SAS Journal of Medicine
Abbreviated Key Title: SAS J Med
ISSN 2454-5112
Journal homepage: https://saspublishers.com

OPEN ACCESS

Anesthesiology and Critical Care

Nosocomial Pneumopathies in Critical Care of the Military Hospital Mohammed V in Rabat-Morocco: Epidemiological, Clinical and Bacteriological Characteristics

Azzouzi Ayoub[1*], Mohamed Said Bouya[1], Abdelghafour El Kondy[1], Reda Touab[1], Walid Atmani[1], Abdelhamid Jaafari[1], Hicham Balkhi[1]

[1]Departement of Anesthesiology and Critical Care, Military hospital Mohammed V, Faculty of Medecine and Pharmacy of Rabat, Mohammed V University, Rabat, Morocco

DOI: 10.36347/sasjm.2022.v08i03.024 | **Received:** 03.02.2022 | **Accepted:** 07.03.2022 | **Published:** 30.03.2022

***Corresponding author:** Azzouzi Ayoub
Departement of Anesthesiology and critical care, Military hospital Mohammed V, Faculty of Medecine and Pharmacy of Rabat, Mohammed V University, Rabat, Morocco

Abstract **Original Research Article**

Nosocomial infections are defined as infections acquired in a care facility, which were neither incubating nor present when the patient was admitted. Nosocomial pneumopathies are a public health problem because they are responsible for significant morbidity and mortality with a considerable additional cost. They are frequent and serious in intensive care; they are the second most common acquired infections in a hospital setting. The diagnosis of nosocomial pneumopathy is based on a range of clinical, biological, radiological and bacteriological arguments. They cause problems of diagnostic, therapeutic and economic. The objective of this work consisted of an epidemiological study of the Nosocomial Pneumopathies (NP) and to evaluate the frequency, risk factors, antibiotic resistance of bacteria isolated, and factors of excess mortality. This prospective study focused on 65 patients hospitalized in the service of intensive care of the Mohammed V military instruction hospital in Rabat over a period of 6 month from 06/04/2017 to 06/10/2017, 52 patients had nosocomial pneumonia. The results of this work showed; that the germs isolated were essentially Gram-negative bacilli (77.5%), led by Acinetobacter Baumanii (37.8%), followed by Pseudomonas aeruginosa (18.9%), and klebsiella pneumoniae (9%). Gram positive cocci (7.2%), dominated by Staphylococcus aureus (7.2%). The polymicrobial character was found in 51% of cases. These isolated germs were multiresistant. During this study, there was a very significant morbidity of pneumonia by extending the duration of hospitalization in intensive care and the duration of ventilation. A very high risk of mortality has also been noted in patients infected in case of infection by non-fermenting germs.

Keywords: Nosocomial, Pneumopathie, Infection, Pseudominas aeruginosa, intensive care, mechanical ventilation.

INTRODUCTION

Despite advances in antibiotic therapy, substitution techniques and the implementation of preventive measures, nosocomial pneumopathies (PN) still represent one of the main causes of morbidity and mortality and are the cause of prolonged hospital stay and an additional cost of intensive care [1]. It represents the second cause of acquired infections and is the first cause of mortality by nosocomial infection (NI) in the United States [2]. Its prevalence in the U.S.A is estimated between 3 to 5%, it is 9.2% in intensive care units [3]. There are few prevention programs on NI in Africa, however the highest prevalence rate is estimated at around 25% [4]. Its diagnisis is difficult and the causative agents are often resistant and their prognosis is serious [5]. The diagnosis of PN is based on clinical, biological, radiological and bacteriological criteria. The early adequacy of antibiotic therapy is a major objective of the treatment of PN. To reduce this morbidity and mortality induced by nosocomial pneumonia, preventive measures are taken [6]. The prognosis of nosocomial pneumonia remains gloomy, due to the seriousness of the underlying diseases [7]. On the proposal of the American Thoracic Society, it is also possible that the term PN is likely to disappear in the future, to be definitively replaced by that of hospital-acquired pneumopathies, including nosocomial

pneumopathies acquired under mechanical ventilation (PNAVM) and those related to care (PAS) [6].

The main objective of this work is to analyze the epidemiological, clinical and bacteriological profile of nosocomial acquired pneumopathies. The secondary objective is to identify the predisposing factors and those that influence the prognosis, to finally arrive at essentially preventive recommendations.

Definition

Nosocomial infection is by convention an infection occurring more than 48 hours after admission to hospital and can be independent or linked directly or indirectly to an act of care[8). The World Health Organization estimates that on average 190 million people are hospitalized each year in the world and that 9 million of them contract a hospital infection on this occasion [10]. The risk of contracting an infection in the hospital is 7% [10]. This figure varies according to the service in which the hospitalized person is located. It can indeed reach 30% in a service such as intensive care [9].

Nosocomial pneumonia is defined as a lung infection acquired after at least 48 hours of hospitalization. The 48 hours correspond to the incubation period of the germ responsible for the disease. The term nosocomial pneumopathies acquired under mechanical ventilation relates to infections acquired after at least 48 hours of invasive artificial ventilation. Pneumopathy in intensive care is suspected on clinical elements and paraclinical symptoms such as the presence of purulent bronchorrhea, the appearance or modification of a pre-existing pulmonary radiological image, an infectious syndrome, and deterioration of hematosis on arterial blood gas. Samples for microbiological purposes can then confirm the infectious nature of this pneumopathy.

Depending on the time to onset of PN, we can classify the nosocomial pneumopathies in: § Early nosocomial pneumopathies (PNP): occurring before the 5th day of hospitalization, and which reveal a phenomenon of colonization of the airways by the endogenous flora of the patient.

§ Late nosocomial pneumonia (NTP): after the 5th day, and which are due to contamination by more resistant bacteria of hospital origin.

MATERIELS AND METHODES

Our work is based on a prospective study of cases of nosocomial pneumopathy collected from the medical and surgical intensive care units (RM/RC), as well as the impact of these pneumopathies, and the costs incurred during the stay of patients in the Mohamed V Military Instruction Hospital in Rabat (HMIMV) over a period of 6 months from 04/06/2017 to 10/06/2017.

The main endpoints for diagnosing PN are divided into clinical, biological and microbiological criteria and are summarized in the following table:

Table-I: Diagnostic criteria for nosocomial pneumonia

Clinical or radiological	biology	microbiology
1-Fever: hypothermia/hyperthermia +38C 2- Purulent tracheal secretions 3-Productive cough 4-Sign of pleural effusion 5-The appearance of new radiological infiltrates: 2 Xray images or more with an evocative image of pneumonia	1-Hyperleukocytosis +12000GB/mm3 2-Leucopenia -4000GB/mm3 3-increase in CRP and Procalcitonine 4-Alteration of exchanges gaseous	1-Sign of bacterial colonization 2-isolation of a pathogen agent in specimens

Minimum criteria for confirming the diagnosis of PN: one radiological image of pneumopathy or abscess + other criteria in the clinic (Fever, cough productive…).

Or, protected distal sampling (PDP) + two criteria in the clinic and radiology. They are included in this study all patients hospitalized for more than 48 hours, including patients with nosocomial pneumopathy and patients without the disease, in Medical Reanimation , Reanimation chirurgicale departments, regardless of their age and sex, and All patients hospitalized for a period of less than 48 hours are excluded, even if they may show signs of nosocomial infection, other than nosocomial pneumopathy. During the study period, we collected 65 bronchopulmonary samples according to the patient's state of consciousness ranging from until the protected distal sampling (PDP), the latter represents bacteriological confirmation of nosocomial pneumopathies. the sample is taken by the department doctor and quickly sent to the laboratory for a direct examination and culture with the performance of a systematic antibiogram. The results were analyzed with the SPSS software.

RESULTS

Study population and demographic information

The number of hospitalized patients was 427,

among these patients, 65 were suspected of having a nosocomial pulmonary infection (INP), and who met the inclusion criteria. In total, 52 cases of nosocomial pneumopathies including: 51 benefited from a positive PDP and a patient whose negative PDP, but who has suggestive clinical, radiological and bacteriological signs. Positivity of more than 103 CFU/ml (colony forming units). Infected patients aged fewer than 60. This difference is statistically significant with p = 0.02. There is a significant association between advanced age and nosocomial pneumonia, which is not the case with sex, with 65% being male which is statistically non-significant with p = 0.8.

Regarding the medical history, cardiovascular disease remains the most common ground in our patients (80%), followed respectively by diabetes (27%), and then smoking (25%).

90% of the reasons for hospitalization are represented by 4 pathologies: cardiovascular, respiratory, traumatic, and surgical and the duration of hospitalization varied between 5 and 161 days with an average duration of 27 days with ±5.

92% of patients had a length of stay of more than one week, against only 8% having a maximum duration of one week. The time to onset of PN varied between 1 and 34 days with an average of 7 days ± 2.

The study highlighted the significant association between COPD and nosocomial pneumopathy with 3 times more risk of developing nosocomial pneumopathy.

Among the risk factors, intubation and mechanical ventilation which multiply the risk by 3 times, thus 37 patients with PN and ventilated represent 72% against 10 of the 13 patients without PN (77%). There is also a significant association between tracheotomy and nosocomial pneumonia. Patients who had been tracheostomy had a 3 times greater risk of developing nosocomial pneumopathy (OR = 3.6), just as patients who had undergone enteral nutrition had almost 2 times more risk of developing nosocomial pneumopathy (OR = 1 ,9).

Furthermore, no significant association was noted between the occurrence of PN and central venous and arterial catheterization.

In multivariate analysis, the variables associated with mortality were introduced into the COX regression, with a p≤ 0.2 in univariate analysis. Chronic obstructive pulmonary disease and controlled mechanical ventilation have been identified as risk factors associated with mortality in patients with nosocomial pneumonia.

Table-II: Factors influencing the onset of Nosocomial Pneumonia

	P	Hasard Ratio	IC 95% for HR	
			inferior	superior
Chronic Obstructive Pulmonary Disease	0.005	2.304	1.048	5.066
Controlled artificial ventilation	0.033	5.841	0.782	43.616
Intubation probe	0.098	2.182	0.626	7.606
Age +60	0.159	2	0.762	5.247
Germs/Death	0.948	65539.648	0	2.60E+149

Diagnosis of nosocomial pneumonia

Clinically, among the 52 patients who presented episodes of PN, 44 had purulent secretions (85%), 37 snoring rales (71%), 35 feverish (68%). radiologically, 48% of patients showed right basal foci, however 19% had no signs of radiological foci. biologically, 91% of patients with PN had elevated leukocyte and CRP levels, and all (100%) had elevated procalcitonin levels.

However, the bacteriological diagnosis is based on taking samples, so the PBDP (protected distal bronchial sample) is the only sample used to confirm PN in 88.5% of patients, the other samples are less contributory.

Direct examination was performed in 91% of patients. The isolated germs were predominantly Gram-Negative Bacillus (BGN) with 78.5%, Gram-Positive Cocci (GPC) represented 10.2%, and 6.3% for Gram-Positive Bacillus (BGP), while yeasts represented 5%.

77.5% of the isolated germs were BGN dominated mainly by Acinetobacter baumanii (37.8%) followed by Pseudomonas aeruginosa (18.9%), and klebsiella pneumoniae (9%). The PGCs presented only 7.2% of all the isolated germs: Staphylococcus aureus was the most common, followed by Streptococcus pneumoniae. The isolated yeasts (1.8%) are represented by: Candida albicans and Candida parapsilosis. In univariate analysis, patients who had non-fermenting gram-negative bacilli in their cultures have an average survival time of 58 days, while patients who did not have BGN NF with a survival time of 90 days. This difference is statistically significant with p=0.001. This shows that the non-fermenting BGNs represent a risk factor for nosocomial pneumonia.

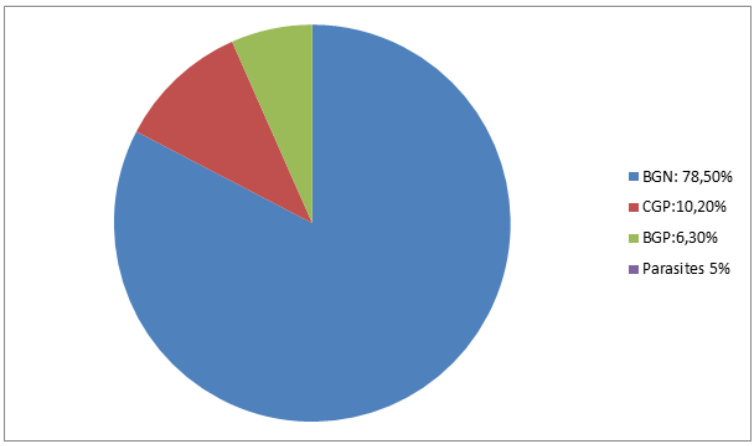

Fig-1: Distribution of germs isolated during direct examination

Medical treatment

Among the 65 patients suspected of having PN, 59 patients admitted to intensive care received antibiotic therapy, which represents 91%, in 47%, antibiotic therapy was guided by the results of bacteriology. The antibiotics most often prescribed in our patients are represented by colimycin, carbapenems, C3Gs, fluoroquinolones, aminoglycosides, glycopeptides. The average duration of antibiotic therapy was 14 days ± 4 with a maximum duration of 21 days and a minimum duration of 'a day.

Of 52 patients who acquired nosocomial pneumonia, only 23 evolved favorably, it represents 44% of cases. Among the 65 patients suspected of having PN, mortality was 54%. And the overall mortality in all patients who acquired PN was 56% (i.e. 29 patients), and therefore the lethality is greater than 50%.

The mortality rate mainly depended on:

§ Choice of antibiotic therapy, the beginning of its installation and its duration: mortality among all patients who have PN and who received antibiotic therapy was 54%.

§ Choice and duration of intubation: 31 patients with PN and intubated died. So the mortality in patients with intubated PN is 89% while it is 11% in non-intubated infected patients.

§ The isolated germ and its resistance in our series: 77% of patients infected with non-fermenting Gram-Negative Bacillus died, while only 23% of patients infected with other germs died. This difference is statistically significant with p=0.04. There is a significant association between non-fermenting BGNs and mortality. Patients who had non-fermenting BGN in their cultures had twice the risk of mortality than patients infected with other germs (OR = 2.4). This shows that infection by non-fermenting BGNs represents an excess mortality factor.

DISCUSSION

Physiopathologie

The mechanisms at the origin of pneumopathies are multifactorial, and their sequences of appearance are still widely discussed [10]. The main initial mechanism is bacterial contamination secondary to macro-inhalation and especially to repeated micro-inhalations.

Oropharyngeal colonization is the pivot of the genesis of pneumopathies [11]. The normal flora of the oropharyx does not contain Gram Negative Bacilli (BGN), but the prevalence of BGN can reach 73% in the most serious patients. Oropharyngeal colonization usually precedes nosocomial pneumopathy. in intensive care patients, dental plaque undergoes significant changes and its colonization precedes or occurs on the same day as pneumopathy [11]. Gastric colonization is a potential source of colonization of the oropharynx and trachea. In intensive care patients, colonization of the stomach by BGN is frequent.However, the notion that the stomach acts as a germ reservoir is controversial [5]. In fact, if in pneumopathies acquired early under mechanical ventilation (less than 4 days) the role of the stomach seems weak, in pneumopathies acquired later, it seems to play a role, influenced by a pH higher than 4 [12]. Tracheo-bronchial colonization almost always precedes pneumopathy and its importance increases with the duration of hospitalization in intensive care.

Predisposing Factors

They must be differentiated from those cited for colonization oropharyngeal, which, although it is an almost mandatory step before pulmonary contamination, does not necessarily cause it. It is therefore possible to individualize, in view of the literature, PN acquisition factors that can be classified according to three different clinical situations:

- The “all-comers” PRs, which, according to Celis, are favored by :
- An age greater than 70 years,
- Chronic lung disease,
- An intubation,

- One inhalation,
- Impaired consciousness,
- Recent thoraco-abdominal surgery.

- Postoperative PN, studied in 1981 by Garibaldi, and favored by:
- Hypoalbuminemia,
- A high ASA score,
- A duration of the preoperative hospital stay greater than
- 7 days,
- A duration of the intervention greater than 4 hours,
- Thoracic surgery.

- PN during mechanical ventilation (which represents a major risk factor, not related to the respirator or its circuits, but rather to the endotracheal prosthesis), apparently favored by (14):

- episodes of reintubation,
- gastric inhalation,
- a duration of ventilation greater than 3 days,
- the existence of chronic obstructive pulmonary disease,

Hence the essential interest of non-invasive ventilation, which Reduces the incidence of nosocomial infection [15]. Some risk factors remain controversial, namely the type of intubation, orotracheal versus nasotracheal, as well as the molecule used to prevent stress ulcers, sucral fate versus antacids or anti-H2 [16, 17].

Germs

Gram-negative bacilli are the main germs in cause (60% of PN). Pseudomonas sp is well ahead (30% of PN), ahead of Acinetobacter sp (10% to 12% of PN), the incidence of which continues to increase, and enterobacteriaceae Klebsiella, Enterobacter and Serratia groups (8% of PRs). Among Gram-positive cocci, staphylococci precede easily the other bacteria of their group: 30% for S. aureus and 10% for S. epidermidis [18-20]. Fungal agents play a significant role among the microorganisms responsible for PN, with, in particular, Aspergillus sp, the incidence of which is increased by corticosteroid therapy and immunosuppression. The role of Candida remains very controversial due to an obvious lack of precise and validated diagnostic criteria.

Diagnostic

Diagnosis is based on clinical, biological, radiological and bacteriological (21). The first three being very non-specific, microbiological diagnosis is necessary.Fever, cough and purulent expectoration are the clinical symptoms. The infectious syndrome associates hyperleu cocytosis and inflammatory syndrome. The radiography thocique most often shows a systematized opacity of the alveolar, associated or not with a pleural effusion. As to Bacteriological diagnosis is sometimes difficult, especially when prior antibiotic therapy has been instituted. He is based on the practice of bronchial samples and makes use of several techniques, endoscopic or not (22):

- Protected telescopic brushing (BTP),
- Bronchoalveolar lavage (LBA),
- Endotracheal aspiration (AT).

Several studies have shown that qualitative bacteriological analysis of endotracheal aspirate cultures obtained via an intubation tube or a cannula tracheostomy was unreliable [23].

On the other hand, the quantitative bacteriological analysis of these cultures is experiencing renewed interest, with recent studies having yielded encouraging results, especially when the significance level was defined as greater than or equal to 106 CFU/ml [24].The joint use of BTP and LBA, with in particular microscopic identification of intracellular germs, increases the sensitivity and specificity of such techniques [25].

Medical Treatment

Preventive

The prevention of nosocomial pneumopathy can be divided into three main components:

1- Education by developing written protocols taught to all caregivers.

2- Monitoring which involves regular readings of the incidence of pneumonia, with the establishment of markers of incidence according to the type of patients treated in order to then be able to facilitate comparisons between the care services of the different hospitals, as well as information on the bacteria involved and their sensitivities to antibiotics.

3-the prevention of the risk of infection, exogenous first of all, which aims to avoid contamination by environmental germs by hygiene measures for nursing staff, especially during care, the isolation of patients suffering from multi-resistant germs and the disinfection of equipment breakdowns according to well-described protocols. whereas the prevention of endogenous infectious risk due essentially to micro-inhalations: half-sitting position, regular aspiration of secretions from the oropharynx and nose every 4 hours, prevention of gastric ulcers remains a subject of controversy. Colonization of the lower airways involves bronchial aspirations using the “no touch” technique (“without contact”), carried out only on demand, depending on the state of congestion. The tracheotomy tubes must be changed regularly. It is also noted that antibiotic prophylaxis is not recommended by any team.

In operated patients, preoperative prevention involves information, smoking cessation at least fifteen days before the operation, physiotherapy in patients

with chronic respiratory disease. Intraoperatively, prevention involves the use of sterile intubation probes, humidification of the airways throughout the intervention, extubation of the patient after recovery of perfect consciousness. Postoperatively, respiratory physiotherapy is used pain management which is a source of atelectasis and getting up as early as possible [13].

Curative

After the establishment of symptomatic treatment, the problem of antibiotherapy quickly arises. Antibiotherapy is in fact a bitherapy, which should, in any case, be reassessed between the third and fifth day in based on clinical and radiological signs and the results of bacteriological samples. Most of the time, if a Gram-negative bacillus is suspected, the bitherapy will combine a beta-lactam with an aminoglycoside or a fluoroquinolone. If Gram cocci are suspected positive, it will combine a glycopeptide with an aminoglycoside or any other antibiotic usually effective on meti-R staphylococci, namely rifampicin, fosfomycin, acid fucidic or pristinamycin. Finally, depending on the severity of the pneumonia and the terrain, and if the vital prognosis is engaged, it is possible to use triple therapy combining a beta-lactam to an aminoglycoside and a glycopeptide. The duration of treatment is usually 15 days, the amino side can be interrupted after the fifth day. The advantage of using aminoglycosides in PRs is that it gives the treatment a rapid synergistic bactericidal effect, a lower risk of selection of resistant mutants, broadening of the spectrum of activity and reduction in the duration of treatment [26].

The relevance of the initial antibiotic therapy seems to be preponderant, particularly in terms of early complications and mortality, as has recently been proven. Indeed, the author estimates the mortality rate attributable to pneumonia at 16.2% when the initial antibiotic therapy was appropriate, and 24.7% when it was not [27].

CONCLUSION

PN is the most common hospital-acquired infection, with high mortality. However, mortality is not always exclusively due to lung infection, and figures that we currently have are certainly exaggerated. It is on them that we can act by arguing the prescriptions, by evaluating the real benefit of daily gestures, aided in this by pre-established protocols made available to all. Prevention programs must be developed, the awareness of health care and medical personnel must be increased, because only an awareness of this scourge will allow, perhaps, pushing him back.

REFERENCES

1. Campbell, G. D., Niederman, M. S., Broughton, W. A., Craven, D. E., Fein, A. M., Fink, M. P., ... & Wunderink, R. G. (1996). Hospital-acquired pneumonia in adults: Diagnosis, assessment of severity, initial antimicrobial therapy, and preventative strategies: A consensus statement. *American journal of respiratory and critical care medicine*, *153*(5), 1711-1725.
2. Vincent, J. L., Bihari, D. J., Suter, P. M., Bruining, H. A., White, J., Nicolas-Chanoin, M. H., ... & Hemmer, M. (1995). The prevalence of nosocomial infection in intensive care units in Europe: results of the European Prevalence of Infection in Intensive Care (EPIC) Study. *Jama*, *274*(8), 639-644.
3. Kollef, M. H. (2000). Inadequate antimicrobial treatment: an important determinant of outcome for hospitalized patients. *Clinical infectious diseases*, *31*(Supplement_4), S131-S138.
4. Pour, M. S. B. S. (2008). Infections nosocomiales en milieu de reanimation au chu gabriel toure: profil epidemiologique, clinique et bacteriologique.
5. Yu, V. L., & Singh, N. (2004). Excessive antimicrobial usage causes measurable harm to patients with suspected ventilator-associated pneumonia. *Intensive care medicine*, *30*(5), 735-738.
6. American Thoracic Society, & Infectious Diseases Society of America. (2005). Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *American journal of respiratory and critical care medicine*, *171*(4), 388.
7. Hugonnet, S., Eggimann, P., Borst, F., Maricot, P., Chevrolet, J. C., & Pittet, D. (2004). Impact of ventilator-associated pneumonia on resource utilization and patient outcome. *Infection Control & Hospital Epidemiology*, *25*(12), 1090-1096.
8. Maoulainine, F. M. R., Elidrissi, N. S., Chkil, G., Abba, F., Soraa, N., Chabaa, L., ... & Aboussad, A. (2014). Épidémiologie de l'infection nosocomiale bactérienne dans un service de réanimation néonatale marocain. *Archives de pédiatrie*, *21*(9), 938-943.
9. Donati, S. Y., & Papazian, L. (2008). Neumopatías hospitalarias en pacientes con ventilación mecánica. *EMC-Anestesia-Reanimación*, *34*(4), 1-18.
10. Johanson Jr, W. G., Seidenfeld, J. J., Gomez, P., De Los Santos, R., & Coalson, J. J. (1988). Bacteriologic diagnosis of nosocomial pneumonia following prolonged mechanical ventilation. *American Review of Respiratory Disease*, *137*(2), 259-264.
11. Bonten, M. J., & Gaillard, C. A. (1995). Ventilator-associated pneumonia: do the bacteria come from the stomach?. *The Netherlands Journal of Medicine*, *46*(1), 1-3.
12. Prod'hom, G., Leuenberger, P., Koerfer, J., Blum, A., Chiolero, R., Schaller, M. D., ... & Francioli, P. (1994). Nosocomial pneumonia in mechanically ventilated patients receiving antacid, ranitidine, or sucralfate as prophylaxis for stress ulcer: a randomized controlled trial. *Annals of internal*

medicine, *120*(8), 653-662.
13. Garibaldi, R. A., Britt, M. R., Coleman, M. L., Reading, J. C., & Pace, N. L. (1981). Risk factors for postoperative pneumonia. *The American journal of medicine*, *70*(3), 677-680.
14. Torres, A., Aznar, R., Gatell, J. M., Jiménez, P., González, J., Ferrer, A., ... & Rodriguez-Roisin, R. (2012). Incidence, risk, and prognosis factors of nosocomial pneumonia in mechanically ventilated patients. *American Review of Respiratory Disease*.
15. Antonelli, M., Conti, G., Rocco, M., Bufi, M., De Blasi, R. A., Vivino, G., ... & Meduri, G. U. (1998). A comparison of noninvasive positive-pressure ventilation and conventional mechanical ventilation in patients with acute respiratory failure. *New England Journal of Medicine*, *339*(7), 429-435.
16. Driks, M. R., Craven, D. E., Celli, B. R., Manning, M., Burke, R. A., Garvin, G. M., ... & McCabe, W. R. (1987). Nosocomial pneumonia in intubated patients given sucralfate as compared with antacids or histamine type 2 blockers. *New England Journal of Medicine*, *317*(22), 1376-1382.
17. Holzapfel, L., Chevret, S., Madinier, G., Ohen, F., Demingeon, G., Coupry, A., & Chaudet, M. (1993). Influence of long-term oro-or nasotracheal intubation on nosocomial maxillary sinusitis and pneumonia: results of a prospective, randomized, clinical trial. *Critical care medicine*, *21*(8), 1132-1138.
18. Rouby, J. J., Martin de Lassales, E., & Poete, P. (1992). Nosocomial bronchopneumonia in the critically III. *Am Rev Respir Dis*, *146*, 1059-1066.
19. Torres, A., De La Bellacasa, J. P., Xaubet, A., Gonzalez, J., Rodríguez-Roisin, R., De Anta, M. J., & Vidal, A. A. (1989). Diagnostic value of quantitative cultures of bronchoalveolar lavage and telescoping plugged catheters in mechanically ventilated patients with bacterial pneumonia. *Am Rev Respir Dis*, *140*(2), 306-310.
20. Fagon, J. Y., Chastre, J., Hance, A. J., Guiguet, M., Trouillet, J. L., Domart, Y., ... & Gibert, C. (1988). Detection of nosocomial lung infection in ventilated patients. *Am Rev Respir Dis*, *138*(1), 110.
21. Andrews, C. P., Coalson, J. J., Smith, J. D., & Johanson, W. G. (1981). Diagnosis of nosocomial bacterial pneumonia in acute, diffuse lung injury. *Chest*, *80*(3), 254-258.
22. Chastre, J., & Fagon, J. Y. (1994). Invasive diagnostic testing should be routinely used to manage ventilated patients with suspected pneumonia. *American journal of respiratory and critical care medicine*, *150*(2), 570-574.
23. Lambert, R. S., Vereen, L. E., & George, R. B. (1989). Comparison of tracheal aspirates and protected brush catheter specimens for identifying pathogenic bacteria in mechanically ventilated patients. *The American journal of the medical sciences*, *297*(6), 377-382.
24. Marquette, C. H., Georges, H., Wallet, F., Ramon, P., Saulnier, F., Neviere, R., ... & Tonnel, A. B. (1993). Diagnostic efficiency of endotracheal aspirates with quantitative bacterial cultures in intubated patients with suspected pneumonia: comparison with the protected specimen brush. *American Review of Respiratory Disease*, *148*(1), 138-144.
25. Chastre, J., Fagon, J. Y., Soler, P., Bornet, M., Domart, Y., Trouillet, J. L., ... & Hange, A. J. (1988). Diagnosis of nosocomial bacterial pneumonia in intubated patients undergoing ventilation: comparison of the usefulness of bronchoalveolar lavage and the protected specimen brush. *The American journal of medicine*, *85*(4), 499-506.
26. Munckhof, W. J., Grayson, M. L., & Turnidge, J. D. (1996). A meta-analysis of studies on the safety and efficacy of aminoglycosides given either once daily or as divided doses. *Journal of Antimicrobial Chemotherapy*, *37*(4), 645-663.
27. Alvarez-Lerma, F. (1996). Modification of empiric antibiotic treatment in patients with pneumonia acquired in the intensive care unit. *Intensive care medicine*, *22*(5), 387-394.