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Ventilator-associated pneumonia: The central role of transcolonization

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ABSTRACT

Ventilator-associated pneumonia remain frequent and serious diseases since they are associated with considerable crude mortality. Pathophysiology is centered on modifications of regional bacterial flora, especially tracheobronchial tree and oropharyngeal sphere. Bacterial migration from an anatomical area to another seems to be the main explanation of these alterations which are called "transcolonization". The association of transcolonization and lack of tightness of the endotracheal tube cuff provides a direct pathway for bacteria from the upper to the subglottic airways, eventually leading to ventilator-associated pneumonia.
Although modification of bacterial flora has been largely studied, the mechanism which underlays the ability of the implantation, growing and interactions with the local microbiome that leads to the observed transcolonization remains to be more clearly deciphered.
The aim of our review is to emphasize the cornerstone importance of the "transcolonization" as a nosological entity playing a central role in ventilator-associated pneumonia.

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1. Introduction

Despite recent progress in the understanding of physiopathological mechanisms responsible of the occurrence of ventilator-associated pneumonia (VAP), and setting up of preventive measures set up over time to reduce their incidence, VAP remain the leading cause of nosocomial infection. The entanglement of extrinsic parameters, centered on the presence of the tracheal tube, and regional bacterial flora modifications, both favor the occurrence of VAP during ICU stay, resulting in a tremendous and worrying persistent mortality.

2. Methodology

We did a literature search on Pubmed database to identify articles reporting research about oral, oropharyngeal, tracheobronchial and gastric modification of bacterial colonization during ICU stay. Search terms were identified from relevant research and reviews on this subject notably about "transcolonization". Three of the authors (RS, CS, FP) selected most relevant articles to be cited.

3. Definitions and epidemiology

Lower respiratory tract infections represent the leading cause of nosocomial infections in ICU [1,2]. They can be distinguished according to the presence or absence of invasive mechanical ventilation at the time of their occurrence. Endotracheal intubation seems to increase the risk of pneumonia by more than tenfold [3]. Among pneumonia occurring after intubation, ventilator-associated pneumonia are defined as infections occurring after at least 48 h of mechanical ventilation [4]. More recently, new definitions have been suggested to delineate better clinical events occurring at the bedside [5]. Usual clinical data remain central in the pneumonia definition, stating that microbiological confirmation of the infectious cause of lung aggression is essential [6,7].

Incidence of VAP is about 10 to 25‰ days of mechanical ventilation and can reach more than 50‰ days of mechanical ventilation [8], affecting between 8 to more than 40% of ventilated patients [4,9]. However, incidence varies with the duration of mechanical ventilation, from 5% (for brief duration ventialtion) to two-thirds of the patients (in case of prolonged ventilation). In the more severe situations, frequency can

Abbreviations: VAP, Ventilator-associated pneumonia; ICU, Intensive care medicine.

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even reach more than 70% of patients with acute respiratory distress syndrome. Lastly, the risk of recurrence during the same hospital stay is also higher than 25% [10].

4. Morbidity and mortality

The occurrence of a respiratory infection is associated with significant morbidity [11] which increases duration of mechanical ventilation and hospitalization [4]. VAP are also associated with considerable crude mortality, ranging from one to three quarters of patients depending on studies [4,12]. On the other hand, this mortality seems to be lower among early infections [9]. Although mortality is especially high among patients receiving ineffective initial antibiotic therapy [13-15]. Nonetheless, VAP attributable mortality is much lower, and seems to be close to zero for a large proportion of patients (medical, trauma, patients with very high or low severity scores) and may rise to about 4.4% in another study [16,17]. These observations highlight the importance of patients own history in the dramatic evolution of this infection [16,17]. Actually, the discrepancy between crude and attributable mortality raises the question of the infection's accountability in patient's death: risk factors of pneumonia could also be markers of frailty, with a high mortality rate regardless of an actual pneumonia occurrence during the stay.

5. VAP pathophysiology: central role of transcolonization

A better understanding of the underlying mechanisms leading to VAP is necessary to prevent such infection and potentially reduce their associated mortality.

Many parameters contribute to the occurrence of a respiratory infectious episode during invasive mechanical ventilation, which can be distinguished according to the anatomical region of interest. Considering this model, systemic and regional issues can be distinguished. Systemic modification represented by immunological disturbances related to the severity of infection are leading either to sepsis or septic shock [16,18-20], and their precise description is beyond the scope of this review. On the other hand, regional pathophysiological factors underlying the occurrence of VAP are centered on the changes occurring within oropharyngeal cavity [11,23-26], consequences of a broad spectrum of modifications, that can be called transcolonization [21,22].

Transcolonization can be defined as a whole microbiological modifications observed within oropharyngeal and tracheobronchial area, leading to an increase risk of respiratory tract infection. Two steps are classically described, first an oral, oropharyngeal, gastric and oesophageal microbiological alteration, and in a second time these alteration are associated by inhalation of microorganisms through the endotracheal tube [11,27-32]. These mechanisms are synthetized in Fig. 1 and in Table 1.

5.1. Transcolonization: oropharyngeal region

Transcolonization has been extensively studied between the 1960s and the 80s [22,33]. Although some arguments remain indirect [21,33-36], numerous studies conducted in intensive care units had confirmed the oropharyngeal flora's modification during ICU stay [26,37-39].

Bacterial flora initially present in the oral cavity is gradually replaced with bacteria usually found in the lower digestive tract (Fig. 2a) [25,34,40-42]. These modifications are particularly noticeable in case of mechanical ventilation, since then oropharyngeal flora is usually modified within the hours following the placement of endotracheal tube [22,24,25,34,39,43].

This observed increase Gram-negative bacteria in the upper airways is not explained by the administration of locoregional treatment, such as antiseptics, or by the sole use of either local or systemic antibiotic therapy [34,44], but seems to be largely due to the migration of bacteria from an area to another.

5.2. Transcolonization: communication from stomach to oropharyngeal region

The first descriptions of the upper airways flora modification reported that a large proportion of the Gram-negative bacilli observed within oropharyngeal region were previously identified in the most distal part of the digestive tract [33,45,46] (Fig. 1; Fig. 2b) that leads to the

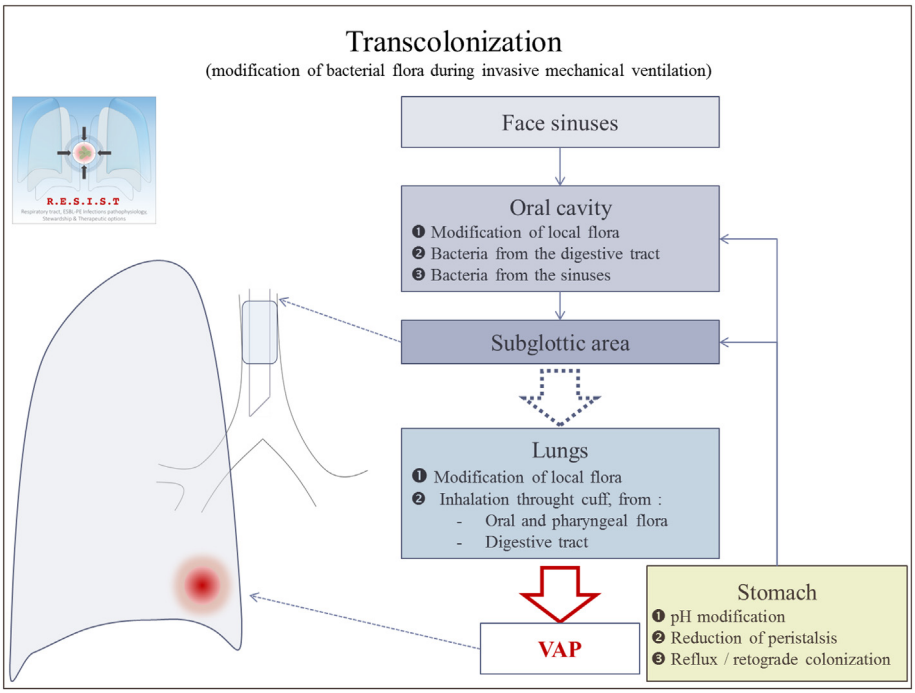

Fig. 1. Transcolonisation. Transcolonization can be defined by the progressive modification of local oropharyngeal and upper digestive (gastric and oesophageal) microbial normal flora, secondary associated with lower airways (tracheal and bronchial) colonization. Kinetic of contamination of one local flora by microbe from the other one is variable.

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Table 1
Main bacterial oropharyngeal and tracheobronchial colonization kinetic studies.

Reference	First author	Prospective/retrospective study	Number of involved centers	Number of included patients	Microbiological study			
					Sites studied	Starting date	Frequency	Length of study
23	Berthelot P	Prospective	Bicentric	59	Stool Stomach Throat Tracheal aspirates	After inclusion	Twice a week	Until the patient was extubated (or until death)
24	Drakulovic MB	Prospective	Monocentric	55	Endotracheal aspirates, gastric juice, and pharyngeal and rectal swabs	within the first 24 h of admission	Once	One day
25	Ewig	Prospective	Monocentric	48	Culture of nasal and pharyngeal sabs, tracheobronchial aspirates and gastric juice.	At ICU admission (and tracheal intubation)	Every day from D1 to D4 and then every 3 days	until the patient was extubated or ventilator-associated pneumonia
26	Bonten M	Prospective	Monocentric	141	Tracheal aspirates, oropharyngeal swab, gastric juice	At ICU admission	Twice a week	
34	Johanson WG	Prospective	Monocentric	213	oropharynx (sampling device and secondary swab) Tracheal aspirates	day 5	once a week	–
35	Berdal J-E	Prospective	Monocentric	74 (second sample 47)	Oropharyngeal swab Tracheal succion sample Bronchoalveolar lavage	Within 48 h	Every 72 h	until the patient was extubated
37	Feldman C	Prospective	Monocentric	10	Oropharyngeal swab Gastric juice Endotracheal aspirates	Admission	Every day until day five	5 days
38	de Latorre FJ	Prospective	Monocentric	80	Oropharyngeal swab Gastric juice Endotracheal aspirates	first 24 h of tracheal intubation	every 48 h	for 2 weeks or throughout the mechanical ventilation period
39	Garrouste-Orgeas M	Prospective	Monocentric	86	oropharyngeal and gastric samples	Admission or within 48 h	Twice a week	until the patient was extubated
40	du Moulin GC	Prospective	Monocentric	60	Tracheal aspirates Gastric aspirates	–	Everyday	–
42	Cardeñosa Cendrero JA	Prospective	Monocentric	123	Tracheal, pharyngeal, and gastric samples		Everyday	until the patient was extubated
45	Atherton ST	Prospective	Monocentric	10	Nose Pharynx Trachea Stomac Faeces	Admission	Everyday	–
46	Driks MR	Prospective	Monocentric	Analysis of the first 52 patient in a study including 130 about antiacid treatments	Sputum samples Gastric aspirates Oropharyngeal swab	After randomization	Everyday	5 days
50	Inglis TJ	Prospective	Monocentric	100	Gastric content Tracheal aspirates	Admission	Estomac/8 h Trachée/2j	–

hypothesis that these bacteria came from stomach. These observations were consistent with the described kinetics of initial bacterial colonization of the gastric content and secondarily of the oral and pharyngeal region [11,22,33,34,37,39,43], including qualitative (reduction of Gram positive cocci in favor of *Enterobacteriaceae* and *Pseudomonas aeruginosa*) [42] and quantitative modifications.

What is worthy is that beyond the oral and pharyngeal secretions, part of the gastric contents can even reach the lower, tracheal and bronchial airways, as it has been nicely demonstrated in various ways. First by the findings of digestive fluid in the airways [22,47] (Fig. 1; Fig. 2b). Second by the migration of radiolabeled elements [22,48]. More recently Saad Nseir's team had highlighted the presence of pepsin in the tracheal aspirations of ventilated patients [49]. At last by the chronology of Gram-negative bacteria colonization in the different regional sites [22,23,26,50].

Theses ecological modifications are prompted by many factors that promote communication between the stomach and the upper aerodigestive tract. This includes the patient's posture (in supine position) [48,51-54] especially in combination with enteral nutrition [52-54], thoracic and abdominal pressure regimen, and treatments reducing lower esophageal sphincter tonus and the presence of a gastric tube [43,55]. Other factors have also been demonstrated to be associated with the risk of tracheal colonization following gastric colonization, such as the notion of corticosteroid therapy or diabetes [42]. All these parameters will benefit the occurrence of gastroesophageal reflux [11,43] which in turn allows colonization of the oral cavity by the digestive tract, and eventually, the aspiration of gastric fluid [21,22,48,49].

Effectiveness of the oral cavity and pharyngeal area invasion by digestive bacteria is favored by intragastric proliferation. Such bacterial multiplication is underlaid by two main mechanisms. First, the reduction of digestive motility, mainly the peristalsis of the proximal small intestine, contributes to favor the retrograde colonization of the stomach [22]. At the same time, numerous events lead to an increase the gastric pH, including continuous enteral nutrition, the presence of bilirubin in the gastric cavity or the use of drugs to reduce gastric acidity production [22,55]. These modifications could make the local environment more

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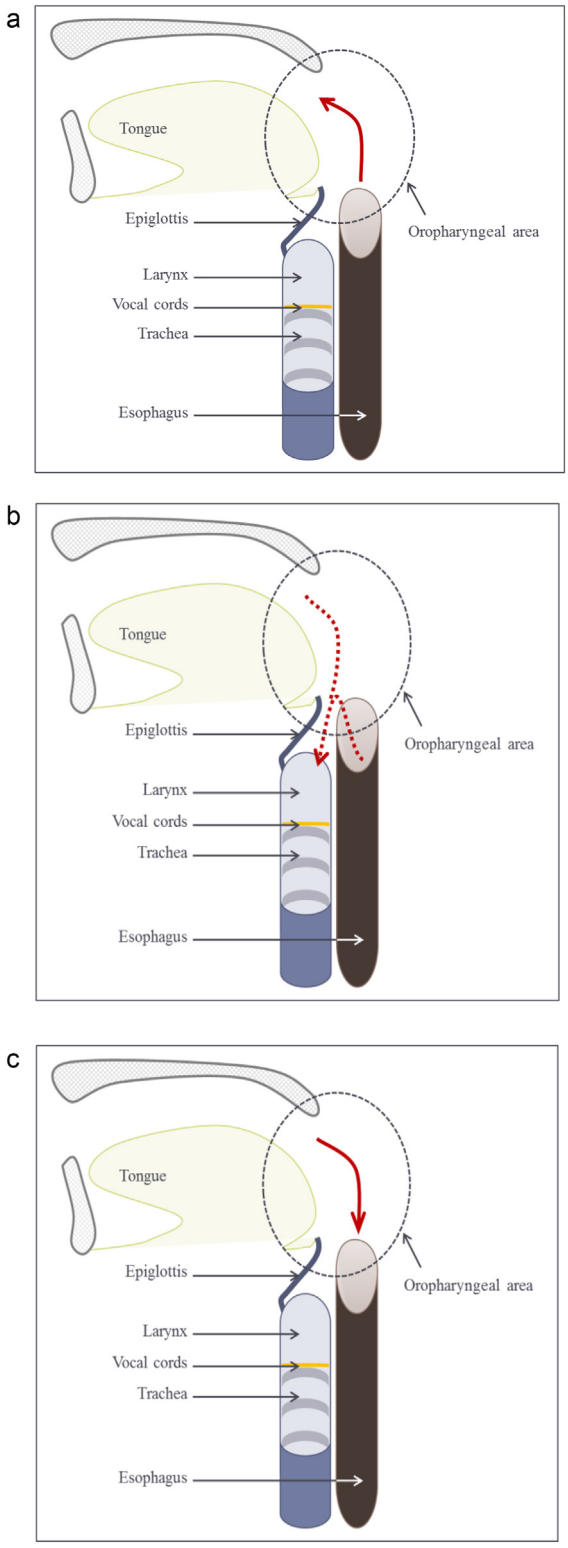

Fig. 2. a. modification of oropharyngeal flora. During hospital stay and notably during mechanical ventilation the oropharyngeal flora of patients is modified from usual and normal flora to an increase in digestive tract (mainly gastric) one with large predominance of *Enterobacteriaceae* [25,34,40-42]. Sequential studies have shown this progressive colonization of oropharyngeal region with gastric bacteria [22,24,25,34,39,43]. b. Communication from stomach and oropharyngeal region to tracheobronchial region. During mechanical ventilation an most broadly during ICU admission, Inhalation of bacteria, particularly Gram-negative bacilli, is a definite component of tracheal colonization [23,24,34,38,60]. c. Communication from oropharyngeal region to stomach. Modification of bacterial flora may appears to start within oropharyngeal region and secondary spread to the stomach [22,26,37,39].

propitious to bacterial survival and growth, especially for Gram-negative bacteria [21,22,24,40,43,45,46,56,57].

However, it must be remembered, however, that the kinetics of "bottom-up" colonization from the stomach to the oral cavity are not the only pathological ways involved, considering the oral and pharyngeal changes they may precede gastric alteration [37,39,42], and even appear without any gastric colonization being found [39,42]. Although the direct involvement of gastric colonization is questionable [42], the various steps previously described are undisputable. As a result, and by syllogism, the role of the modification of the gastric flora, partial and indirect, may be little debatable [22,46].

5.3. Transcolonization: communication from oropharyngeal region to stomach

Beside this classic way of colonization, other studies have highlighted many situations where modification of bacterial flora appears to start within oropharyngeal region and secondary spreads to the stomach [22,26,37,39] (Fig. 2c). In these latter cases, the modification of the oral flora could be related to a modification of the expression of bacteria already locally present or to the contiguity invasion of contiguity by pharyngeal or nose and sinus bacteria [21,37,42]. The importance of the sinus origin is reinforced by observations showing that sinus infections, favored by the presence of tubes (nasogastric and possibly nasotracheal tube) in the context of intensive cares are associated with an increasing risk of respiratory infection [27,58].

It also seems that one of the elements of interest in the colonization of the oral cavity is the monoclonal nature of the newly implanted bacteria, where the agents usually present are typically polyclonal [35].

5.4. Transcolonization: communication from stomach and oropharyngeal region to tracheobronchial region

The temporality of oral, pharyngeal, and digestive tract bacterial colonization is variable, and depends on the studies and observations. This apparent discrepancy may be based on the microbial agents involved [26,37,38,59], notably the presence of non-fermenting Gram negative bacilli [44] which are usually primarily found in tracheobronchial tree. However, in most situations the changes in the upper airways constitute the initial event, followed by tracheobronchial colonization. Inhalation of bacteria, especially Gram-negative bacilli, is a definite component of tracheal colonization [23,24,34,38,60] (Fig. 2b). Then contamination of lower airways by oral and pharyngeal flora will generate a progressive equilibrium leading to the similarity beteween the bacterial colonizations of both areas [26,35,37,59].

5.5. Transcolonization: role of mechanical ventilation in lower airways bacterial colonization

During invasive mechanical ventilation, the supine position of the patient is favoring the leakage of fluid from the supra-glottal space to the tracheobronchial space [51-53,61] and the whole system of defense and prevention of invasion of the lower airways is disrupted by the outbreak of the tracheal tube and positive pressure ventilation itself [11].

The presence of the endotracheal tube plays a central role in inhalation, first by inhibiting the natural mechanical protective systems constituted by airway closure, then by disrupting the mucociliary clearance [11] and ultimately by favoring the flow of secretions from the upper aerodigestive tract to the subglottic space. All these mechanisms lead to the presence of contaminated secretions from the upper airways and digestive tract to the region above the endotracheal tube cuff [21,43].

Therefore, the contamination of the lower airways is then favored by the loss of sealing between the lower respiratory tract and the area above endotracheal cuff. The lack of tightness of the tracheal tube cuff

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has previously been studied [28]. This inability to prevent the flow of contaminated secretions from the upper airways refers to many factors:

First, shape and thickness of the cuff wall lead to the occurrence of microchannels formed by folds during cuff inflation inside trachea, favored by the difference of diameter in-between cuff and trachea [28,62-65]. This mechanism plays a central role in tracheal contamination [49] but remains insufficient to explain clinical consequences as neither the modification of the cuff shape, using conical cuff, nor modification of material (polyurethane thinner than usual polyvinyl chloride) are sufficient to prevent the occurrence of tracheobronchial colonization [28] or pneumonia [28,66].

Secondly, beside structural alteration, dynamic elements take their part in the physiopathology of tracheal colonization. The variations of endotracheal cuff pressure has understandable role [67] as any pressure drop would be responsible for a lack of sealing favoring the flow of contaminated secretions from upper airways to the lowers ones. This hypothesis has been widely confirmed by flora modification [68], even if the effectiveness of its continuous control remains uncertain [49,67,69].

On the same way, transmitted parietal cuff pressure, during positive pressure ventilation seems to play a similar role. Low positive expiratory pressure level is associated with greater permeability [64,70], while high levels reduce the risk of seepage through the cuff [62-64,68], correlating with the level of PEEP in bench models [63,64,68]. In contrast, inspiratory effort, by creating a depression, is probably an important factor that promotes flow towards tracheobronchial tree [63,68].

Lastly, patients mobilizations, notably during intrahospital transports, is also involved in such aspiration [71] by increasing the risk of tracheal tube displacement during movements. Thereby they favor the flow of liquid accumulated through the tracheal tube cuff towards the lower airways. Other clinical parameters, such as deglutition may play a similar role in the lack of impermeability [65].

All sealing impairments will allow part of the contaminated secretions to invade tracheobronchial tree [28,43], and alveolar spaces [60]. In clinical practice, the presence of former pharyngeal germs in the tracheal area is found in about half of the patients [4], or even more [37] and the presence of gastric germs in about 15% to half of the pneumonia [22,34,36,38,60].

5.6. Transcolonization: cleaning lower airways bacteria

Once the bacteria have invaded lower respiratory tract, cleaning bronchial tree remains physiologically possible by rejecting microbes to the supraglottic region through mucociliary clearance. Unfortunately, during invasive mechanical ventilation, mucociliary transport is impaired [72,73]. First because of the obstacle constituted by the endotracheal tube cuff and second by a disturbance of the ciliary beats whose frequencies, regularities and even directions can change leading to a stasis bronchial secretions, or even to a flow towards the lung [74] thus carrying the contaminated secretions to the alveolar spaces.

6. Is there an involvement of colonization in VAP?

If the accumulation of contaminated secretions above the tracheal tube cuff lead to their dissemination within bronchial tree [75], these mechanisms are still insufficient to explain the occurrence of VAP, as aspiration of oral secretions is physiological [76]. In addition, the presence of bacteria in the lower airways, including distal spaces, is not systematically associated with a regional inflammatory response [21,41,77]. However, tracheobronchial colonization remains an undeniable factor in the occurrence of secondary respiratory infection [22,34,36-38,40,41,52,78], as the presence of pathogens responsible for VAP have previously colonized the tracheobronchial tree in more than 90% of patients in some series [42,60].

Finally, the involvement of bacteria from the upper airways and digestive tract is not systematic like the occurrence of pneumonia without such previous colonization is still possible [26,38,59]. The pathogens can thus be found in the lower airways without having previously been detected in the oropharyngeal region or in the gastric samples [44]. In these situations, the newly implanted flora in the lower airways may be secondarily associated with the emergence of identical bacteria in the upper airways and in the digestive tract [22,26,38]. In the same way, tracheal and bronchial colonization may precedes intubation in a large number of patients, with chronic or non-chronic bronchial disease [26,28,34,38,42,77].

All of these observations underline the importance of a better understanding of the mechanisms involved in transcolonization and the real role played by these modifications in the following ventilator-associated pneumonia.

7. Conclusion

Mechanically ventilated pneumonia remains, despite many measures, the leading cause of nosocomial infection in ICU patients. Modification of the oropharyngeal flora and transcolonization play a central role in the risk of infection. A better understanding of its physiopathology must prevail in the context of the prevention of this infectious risk.

Ethics approval and consent to participate

Not applicable.
All the authors consent for publication

Availability of data and material

Not applicable.

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