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WHAT'S NEW IN INTENSIVE CARE

Ventilator associated tracheobronchitis and pneumonia: one infection with two faces

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Patients admitted to an intensive care unit often require invasive mechanical ventilation (iMV). While iMV is a lifesaving intervention, it is also carrying some risks such as ventilator induced lung injury and the development of ventilator associated lower respiratory tract infections (VA-LRTI) [1]. The latter are clearly associated with a consumption of healthcare resources, namely prolonged use of invasive mechanical ventilation from prolonged weaning and prolonged stays in the intensive care unit (ICU) [2]. More recently, ICU physicians have become aware that nosocomial infections can not only prolong hospital stay but are also associated with worse long term outcomes when compared to community acquired infections [3].

Studies on VA-LRTI have traditionally focussed on ventilator associated pneumonia. An intermediate process is called ventilator associated tracheobronchitis (VAT). This entity has sparked many discussions and it has also been considered a neglected disease in different published manuscripts. VAT and ventilator associated pneumonia (VAP) showed similar microbiology and C-reactive protein and procalcitonin have shown a marked overlap in both VAP and VAP not allowing adequate discrimination [4]. The main concern with VAT has been that this clinical entity has been used to "mask" the true rates of VAP and therefore to decrease the incidence of VAP in some healthcare systems where pneumonia is considered an avoidable complication without any true change in the consumption of antibiotics [5]. Regarding pathophysiology, VAT might represent an intermediate process between colonisation and pneumonia and prevention strategies to VAP applies to VAT [2]. In addition, some ventilated adults might develop high bacterial burdens in their lungs early in their course, but clear the bacterial colonization from their lungs without developing signs of infection in the form of either VAT or VAP. Also after VAP treatment, a positive bacterial growth can remain, however, this just represents a colonization and should not be treated. Pneumonia is not a black or white disease; there is a continuum between colonisation and pneumonia that results from the interplay between host, bacteria and iMV. It is easy to understand that pneumonia starts with a colonised airway and when the local defences are overcome, lung consolidation and alveolar space infection occur [6]. It has been recently reported that VAP represents a temporal period of immunoparalysis and VAT could be used to find the appropriate fit to fix the immunological puzzle [7].

The key question is how often and what is the incidence of VAT across different registries. In the literature, there is high variability when comparing published observational studies [8]. This is probably related to the different definitions that have been proposed by different authors [9]. Definitions would need to strike a balance between specificity and sensitivity, as they do with many other diseases and clinical entities. The authors of this article consider that one confusion factor that led to the reporting of extraordinary high rates in some populations is the lack of microbiological documentation [10]. We are in favour of the use of a proper assessment of the airway through the use of bronchoscopy. This will increase the specificity of the sample to avoid unnecessary antibiotic treatments [11]. An additional layer of complexity is the problems of imaging. The most widely used diagnostic tool has been and likely will be for many years the use of portable chest X-rays. The exclusive difference from VAP is that VAT is a VA-LRTI not affecting the lung parenchyma. It is widely acknowledged that portable X-rays offer poor sensitivity and specificity when compared to computed

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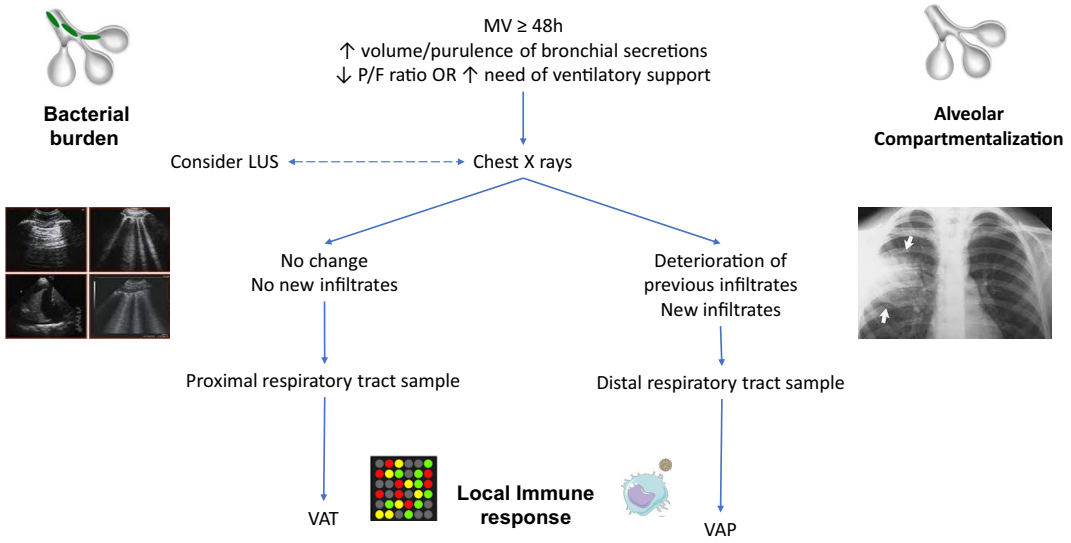

Fig. 1 Ventilator associated lower respiratory tract infections (VA-LRTI). Algorithm or decision-making algorithm on treatment decisions at bedside—including knowledge gaps with interactions of immunity, bacterial burden and impaired local lung immune defences. *VAT* ventilator associated tracheobronchitis, *VAP* ventilator associated pneumonia, *MV* mechanical ventilation, *LUS* lung ultrasound

tomography (CT) scans. As mentioned, a CT scan is considered the gold standard for academic purposes, yet this technique is not without potential complications during the transfer, which have been documented repeatedly. A potential solution that needs further validation is the implementation of lung ultrasound (LUS). This procedure is user friendly, not invasive and can be repeated as many times as it is needed at the bedside. Although LUS is not sufficient to make the diagnosis of VAP, emergence of subpleural consolidations seems to be the earliest sonographic sign, a LUS finding that may prompt the physician to look more actively for VAP symptoms in the following days [12]. Also, incorporation of LUS in scores might help in VAP diagnosis, although further validation is needed. An important limitation for LUS includes high operator variability and a lack of unequivocal consolidation patterns, especially in patients with acute respiratory distress syndrome (ARDS), a condition in which lung architecture is damaged [13] (Fig. 1).

There are some authors that have considered using the term VA-LRTI as it was introduced at the beginning of this manuscript. This is to allow VAT and VAP to be viewed and therefore considered as a paired entity and will allow discussion of definitions to be left behind to focus on the practical management of patients. The two entities will not be treated with the same duration of antibiotic therapy. However, this will allow us to avoid unnecessary delays in diagnosis and treatment that will adversely affect the patient. When physicians utilize VA-LRTI diagnosis strategies, there are conflicting areas that need to be addressed. Perhaps one way is to decrease the antibiotic duration of antibiotics in patients with VAT compared to VAP. A potential randomised trial might be to have different arms with different treatment duration, however, evidence is lacking and studies ongoing will shed light into a definitive action. This is rigorous and valid but we have seen many examples that "one size does not fit all"[14]. The use of short antibiotic administration has been widely considered in patients with community acquired pneumonia showing that is safe and easily implemented. The potential use of short regimens would be ideal for VAT and probably supported with the use of biomarkers to determine treatment duration and favourable infection clearance. Another strategy that could potentially provide good outcomes is the use of nebulised antibiotics. The use of nebulised antibiotics have been considered for almost 20–30 years but recently negative studies in patients with VAP has made to reconsidered that there is a high complexity of such antibiotic administration in patients under iMV. Because different nebulisers, different ventilatory settings and mismatched perfusion ventilation in some lung areas create a huge range of variability and confusion factor in whether nebulise antibiotic techniques are the solution and how to administer them [15].

In summary, VAT and VAP have the same pattern of acquisition, a pathogen that colonises the proximal airways and progresses to deeper airways (VAT) until local defences are overwhelmed and there is alveolar damage and infection at that level (VAP). Using the term

VA-LRTI, we can simplify this pathophysiology puzzle and determine the common cause. A course of 7 to 10 days of antibiotics has been successfully implemented for the treatment of VAP and probably shorter courses and nebulised antibiotics could represent a treatment for VAT. The transition for VAT to VAP is determine by the local defences of the host and not treating this intermediate process exposes the patient to a random risk. We aim for a validated and universal VAT definition where LUS protocols can provide further information about the absence of lung parenchyma infiltrates and therapeutic strategies based on nebulised and short antibiotic courses. VAT is a clinical disease and not an administrative problem in a critically ill patient.

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References

1. Zakharkina T, Martin-Loeches I, Matamoros S, Povoa P, Torres A, Kastelijn JB, Hofstra JJ, de Wever B, de Jong M, Schultz MJ, Sterk PJ, Artigas A, Bos LDJ (2017) The dynamics of the pulmonary microbiome during mechanical ventilation in the intensive care unit and the association with occurrence of pneumonia. Thorax 72:803–810
2. Martin-Loeches I, Povoa P, Rodríguez A, Curcio D, Suarez D, Mira JP, Cordero ML, Lepecq R, Girault C, Candeias C, Seguin P, Paulino C, Messika J, Castro AG, Valles J, Coelho L, Rabello L, Lisboa T, Collins D, Torres A, Salluh J, Nseir S (2015) Incidence and prognosis of ventilator-associated tracheobronchitis (TAVeM): a multicentre, prospective, observational study. Lancet Respir Med 3:859–868
3. Martin-Loeches I, Torres A, Povoa P, Zampieri FG, Salluh J, Nseir S, Ferrer M, Rodriguez A, Martin-Loeches I, Povoa P, Zampieri F, Salluh J, Nseir S, Rodríguez A, Curcio D, Mira JP, Cordero ML, Lepecq R, Girault C, Candeias C, Seguin P, Paulino C, Messika J, Castro AG, Coelho L, Rabello L, Lisboa T, Torres A, Salluh J, Nseir S, Fernández RO, Arroyo J, Gabriela M, Alvarez R, Reyes AT, Dellera C, Molina F, Franco DM, Parada EG, Yepez ES, Oña FP, Tutillo DM, Barahona D, Lerma FA, Álvarez AA, Gallego JM, Morillas FJ, Aguilar AL, Lorenzana ML, Iniesta RS, Almirall J, Albaya A, Santana SR, Fernandez C, Potro MA, Cortes PV, Jimenez B, Sierra R, Del Valle Ortiz M, Cruza N, Olaechea PM, Zirena AC, Gonzalez PP, Gomez TR, Crespi LS, Galleymore PR, Marcos RJ, Palazón C, Rueda BG, Ballesteros JC, Arnilla MP, Socias A, Amador J, Silvero EM, Redín LM, Elson MZ, Pericas LC, Rodríguez JÁ, Nieto M, Torres A, Molinos E, Josefi A, Catorze N, Póvoa P, Candeias C, Coelho L, André P, Ángel M, García G, Ramirez CS, Calizaya M, Estella A, Albis A, Aguilar G, Torrents E, Puente MG, Sanchez AG, Lisboa T, Azambuja P, Knibel MF, Ranzani O, Camargo LD, Junior AP, Ferreira CB, Lobo S, Rabello L, Park M, de Carvalho AG, Valencia M, Castro AG, López AA, Caballero JM, Nseir S, Jaffal K, Parmentier-Decrucq E, Préau S, Rousselin C, Blazejewski C, Masse J, Robriquet L, Satre-Buisson L, Mira JP, Martin N, Lepecq R, Mentec H, Girault C, Marchalot A, Messika J, Ricard JD, Seguin P, Mégarbane B, Valade S, Azoulay E, Boussekey N, Leroy O, Reignier J, Clavel M, Pichon N, Baudry T, Argaud L, Beuret P, Hssain AA, Nyunga M, Alves I, Dewavrin F, Brunin G, Mérat S, Pasquier P, Brun F, Palud A, Voisin B, Grenot R, Van Grunderbeeck N, Thévenin D, Misset B, Philippart F, Frat JP, Coudroy R, Cabaret P, Ledein M, Slimane FZ, Miguel-Montanes R, Weiss N, Bolgert F, Just B, Group TAs (2019) The association of cardiovascular failure with treatment for ventilator-associated lower respiratory tract infection. Intensive Care Med 45:1753–1762
4. Coelho L, Rabello L, Salluh J, Martin-Loeches I, Rodriguez A, Nseir S, Gomes JA, Povoa P (2018) C-reactive protein and procalcitonin profile in ventilator-associated lower respiratory infections. J Crit Care 48:385–389
5. Colombo SM, Palomeque AC, Li Bassi G (2020) The zero-VAP sophistry and controversies surrounding prevention of ventilator-associated pneumonia. Intensive Care Med 46:368–371
6. Keane S, Martin-Loeches I (2019) Host-pathogen interaction during mechanical ventilation: systemic or compartmentalized response? Crit Care 23:134
7. Almansa R, Nogales L, Martín-Fernández M, Batlle M, Villareal E, Rico L, Ortega A, López-Campos G, Andaluz-Ojeda D, Ramírez P, Socias L, Tamayo L, Vallés J, Bermejo-Martín JF, Martín-Loeches I (2018) Transcriptomic depression of immunological synapse as a signature of ventilator-associated pneumonia. Ann Transl Med 6:415
8. Nseir S, Povoa P, Salluh J, Rodriguez A, Martin-Loeches I (2016) Is there a continuum between ventilator-associated tracheobronchitis and ventilator-associated pneumonia? Intensive Care Med 42:1190–1192
9. Craven DE, Hjalmarson KI (2010) Ventilator-associated tracheobronchitis and pneumonia: thinking outside the box. Clin Infect Dis 51:S59–S66
10. Keane S, Vallecoccia MS, Nseir S, Martin-Loeches I (2018) How can we distinguish ventilator-associated tracheobronchitis from pneumonia? Clin Chest Med 39:785–796
11. Martin-Loeches I, Chastre J, Wunderink RG (2023) Bronchoscopy for diagnosis of ventilator-associated pneumonia. Intensive Care Med 49:79–82

12. Bouhemad B, Dransart-Rayé O, Mojoli F, Mongodi S (2018) Lung ultrasound for diagnosis and monitoring of ventilator-associated pneumonia. Ann Transl Med 6:418
13. Wong A, Galarza L, Forni L, De Backer D, Slama M, Cholley B, Mayo P, McLean A, Vieillard-Baron A, Lichtenstein D, Volpicelli G, Arntfield R, Martin-Loeches I, Istrate GM, Duška F, Wong A, Galarza L, Forni L, De Backer D, Slama M, Cholley B, Mayo P, McLean A, Vieillard-Baron A, Lichtenstein D, Volpicelli G, Arntfield R, Martin-Loeches I, Istrate GM, Duška F, on behalf of ECCUG (2020) Recommendations for core critical care ultrasound competencies as a part of specialist training in multidisciplinary intensive care: a framework proposed by the European society of intensive care medicine (ESICM). Crit Care 24:393
14. Martin-Loeches I, Coakley JD, Nseir S (2017) Should we treat ventilator-associated tracheobronchitis with antibiotics? Semin Respir Crit Care Med 38:264–270
15. Ehrmann S, Chastre J, Diot P, Lu Q (2017) Nebulized antibiotics in mechanically ventilated patients: a challenge for translational research from technology to clinical care. Ann Intensive Care 7:78