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Bacteriological Aspects of Late Pneumonia in Ventilated Patient in Intensive Care Units: A Single Center Study in Morocco

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Abstract

Background: The resistance to antimicrobial among patients with late Ventilator-associated pneumonia (VAP) has become increasingly more common in many ICUs in Morocco. There are scarce studies assessing VAP importance in Morocco.

The aim of this study is to determine the bacterial ecology and resistance profile of late VAP in intensive care units in an academic hospital of Rabat.

Methods: A total of 215 sputum samples were collected from endotracheal aspirate in patients with diagnosis of late VAP during the study period, defined from April 1st 2012 to April 2013. The bacteriology interpretations was done following the Referential of Medical Microbiology (REMIC 2010) and were quantitatively cultured with a cut-off of ≥ 10 UFC/ml for endotracheal aspiration samples.

Results: Overall, the Gram-negative bacilli (GNB) represent 81.42% of isolates, while Gram-positive was less represented with a rate of 18.56%. Non-lactose fermenting GNB made up the half of pathogens with the rate of 55.23% and the prevalence of Enteric GNB reaches 26.19%. *Pseudomonas aeruginosa* is the most isolates with the rate of 28.57%, followed by *Acinetobacter baumannii* (24.76%), *Staphylococcus aureus* (9.5%) and *Klebsiella pneumonia* (8.09%). A high level of multi-drug resistance pathogens was found with a rate of 39.52%. They included *Pseudomonas aeruginosa* (14.28%), *Acinetobacter baumannii* (19.04%) and *Klebsiella pneumonia* (5.71%) whereas all *S. aureus* were methicillin-sensitive.

Conclusion: The local bacterial pathogens isolates displayed high levels of antibiotic resistance. Enteric GNB naturally resistant to Polymyxin E and *Corynebacterium* species are likely to be emerging pathogens. This study significantly highlights the need to take into account these potentially drug-resistant isolates when making empiric antibiotic treatment.

Keywords: Ventilator-associated pneumonia (VAP); Antimicrobial resistance; Nosocomial infections

Background

Ventilator-associated pneumonia (VAP) is a very common type of infection in intensive care unit (ICU) patients [1]. Late onset VAP is defined as VAP developing ≥ 5 days of mechanical ventilation. It is caused by multidrug-resistant (MDR) pathogens, and is associated with increased morbidity and mortality [2,3].

VAP could be considered a form of aspiration (gravity) pneumonia in intubated patients. Indeed, pooled secretions present in the sub-glottic area above inflated endotracheal tube cuff may be aspirated into the lower airways [4]. The international nosocomial infection control consortium (INICC) data suggests a VAP incidence as high as 13.6/1000 mechanical ventilation (MV) days [1]. In developing countries, the rates of VAP infections varied from 10 to 41.7/1000 MV-days, and were generally higher than NHSN benchmark rates [5].

In Morocco, the incidence of VAP in a tertiary medical ICU of Rabat was 43.2 per 1,000 ventilator-days [6] and the prevalence was found to be 71.4 % to 93% [7,8].

VAP are associated with mortality rates ranging between 20% and 70% that can be even more important when VAP are caused by multiple drug-resistant pathogens or when the first antibiotic is inadequate [9-11]. It is also linked with extended ICU and hospital stay, delay in recovery, and augmented health care expenses [12-14].

Many studies investigated the risk factors for VAP infections and found that the male sex, elderly age, higher APACHE II scores, prolonged antibiotic usage, immunosupression, reintubation, etc… are the most common ones [15].

Because of the grave consequences of VAP, its prevention has gained the attention of policy makers for developing patients' safety plans [9,16].

The Institute for Healthcare Improvement (IHI) [17,18] has promoted VAP prevention and safety of patients on mechanical

ventilation by implementing a set of interventions known as the 'ventilator bundle' [19]. This bundle includes four components: (1) elevation of the head of the bed to between 30 and 45 degrees, (2) daily interruption of sedation and daily assessment of readiness to extubate, (3) peptic ulcer disease prophylaxis, and (4) deep vein thrombosis prophylaxis. Others reports added to these approaches: staff education programs and implementation of hand hygiene [5] and showed that the VAP rate can be reduced significantly by applying theses preventive measures [20-23].

The VAP causative agents varies according to the population of patients in the ICU, the durations of hospital and ICU stays, and the specific diagnostic method(s) used [5,24-28]. *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Enterobacteriaceae* producing extended-spectrum beta-lactamase (ESBL) and methicillin-resistant *Staphylococcus aureus* (MRSA) are the species most frequently isolated [24,29,30]. In developping countries, Gram-negative bacilli were responsible for the majority of VAP episodes (41-92%) followed by Gram-positive cocci (6-58%) [31-35].

In Morocco, most studies reported the ecology of VAP including both early and late ones (the latter representing 55 to 66% of cases). Bacteriological profile in these studies was dominated by BGN (48,3-68,3%), *Staphylococcus* (21,2-5,5%) and *Enterobacteriaceae* (10,7-15%) with predominance of multidrug resistance especially for BGN [36,37].

The aim of this study is to describe the bacterial ecology and resistance profile of late VAP in a tertiary ICU in Morocco in order to adapt the empirical antibiotic therapy of late VAP and to prevent the emergence of MDRB.

Methods

This retrospective and descriptive study was conducted between April 2012 and April 2013 at the bacteriology laboratory of Mohammed V Military Instruction Hospital in Rabat. This hospital contains 700 beds capacity with a medical and a surgical care unit of 12 beds each. We included all pulmonary origin samples of intensive care units hospitalized patients who developed later VAP (occurring five days after ventilation [2,3]. VAP was defined according to CDC criteria [3]: a new and persistent infiltration present for more than 48 hours on a chest radiograph, plus two or more of the following: 1) fever of more than 38°C or less than 36°C; 2) leukocytosis of more than 10,000 or leucopenia of less than 5,000 cells/mL; 3) purulent tracheobronchial secretion; and 4) gas exchange degradation. Positive microbiological culture confirmation was also required [38].

Samples were collected by endotracheal aspiration (EA), bronchial aspiration (BA) and protected distal samples or broncho-alveolar washing. They were treated and interpreted according to REMIC recommendations [39], with a quantitative culture threshold of AET ≥ 10^5 CFU/ml. The antibiotic sensitivity tests were performed and interpreted according to CA SFM [40]. Multidrug resistant bacteria included meticillino resistant *Staphylococcus aureus* (MRSA), *Enterobacteriaceae* producing extended-spectrum beta-lactamases (ESBLs) and/or hyper-produced cephalosporinases (HCP) and/or carbapenemase (Carb), non-fermenting negative gram bacilli resistant to third generation cephalosporins or imipenem [29,41]. The microbiological data extraction was performed using the expert system module (OSIRIS® software Biorad, French).

Results

During the study period, we collected 215 significant culture samples with 210 isolates; 112 (53.33%) from the medical intensive care unit and 98 (46.66%) from the surgical one. The Gram negative bacilli represented 81.42% of isolates while Gram positive cocci and Gram positive bacilli are less represented with a rate of 11.42% and 7.14% respectively. Non-lactose fermenting Gram negative bacilli made up the half of pathogens with 55.23% and the frequency of enteric bacilli was 26.19% of all isolates (Table 1).

Famille	Espece	Nombre N	Percentage (%)
BGN non Fermentant 116 (55.23%)	*Pseudomonas aeruginosa*	60	28.57
	Acinetobacter baumannii	52	24.76
	stenotrphomonas maltophilia	3	1.42
	Achromobacter Xylosoxydans	1	0.47
Enterobacteries 55 (26.19%)	*Klebsiella pneumonia*	17	8.09
	Proteus spp	11	5.23
	Serrratia sp	11	5.23
	Enterobactor sp	7	3.33
	E. Coli	5	2.38
	Providencia sp	4	1.9
Coccia gram positif 24 (11.42%)	*Staphylococcus aureus*	20	9.52
	Staphylococcus pneumoniae	2	0.95
	Staphylococcus CN	1	0.47
	Enterococcus faecalis	1	0.47
Bacilles a gram positif 15 (7.14%)	*Corynebacterium striatum*	8	3.8
	Corynebacterium sp	7	3.33

Table 1: Distribution of bacteria species isolated (n=210).

Bacteria	Our study n=210	Erden et al. n=327	Kollef et al. n=499	Chastre et al. n=2490
P. Aeruginosa	28.60%	23.20%	21.20%	24.40%
A.baumanii	24.70%	37.00%	3.00%	7.90%
K.pneumoniae	8.10%	1.20%	8.40%	-
S.aureus	9.50%	27.80%	42.50%	20.40%
Corynebacterium	7.14%	-	22.90%	-

Table 2: Frequency of principal's species based on studies.

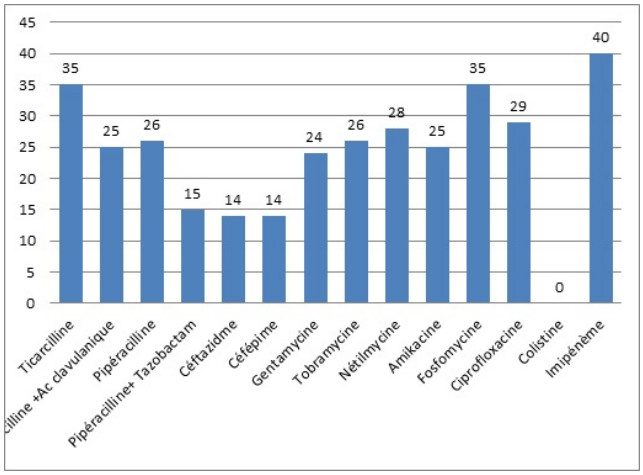

Figure 1: Resistance rates (R+I)* of *P. aeruginosa* isolates (n=60).

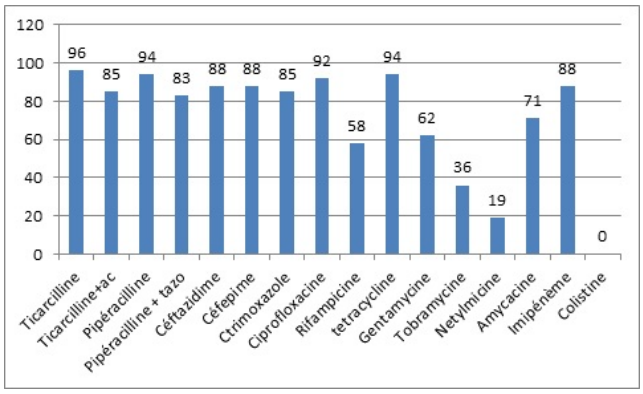

Figure 2: Resistance rates (R+I) of *A. baumannii* isolates (n=52).

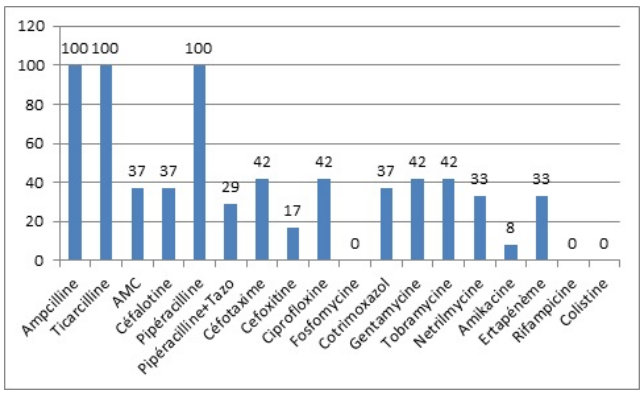

Figure 3: Resistance rates (R+I) of *K. pneumonia* isolates (n=17).

Pseudomonas aeruginosa were the most isolates with the rate of 28.57%, followed by *Acinetobacter Baumannii* (24.76%), *Staphylococcus aureus* (9.52%) and *Klebsiella pneumonia* with the rate of 8.09% (Table 2). The *corynebacteria* represented 7.14% of all isolates with a resistance rate of 7.10%.

Antimicrobial susceptibility profiles of *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* showed a high level of multidrug resistance up to 39.52% (Table 3) especially for *Acinetobacter baumannii*, *Pseudomonas aeruginosa* (Figures 1-3). They included imipenem-resistant *Pseudomonas aeruginosa* strains (14.28%), *Acinetobacter baumannii* carbapenem-resistant strains (19.04%) and ESBL and carbapenem-resistant *Klebsiella pneumonia* strains (5.71%). All *S. aureus* isolates were sensitive to methicillin and glycopeptides.

Species	ESBL(n)	OEC(n)	Carb(n)	Imper(n)	%MDR
P.aeruginosa (n=60)	0	4	3	23	14.28
A. baumannii (n=52)	0	1	40	0	19.52
K. pneumoniae (n=17)	6	0	6	0	5.71

MDR: Bacteria multiple drug resistance, ESBL: Extended-Spectrum Beta-lactamase,

OEC: overexpressed cephalosporinase, Carb: carbapenemase. Imper: impermeability.

Table 3: Betalactams Resistance profile of the main bacteria isolated.

Other species isolated were represented by *Proteus*, *Providencia* and *Serratia* that all accounted for 12.36% of all isolates and *Corynebacteria* with a rate of 7.14%.

Discussion

In our study, the late VAP bacterial epidemiology is dominated by Gram-negative bacilli with 81.42%. The Gram-negative, non-fermenting bacteria accounted for 67.83% and the enterobacteria for 32.16%. This dominance could be explained by the VAP physiopathology; lung contamination being due in one hand by modified endogenous flora of oropharynx and gastric fluid, mainly represented by enteric Gram-negative bacteria and *Pseudomonas aeruginosa* [42-44] and in the second hand, by exogenous flora from respiratory instruments or aerosols [3,42-45].

Pseudomonas aeruginosa, *Acinetobacter baumannii*, *Klebsiella pneumoniae* and *Staphylococcus aureus* are the predominating species. They are usually isolated in nosocomial infections, particularly in intensive care units [46]. However, the frequency of these species is very variable depending on regions, the structure and intensive care unit types [24,42,46,47].

The overall MDRB rate of late VAP in our study is very high (39.52%), but it is still inferior to that of other series namely in Greece [48] and in Brazil with a rates of 50% and 59% respectively [29]. The MDRB are represented first by Carbapenemase-producing *A. baumannii* isolates with the rate of 76.92% that remained only sensitive to polymyxin E, tobramycin and netilmicin (Figure 2). The imipenem *P. aeruginosa* resistance rate is 38.33% in our study with impermeability more prevailing than carbapenemases (Figure 1).

This resistance profile lead in most of case, to using polymixine E (colistine) as the only efficient drug given by parenteral route and by aerosol to the MDRB infections especially *Acinetobacter* and *Enterobacteriaceae* producing carbapenemases [49-52]. Therefore, we

recorded an increase incidence of bacterial species that are naturally resistant to polymyxin E (Proteus, Providencia, Serratia and *Corynebacteria* especially, multi-resistant one: *Corynebacterium striatum*). These results are in line with their reported increasing responsibility for VAP [46] and are a risk factor for inducing resistance to colistin in particular in case of its inadequate and inappropriate use as confirmed by other authors [49,50]. This resistance, non-noted in our region, appeared at the beginning of the century and is due to a modification of the lipid A of the bacterial plasma membrane and the presence of an efflux [53,54].

S. aureus accounted for only 9.52% of the isolates in our work, in contrast to other studies where it occupies the first place in Kollef et al. study [55] and the second place after *A. baumannii* in Erdem et al. one [56]. This low *S. aureus* rate is probably multifactorial including low nasal carriage in our context [57].

The frequency by species of ESBL *Klebsiella pneumoniae* isolates and carbapenemase *Klebsiella pneumoniae* isolates (35.29%) was higher than that found by some authors [29,41,58]. The emergence of these MDRB are attributable to multiple proven risk factors that include stay duration more than 5 days, recent antibiotic use, previous hospitalization, the frequency of these bacteria in intensive care units [46], and the empirical broad-spectrum antibiotics [29].

Conclusion

The late VAP is caused in most of cases, by BGN especially non-fermenting ones followed by Enterobacteria and in third rank gram positive bacteria. These species are most often multidrug resistant bacteria. This ecology indicates prescription of second line antimicrobial drug and especially colistine for *Acinetobacter baumannii* and *P. Aeruginosa* which expose to the emergence of naturally resistant species to this drug and some gram-positive bacteria. Hence, we recommend urgent implementation of efficient preventive actions, of note VAP bundles that had been proven to reduce the incidence of VAP.

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Ethics Approval and Consent to Participate

The study was approved by the ethic committee of faculty of Medicine and Pharmacy of Rabat, Morocco. In intensive care units, Patients families signed systematically a written consent for all the samples needed for intensive care and the possible use of the results (with respect of anonymity) for scientific purposes.

Consent to Publish

All the authors approve this paper publication in your journal.

Potential Conflicts of Interest

All authors report no conflicts of interest relevant to this article.

Authors Contributions

FM, LA, EM conceived of the Study conception and design: AN, MA participated in Data acquisition. FM, LA, MA performed analysis and interpretation of data. FM, LA: participated in drafting the manuscript. FM, EM had been involved in Critical revision of the manuscript for important intellectual content. AN performed statistical analysis. FM, LA, AN, MA and EM have given final approval of this version to be published.

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