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Epidemiology and Appropriateness of Antibiotic Prescribing in Severe Pneumonia after Lung Resection

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Abstract

Background: Post-operative pneumonia (POP) is a severe complication of major lung resection. Our objective was to describe the current epidemiology and appropriateness of antibiotic prescriptions in severe POP, four years after implementation of an antimicrobial stewardship program based on weekly multidisciplinary review of all antibiotic therapies.

Methods: Retrospective analysis of a prospectively collected database. We included all cases of severe POP occurring within 30 days after major lung resection of our 1500-bed hospital between 2013 and 2015. Criteria for severe POP were: acute respiratory failure, severe sepsis or rapidly extensive pulmonary infiltrate. We collected data on incidence, clinical outcomes and microbiological analyses. Appropriateness of antibiotic prescribing was assessed by quality indicators previously validated in the literature.

Results: Over the study period, 1555 patients underwent major lung surgery. Severe POP occurred in 91 patients (5.8%, confidence interval, CI: 4.7% ; 7.0%), with mortality rate of 9.0% (8/91, CI: 3.0% ; 14.6%). In POP with positive microbiological analyses, the proportion of gram-negative bacteria other than *Haemophilus* was of 76% (50/66). All patients (91/91) had respiratory samples taken within 24h after the start of antibiotics, empirical therapy was concordant with the guideline in 80% (69/86), and switched to pathogen-directed therapy in 74% (46/62). In 71/91 patients (78%), antibiotic duration was ≤ 7 days.

Conclusions: We report a high proportion of gram-negative bacteria in severe POP. Four years after implementation of the program, quality indicators of antibiotic prescribing were all $>70\%$. Rate of de-escalation to pathogen-directed therapy could however be improved.

Postoperative pneumonia (POP) is a frequent and severe complication of major lung resection surgery. Incidence ranges from 10 to 30% [1-3], with significant mortality (up to 30%) [4]. Preventive measures include adequate surgical antibiotic prophylaxis [5], gastrointestinal tract management [6], decontamination of the oropharynx [7], preoperative physiotherapy [8]. The individual impact of these measures on the incidence of POP is difficult to assess and still matter of debate [9-10]. Thus POP still has significant burden, especially in high-risk patients, i. e. those with chronic obstructive pulmonary disease, malnutrition, diabetes mellitus, or other major comorbidities [4]. POP is also a cause of major exposure to broad-spectrum antibiotics. We thus implemented in 2012 in our center an antimicrobial stewardship program involving intensive care physicians, infectious diseases specialists, microbiologists and surgeons, to improve the quality of care in POP. Based on national and international standards [11], the objective was to promote microbiological sampling and optimization of antibiotic therapy, i.e. adequate empirical treatment, early de-escalation and short antibiotic duration. In this study, our goal was to provide data on current epidemiology of severe POP after major lung resection and to assess appropriateness of antibiotic prescribing four years after implementation of the program.

Material and Methods

Patients

This study was performed at the Thoracic Surgery Department of Cochin hospital, Paris, France, a 1500-bed university hospital. All patients undergoing lung resection between 1st January 2013 and 31st December 2015 were retrospectively screened from the medical records database, and episodes of severe POP occurring within 30 days after surgery were eligible for this study. Pneumonia was defined as follows: new lung infiltrate plus clinical evidence that the infiltrate is of an infectious origin, i.e. new onset of fever ($> 38.5^{\circ}\text{C}$), purulent sputum, leukocytosis, and decline in oxygenation [11]. POP was severe if the

primary physician decided to refer the patient to the intensive care unit, based on criteria from national and international guidelines [11-13].

Antimicrobial stewardship policy

As recommended by international guidelines [14], the antimicrobial stewardship program relied on several interventions: 1) Implementation of a facility-specific antibiotic guideline adapted from international/national recommendations based on local epidemiology (figure 1); 2) Preauthorization for a list of restricted antibiotics (i.e. carbapenems, linezolid etc.); 3) Prescriber-led daily reassessment of the appropriateness of antibiotic regimen in the intensive care unit (ICU); 4) Weekly multidisciplinary meeting between physicians of the ICU, microbiologists, infectious diseases (ID) specialists and thoracic surgeons to review all patients on antibiotics and deliver educational messages on antimicrobial stewardship to the ICU physicians.

Local guideline

The guideline included recommendations on surgical antibiotic prophylaxis and on management of patients with suspected pneumonia (figure 1). Microbiologically confirmed POP was defined by either positive blood culture, positive urinary antigen, positive sputum culture $\geq 10^6$ CFU /ml, distal bronchial aspirate $\geq 10^6$ CFU/ml, BAL culture $\geq 10^4$ CFU or protected specimen brush $\geq 10^3$ CFU /mL /mL. If >1 micro-organism was above significant cut-off values on culture, the POP was considered plurimicrobial. Depistage of nasal carriage of Meticillin-Resistant *Staphylococcus aureus* (MRSA) and rectal carriage of Extended Spectrum Beta-lactamase-producing *Enterobacteriaceae* (ESBL-E) were performed at ICU admission and weekly forwards in all patients.

Data

Data on clinical presentation, microbiological results, treatment procedures and outcomes were prospectively recorded in a standardized questionnaire and entered in a computerized

database (Epithor Project - French Society of Thoracic and Cardiovascular Surgery). The local database was retrospectively searched in January 2017 to identify patients meeting the inclusion criteria. To assess appropriateness of antibiotic prescribing, the following validated quality indicators were calculated [15] : 1) The proportion of patients with respiratory samples taken within 24h after the start of systemic antibiotics; 2) The proportion of patients started with empiric antibiotic therapy according to the local guideline; 3) The proportion of patients in whom empirical antibiotics displayed *in vitro* activity against microorganisms subsequently isolated on culture, 4) The proportion of patients with empirical systemic antibiotics who were correctly switched to pathogen-directed therapy according to culture results, 5) The proportion of patients with antibiotic duration ≤ 7 days.

Comparison with historical data

Incidence rates and microbiological data over the 2013-2015 period were compared to those previously reported in 2001 and 2002 in our center [5, 16]. Based on available data, three out of five quality indicators were retrospectively calculated in an historical cohort of 47 POP patients hospitalized in our center in 2003-2006, and compared to those of 2013-2015.

Statistical analysis and Ethics

Results are expressed as n (%) for categorical variables and median (minimum; maximum) for continuous variables. Incidence and mortality rates are presented with their 95% confidence intervals (calculated as confidence interval (CI) for proportions as $p \pm 1.96 \times \sqrt{[p.(1-p)/n]}$). Comparisons were done using the Wilcoxon and Fisher's exact tests for continuous and categorical variables, respectively. Statistical analysis was performed using the R software version 3.1.2 (R Development Core Team, R Foundation for Statistical Computing, Vienna, Austria, <http://www.r-project.org/>). the research was conducted in accordance with the Declaration of Helsinki and national and institutional standards. The project was approved by the Institutional Review Board of the French Society of Thoracic and Cardio-Vascular Surgery (reference : CERC-SFCTCV-2018-3-21-10-38-25-KeAl).

Results

Participants

Between 1st January 2013 and 31st December 2015, 1555 patients underwent major lung resection in our department and 152 (9.8%, CI= [8.3% ; 11.3%]) were diagnosed with POP within 30 days post-surgery (figure 2). Among them, 91/1555 (5.8%, CI= 4.7% ; 7.0%) had criteria for severe POP and were included in the study. Data on demographics, surgical procedures and clinical features are reported in table 1. Median ICU length of stay was 12 days (1; 90), and overall mortality rate 9.0% (8/91, CI= 3.0% ; 14.6%).

Microbiology

Respiratory samples were obtained in all 91 patients before the start of antibiotics, either non-invasively (26%) or invasively (74%). As shown in table 2, 66/91 (72%) patients had microbiologically confirmed pneumonia and 118 microorganisms reached significant cut-off values on culture. Predominant species were *Enterobacteriaceae* (41/66, 61%), *Haemophilus influenzae* (13/66, 20%), *Staphylococcus aureus* (10/66, 15%) and *Pseudomonas aeruginosa* (9/66, 14%). One MRSA and one ESBL-*E. coli* were cultured on respiratory samples, but not in patients with carriage detected on admission to the ICU. Microorganisms were susceptible to amoxicillin-clavulanate in 30 (46%) cases, to third generation cephalosporins in 52 (79%) and to piperacillin-tazobactam in 57 (86%).

Quality indicators of antibiotic use

As reported in table 3, all patients (100%) had microbiological sampling before the start of antibiotics. Empirical antibiotics were concordant with the guideline in 69/86 patients (80%), were active against cultured micro-organisms in 53/62 (86%), and were correctly changed to pathogen-directed therapy in 46/62 (74%) patient. Antibiotic duration was ≤ 7 days in 78% of cases. Among 47 patients of the historical 2003-2006 cohort, 100% had respiratory sampling,

empirical antibiotics were concordant with the guideline in 64% (30/47) and antibiotics changed to pathogen-directed therapy in 70% (21/30).

Comment

Four years after implementation of a multidisciplinary antimicrobial stewardship program in thoracic surgery, all quality indicators of antibiotic prescribing were above 70%. Comparison with historical patients showed that biggest improvements were made in the subset of patients with empirical therapy concordant with the guideline (64% in 2003-2006 and 80% in 2013-2015), and to a lesser extent to those de-escalated to pathogen-directed therapy (70% in 2003-2006 and 74% in 2013-2015).

There is now strong evidence of the positive impact of antibiotic stewardship programs on appropriateness of antibiotic prescribing, decrease of antimicrobial resistance, incidence of *Clostridium difficile* infections, and patients' outcomes [17, 18]. However, data on implementation and impact of such programs in surgical settings are scarce, and mainly addressed the question of perioperative antibiotic prophylaxis or intra-abdominal postoperative infections [19-21]. Here, we showed high adherence to the program, likely facilitated by close interaction between microbiologists, ICU physicians, ID specialists and surgeons, who shared the responsibility of medical decisions during the weekly meeting. The rate of de-escalation to pathogen-directed therapy (74%) could however be improved. De-escalation is a pivotal component of most stewardship programs, but has no consensual definition, and its impact on antimicrobial resistance is still a matter of debate [22-24]. The decision to adjust the antibiotic regimen strongly depends on multiple factors (baseline severity, clinical resolution, adequacy of source control, microorganism, etc.). Our results illustrate that even in settings with good practices of antibiotic prescribing, implementation of systematic de-escalation in patients with severity criteria is still challenging.

Incidence of POP was of 10% in 2013-2015. As comparison, incidences of 25% (42/168) and 14% (38/277) were previously reported in the same center in 2001 and 2002 respectively [5,

16]. One hypothesis to explain the rapid drop of incidence was a change of antibiotic prophylaxis protocol in early 2002. Indeed, there is strong correlation between intraoperative bronchial colonization and pathogens cultured in respiratory samples of POP patients [16]. Thus following international guidelines [25] our surgical prophylaxis protocol by cefamandole was switched to amoxicillin-clavulanate, in order to target bacteria involved in wound infections (ie *Staphylococcus*) as well as those usually recovered from intraoperative bronchial colonization (ie *Haemophilus*, *Streptococcus pneumoniae*). The change of antibiotic prophylaxis was followed by a significant decrease of both incidence and 30 day-mortality of POP patients [5]. Ten years after, the incidence of POP remained stable and far below the incidence reported in 2001. Interestingly, mortality rates of severe POP followed the same pattern : 19% in 2001 [16], 11% in 2002 [5] and around 10% in 2013-2015. It is difficult to formally compare the three periods since case definitions were not strictly identical and many changes may have occurred over time: case mix, epidemiological trends, global improvement of pre-surgical preparation, surgical techniques and postoperative management etc.). However, these encouraging results suggest that programs based on reduction of broad-spectrum antibiotics use and shortening treatment durations are not associated with negative outcomes, even in severe patients.

The burden of severe POP is however still high: in our cohort, median length of stay was of 19 days, and mortality rate 9%. As a comparison, we estimated from the hospital coding database that over the same period, mean length of stay was of 9.6 days in thoracic surgery patients without POP (n=1694) and 12.5 days in POP patients without severity criteria (n=64), with mortality rates of 1% and 2% respectively. Widespread implementation of programs of video-assisted and/or robot/assisted thoracic surgery, together with Early Recovery After Surgery, and prehabilitation programs (all currently ongoing in our department), will probably further reduce incidence and severity of POP.

Interestingly, isolation of gram-negative bacteria other than *Haemophilus* (mainly *Enterobacteriaceae*) increased from 38% (9/24) in 2001 to 42% (10/24) in 2002 and 76% (50/66) in 2013-2015, as opposite to *Haemophilus influenzae* and *Streptococcus* sp. These trends were already observed in 2002, over the 12 month-period immediately following the change of antibiotic prophylaxis. The increase of isolation of gram-negative bacteria was mainly related to pathogens with either natural (*Enterobacter* and *Morganella* species) or acquired resistance to amoxicillin-clavulanate (10 over 21 strains of *E. coli* were resistant to amoxicillin-clavulanate in 2013-2015). It is nevertheless important to note that this was not associated to an increase of the overall incidence of POP that remained below the incidence estimated during the cefazoline-era in our setting and others [3, 16]. The emergence of *Enterobacteriaceae* as causative agents of POP must be considered when choosing empirical antibiotic treatment. Indeed, piperacillin-tazobactam, which showed antibacterial activity against 86% of pathogens cultured in our setting, remains the preferred choice. However, the recent increase of carriage of multi-resistant gram negative *Enterobacteriaceae* in France, both in community and health-care settings, supports close monitoring of microbiological epidemiology of POP in the future, to adapt the local guideline if necessary.

Limitations of this study include its retrospective and monocentric design, which hampers generalizability of our results. Indeed, epidemiology of health-care associated infections show striking differences from a country to another and even from different settings within the same country. However, local epidemiological data are important to adapt regional and national antibiotic policies, detect emergence of antimicrobial resistance and allow comparisons over time. In addition, our work focused on patients referred to the ICU, and we could not provide individual data on all post-operative pneumonia patients. Statistics on outcomes of patients without pneumonia and those not referred to the ICU were estimated based on CIM10 codes extracted from the hospital database.

Several lessons can be drawn from our results: First, in microbiological samples of severe pneumonia patients, we highlighted a high proportion of gram-negative pathogens, mostly (54%) resistant to amoxicillin-clavulanate, supporting the use of third-generation cephalosporins or piperacillin-tazobactam as empirical antibiotics in our setting. Second, despite extensive microbiological sampling, microbiological analyses were negative in 27% of POP. This underlines the need for more performant microbiological tools, and molecular techniques could offer promising opportunities in this field. Third, quality indicators of antibiotic use were high, highlighting the potential interest of multidisciplinary antimicrobial stewardship programs in surgery settings. Prospective studies or randomized trials are needed to provide high quality -evidence on the impact of such programs on antibiotic prescribing, patients' outcomes and antimicrobial resistance.

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Table 1: Patients characteristics at time of surgery and clinical outcomes. Categorical variables are reported as n (%) and continuous variables as median (minimum; maximum).

	Patients with severe post-operative pneumonia (n=91)
Male gender	71 (78)
Age, years	69 (42; 84)
Weight, kg	72 (32; 140)
Body Mass Index (kg/m ²)	25 (15; 45)
Performance status = 0	3 (3)
Denutrition (=Weight loss ≥10%)	23 (25)
Charlson comorbidity index	6 (0; 11)
Severe Acute Physiology Score 2	23 (7; 65)
Rythmic or ischemic cardiopathy	52 (57)
Chronic renal failure	9 (10)
Diabetes mellitus	24 (27)
History of infection in the past six months	14 (15)
History of non-pulmonary cancer	18 (20)
Chronic immune suppression ¹	11 (12)
Chronic alcohol abuse	22 (24)
Active smokers	42 (46)
Smoking cessation ≥ 60 days	43 (47)
Chronic obstructive pulmonary disease	59 (65)
Forced expiratory volume (FEV1), %	76 (36; 111)
FEV1/FVC, %	70 (35; 102)
Context of urgent surgery	5 (6)

Neoadjuvant chemotherapy	17 (19)
Neoadjuvant radiotherapy	7 (8)
Resection types	
Pneumonectomy	18 (20)
Lobectomy	54 (59)
Segmentectomy	17 (19)
Chest wall extended resection	9 (10)
Wedge resection	5 (6)
Sleeve resection	2 (2)
Histology	
Adenocarcinoma	48 (53)
Epidermoïd carcinoma	35 (39)
Other cancers	5 (6)
Other ²	3 (3)
Stage (n=89)	
I-II	69 (79)
III-IV	18 (21)
CLINICAL FEATURES	
Time between surgery and POP, days	3 (0; 17)
Acute respiratory failure	72 (79)
Septic shock	32 (35)
Acute renal failure	14 (15)
Renal replacement therapy	6 (7)
Bronchopleural fistula	8 (9)
Invasive ventilation	36 (40)
Duration of invasive ventilation	11 (1; 105)
Median length of stay in ICU, days	12 (1; 90)

Median hospital length of stay, days	19 (1; 125)
30-day mortality	8 (9)
Median time from surgery to death, days	20 (9; 29)

¹Chronic immune suppression: active cancer, malignant hematological disease, HIV infection, corticosteroids >10 mg equivalent-prednisone per day

²Bullous emphysema (n=1), mycobacteria infection (n=1), aspergilloma (n=1)

Table 2: Micro-organisms cultured at significant levels in 66 POP patients. Samples were obtained either non-invasively (sputum) or invasively per fibroscopy (endotracheal aspiration, bronchoalveolar lavage or protected distal catheter sampling). Results are expressed as n(%).

	POP patients with positive microbiological samples (n=66)
<i>Haemophilus influenzae</i>	13/66 (20)
<i>Beta-lactamase positive</i>	4
Gram-negative bacteria other than <i>Haemophilus</i>	50/66 (76)
<i>Enterobacteriaceae</i>	41/66 (62)
<i>Escherichia coli</i>	21
<i>Resistant to amoxicillin-clavulanate</i>	10
<i>Resistant to third generation cephalosporins</i>	2
<i>Enterobacter</i> species	12
<i>Resistant to third generation cephalosporins</i>	4
<i>Klebsiella</i> species	7
<i>Morganella</i> species	5
Other <i>Enterobacteriaceae</i>	11
<i>Pseudomonas aeruginosa</i>	9/66 (14)
<i>Muti-resistant P. aeruginosa</i>	1
<i>Staphylococcus aureus</i>	10/66 (15)
<i>Methicillin-resistant</i>	1
<i>Streptococcus pneumoniae</i>	6/66 (9)
<i>MIC penicillin G ≥ 0.125</i>	3

Streptococcus sp

2/66 (3)

Plurimicrobial

28/66 (42)

¹endotracheal aspiration, bronchoalveolar lavage or protected distal catheter sampling

Table 3: Quality indicators of antibiotic use in 91 patients with severe POP. Results are expressed as n(%).

	Patients with severe post- operative pneumonia (n=91)	Patients of the historic cohort 2003- 2006 (n=47)
Respiratory samples taken within 24h after the start of antibiotics	91/91 (100)	47/47 (100)
Patients with empiric antibiotic therapy	n=86	n=47
Empirical therapy concordant with the local guideline	69/86 (80)	30/47 (64)
Piperacillin-tazobactam alone	57	
Piperacillin-tazobactam+Amikacin	6	
Piperacillin-tazobactam+Rovamycin	3	
Other	3	
Empirical therapy non-concordant with the local guideline	17/86 (20)	17/47 (36)
Cefotaxime-metronidazole	5	
Cefotaxime alone	3	
Amoxicillin-clavulanate	3	
βlactam-fluoroquinolone	2	
Other	4	
Patients with empirical antibiotic therapy and positive microbiological analyses	n=62	n=30

Empiric antibiotics active against cultured micro-organisms	53/62 (86)	28/30 (93)
Empiric antibiotics correctly changed to pathogen-directed therapy	46/62 (74)	21/30 (70)
Duration of antibiotics \leq 7 days	71 (78)	not available

Figure Legends

Figure 1: Local guideline for management of patients with suspected post-operative pneumonia. Of note, all surgery patients received surgical antibiotic prophylaxis with amoxicillin-clavulanate (2 grams at induction of anesthesia, 1 gram after 4 hours and 1 gram 8 hours after the end of the surgical procedure). In case of allergy, levofloxacin was administered for prophylaxis.

Figure 2: Flowchart of study participants. Between 1st January 2013 and 31st December 2015, 1555 patients underwent major lung resection, 152 were diagnosed with post-operative pneumonia within 30 days post-surgery and 91 with severity criteria were referred to the intensive care unit.

1555 patients undergoing lung resection
1st January 2013 – 31 December 2015

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graph TD; A[1555 patients undergoing lung resection  
1st January 2013 – 31 December 2015] --> B[152 patients with post-operative  
pneumonia within 30 days post-surgery]; B --> C[91 patients with severe pneumonia];
```

152 patients with post-operative
pneumonia within 30 days post-surgery

91 patients with severe pneumonia

Day 0

Day 3

Day 7

Suspected post-operative pneumonia



Severity criteria?

If yes, refer patient to the ICU

Perform **microbiological tests** (blood sample, urinary antigen assay for *S. pneumoniae* and *L. pneumophila*, quantitative culture of respiratory samples)

Start **Piperacillin-tazobactam** as empirical therapy

± **Aminoglycoside** (if septic choc or suspicion of *P. aeruginosa* infection)

± **Rovamycin** (if extra-pulmonary symptoms and/or interstitial infiltrations)

± **Cotrimoxazole** (if immune suppression)

Evaluate clinical response and results of microbiological tests



Micro-organisms detected at a significant level?
Clinical improvement?

If yes, **de-escalate** antibiotic regimen to pathogen-directed therapy

Evidence of empyema or lung abscess?

Evidence of severe infection related to *P. aeruginosa* ?

If no to both questions, **discontinue antibiotics**

If yes, consider an additional 7-15 day course of antibiotics