitus. Based on body mass index (BMI), 65 patients (34.0%) had a normal weight, whereas 126 patients (66.0%) were overweight (nine patients had missing values for BMI). Patient characteristics are summarized in Table 1. The majority of patients had adenocarcinoma (72.5%), followed by squamous cell carcinoma (15.5%); the remaining patients presented with other histological subtypes. The predominant tumor stage was IA (59.0%), with stages ranging from IA to IV. Surgical procedures were performed either through open thoracotomy (71.5%) or VATS. The most common resection was lobectomy (83.5%), followed by bilobectomy, segmentectomy, and pneumonectomy (Table 2).

Postoperative pneumonia

Among the 200 patients, POP was observed in 47 cases (23.5%). In these cases, the prophylaxis type was quite evenly spread: 23 (out of 107) patients (21.5%) had received

Table 1

Baseline characteristics of the study population.

Characteristic	*N* (%)	Cefazoiln	Amoxicillin–clavulanic acid	
Number of patients	200	107	93	
Median age, years (range)	68 (44–83)	68 (44–82)	68 (45–83)	$P = 0.850$
Sex, male	103 (51.5)	57 (53.3)	46 (49.5)	$P = 0.671$
Sex, female	97 (48.5)	50 (46.7)	47 (50.5)	
Smokers	100 (50.0)	60 (56.1)	40 (43.0)	$P = 0.182$
COPD	50 (25.0)	27 (25.2)	23 (24.7)	$P = 1.000$
Diabetes type 2[a]	19 (9.5)	8 (7.5)	11 (11.8)	$P = 0.339$
BMI, normal[a]	65 (34.0)	45 (44.6)	23 (25.6)	$P = 0.007$
BMI, overweight[a]	126 (66.0)	56 (55.4)	67 (74.4)	

Values are presented as a number (percentage) unless otherwise indicated. Age is presented as median (range). COPD, chronic obstructive pulmonary disease; BMI, body mass index.
[a]For nine patients, the data are missing.

cefazolin prophylaxis, and 24 (out of 93) patients (25.8%) amoxicillin–clavulanic acid prophylaxis. The difference between the two antibiotic regimens was not statistically significant ($P = 0.507$) (Table 3).

Only one patient (0.5%) died within 30 days after surgery. The cause of death was unrelated to pneumonia.

Colonization status and pneumonia

A total of 178 (89.0%) patients were colonized with bacteria, while in 22 (11.0%), no bacterial growth was detected on any culture media. Among the colonized patients, 36 out of 178 (20.2%) harbored PPMs. Cross-tabulation analysis demonstrated that the incidence of POP was almost identical between those colonized with PPMs ($n = 9$; 25.0%) and those not colonized with PPMs ($n = 38$; 23.2%; $P = 0.830$). A similar pattern was observed for colonized ($n = 42$; 23.6%) and not colonized ($n = 5$; 22.7%; $P = 1.000$) groups of patients (Table 4).

Table 2

Tumor and surgical characteristics of the study population.

Characteristic	*N* (%)	Cefazolin	Amoxicillin–clavulanic acid
Histological type: adenocarcinoma	145 (72.5)	73 (68.2)	72 (77.4)
Histological type: squamous cell carcinoma	31 (15.5)	19 (17.8)	12 (12.9)
Histological type: other	13 (6.5)	7 (6.5)	6 (6.5)
Histological type: typical and atypical carcinoid	11 (5.5)	8 (7.5)	3 (3.2)
Tumor stage: predominant IA	118 (59.0)	60 (56.1)	58 (62.4)
Tumor stage: range	IA–IV	IA–IV	IA–IV
Surgical approach: thoracotomy	143 (71.5)	79 (73.8)	64 (68.8)
Surgical approach: VATS	57 (28.5)	28 (26.2)	29 (31.2)
Type of resection: lobectomy	169 (84.5)	91 (85.0)	78 (83.9)
Type of resection: bilobectomy	2 (1.0)	0 (0.0)	2 (2.2)
Type of resection: segmentectomy	27 (13.5)	15 (14.0)	12 (12.9)
Type of resection: pneumonectomy	2 (1.0)	1 (0.9)	1 (1.1)

Comment

In this prospective double-blind comparative study of 200 patients undergoing lung resection for NSCLC or typical/atypical carcinoid, POP occurred in 23.5% of patients, with no significant difference between those receiving cefazolin and those receiving amoxicillin–clavulanic acid. Furthermore, colonization with PPMs did not confer an increased risk compared with colonization by non-pathogenic bacteria or non-colonized patients for developing POP. Only one patient died within 30 days, and the cause of death was unrelated to pneumonia.

Postoperative pulmonary complications remain a major clinical challenge after lung cancer surgery, despite advances in perioperative care and minimally invasive surgical approaches. Previous studies have reported POP rates ranging from approximately 1.5 to 25% after pulmonary resections[5,7,17,20]. The incidence observed in our cohort lies toward the upper range of these reports[4,5,17]. One possible explanation is the pragmatic diagnostic definition used in this study, which included radiographic infiltrates combined with inflammatory markers and clinical signs. In clinical practice, differentiating early postoperative atelectasis from infectious infiltrates may be difficult, and our approach favored diagnostic sensitivity to avoid missing clinically relevant infections. Nevertheless, this strategy may have contributed to an overestimation of the true POP incidence.

The relationship between antibiotic regimen characteristics – such as spectrum of activity and duration of administration – and the incidence of POP after pulmonary resection remains a subject of ongoing debate. In our study, the absence of a significant difference in POP rates between the compared regimens aligns with some reports in the literature, yet contrasts with others[4,10]. Turna *et al* found that cefuroxime, a second-generation cephalosporin with a narrower antimicrobial spectrum, was marginally more effective than cefepime, a fourth-generation cephalosporin with broader Gram-negative coverage[10]. This observation challenges the assumption that broader-spectrum agents inherently offer superior protection against POP. To our knowledge, no previous study has directly compared cefazolin with amoxicillin–clavulanic acid in a randomized, parallel-group design. Schlusser *et al*, for example, conducted a sequential study in which

Table 3

Incidence of postoperative pneumonia according to antibiotic prophylaxis.

Antibiotic regimen	Pneumonia (*n*, %)	No pneumonia (*n*, %)	Total (*n*, %)	
Cefazolin ($n = 107$)	23 (21.5)	84 (78.5)	107 (100.0)	$P = 0.507$
Amoxicillin–clavulanic acid ($n = 93$)	24 (25.8)	69 (74.2)	93 (100.0)	
Total ($N = 200$)	47 (23.5)	153 (76.5)	200 (100.0)	

POP, postoperative pneumonia.

Table 4

Incidence of postoperative pneumonia according to colonization status.

Colonization status	Pneumonia (*n*, %)	No pneumonia (*n*, %)	Total (*n*, %)	
Colonized ($n = 178$)	42 (23.6)	136 (76.4)	178 (100.0)	$P = 1.000$
Not colonized ($n = 22$)	5 (22.7)	17 (77.3)	22 (100.0)	
PPM present ($n = 36$)	9 (25.0)	27 (75.0)	36 (100.0)	$P = 0.830$
No PPMs ($n = 164$)	38 (23.2)	126 (76.8)	164 (100.0)	
Total ($N = 200$)	47 (23.5)	153 (76.5)	200 (100.0)	

PPMs, potentially pathogenic microorganisms; POP, postoperative pneumonia.

patients received cefazolin 3 g/24 h over 24 hours during the first 6 months and amoxicillin–clavulanic acid 6 g/24 h over 48 hours during the following 12 months, reporting a lower incidence of POP in the latter group[7]. However, in that study, antibiotics were administered postoperatively for an extended duration rather than as a single perioperative dose, and the sequential design left the study more susceptible to temporal and institutional confounding. By contrast, our randomized, double-blind, parallel design allowed for a direct head-to-head comparison under uniform conditions, thereby allowing a more direct comparison of the relative effectiveness of these two regimens.

Another important aspect of our study was the evaluation of colonization status. The prevalence of colonization with PPMs in our cohort was lower (20.2%) than rates reported in previous studies on lung cancer patients[8,13]. Koslow *et al* recommended routine preoperative bronchoscopic sampling for bacterial cultures in lung cancer patients, based on their finding that the presence of PPMs was the only independent predictor of postoperative pulmonary infection[13]. Similarly, D'Journo *et al* reported frequent airway colonization in lung cancer patients, with a heterogeneous microbiological profile, but found no clear correlation with postoperative infection rates[8]. Dancewicz *et al* likewise observed that approximately one-third of patients exhibited significant bronchial colonization with PPMs, yet its predictive value for pneumonia remained limited[21]. In contrast, our study demonstrated no significant difference in pneumonia incidence between patients colonized with PPMs and those with non-pathogenic flora, despite employing sterile sampling techniques during bronchoscopy to ensure standardized sampling. These findings suggest that colonization status alone can meaningfully guide PAP and instead highlight the importance of broader clinical risk stratification when assessing pneumonia risk.

However, the number of patients colonized with PPMs in our study was relatively small, which limits the statistical power to detect moderate associations. Therefore, our results should be interpreted cautiously and should not be considered definitive evidence that colonization has no clinical relevance. Larger studies are needed to determine whether specific microbial profiles or higher bacterial loads may influence postoperative infection risk.

Taken together, our findings support the continued use of standard perioperative prophylaxis with cefazolin in lung cancer surgery and do not provide clear evidence supporting the routine tailoring of antibiotic prophylaxis based solely on preoperative bronchial colonization status. Future research should focus on identifying robust preoperative and perioperative risk factors that could allow more targeted preventive strategies for patients at the highest risk of POP.

Study limitations

This study has several limitations. First, patient allocation was performed sequentially rather than using a fully randomized allocation sequence. Although blinding was maintained, sequential allocation may introduce the possibility of selection bias and should be considered when interpreting the results. Second, this was a single-center study, which may limit the generalizability of our findings to other clinical settings. Third, the number of patients colonized with PPMs was relatively small, reducing the statistical power to detect moderate associations between colonization status and POP. Fourth, the diagnostic criteria for POP were based on clinical and radiographic findings and may have included cases in which early postoperative atelectasis could not be completely distinguished from infection. Finally, sputum samples were not obtained from all patients diagnosed with POP, and postoperative bronchoscopy was not routinely performed, which limited our ability to identify causative pathogens in every case.

Conclusion

In this prospective double-blind comparative study, the incidence of POP following lung cancer surgery did not significantly differ between patients receiving cefazolin and those receiving amoxicillin–clavulanic acid as perioperative prophylaxis. Preoperative bronchial colonization, including colonization with PPMs, was not associated with a higher incidence of POP in this cohort. However, given the limited number of patients with pathogenic colonization and the single-center design, these findings should be interpreted cautiously. Further multicenter studies are needed to better define the role of airway colonization and to identify patients who may benefit from individualized prophylactic strategies.

Ethical approval

The study was approved by the National Medical Ethics Committee of the Republic of Slovenia (No. 0120-163/2021/3).

Consent

Written informed consent was obtained from all patients.

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This research received no external funding.

Author contributions

S.P. contributed to the study design, data collection, data analysis, and manuscript writing. B.B. and A.R. contributed to manuscript revision and critical editing. V.T. contributed to microbiological analyses and the interpretation of data. V.D., M.M.M., and A.R. performed bronchoscopic procedures. A. S. performed statistical analysis. M.M. contributed to data collection. M.B. and A.R. supervised the study and provided final approval of the manuscript. All authors have read and approved the final manuscript.

Conflicts of interest disclosure

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.

Research registration unique identifying number (UIN)

Not applicable.

Guarantor

Sabrina Petrovic is the guarantor of this work.

Provenance and peer review

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Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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