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Next steps for confirming BAL amylase as a useful biomarker for ventilator-associated pneumonia

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Ventilator-associated pneumonia (VAP) is a common infectious complication in the intensive care unit (ICU) setting, occurring in 10% of mechanically ventilated patients.(1, 2) It is associated with prolonged duration of mechanical ventilation and hospitalization, increased costs, and has an attributable mortality estimated at 13% in a recent meta-analysis.(3, 4)

When VAP is suspected, broad-spectrum antibiotics are started, and cultures are sent for confirmation. If nothing grows on culture, then antibiotics are typically stopped at 48–72 hours. Ruling out VAP earlier, however, could avoid unnecessary antibiotic use(5)—which is increasingly recognized as an important means to preventing antimicrobial resistance. Alpha-amylase levels may help rule in or rule out the diagnosis earlier.

Alpha-amylase originates in the gut and oropharynx, but can end up in the lung if a patient aspirates gastric or oropharyngeal contents. Aspiration is common in critically ill patients, and is strongly associated with developing VAP.(6) Alpha-amylase levels in the lung can serve as a marker of aspiration.(7)

In this issue of *Critical Care Medicine*, Samanta and colleagues performed a prospective observational cohort study of patients with clinically suspected VAP. All patients underwent mini bronchoalveolar lavage (BAL), and lavage fluid was sent for both alpha-amylase level and quantitative culture. The primary hypothesis was that patients with culture-confirmed VAP would have higher levels of alpha-amylase.

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The study enrolled 151 patients from a single tertiary academic medical center, who had a mean APACHE II score of 18. Mini BALs were completed on all patients within 72 hours of intubation, and respiratory culture confirmed the diagnosis of VAP in 65%. As hypothesized, alpha-amylase levels were higher in those patients ultimately confirmed to have VAP. 163 units/L was identified as the alpha-amylase cut-off that best discriminated between patients with and without VAP (as defined by positive BAL culture), and yielded a sensitivity of 73%, and specificity of 69% for VAP diagnosis.

This study is the first prospective evaluation of alpha-amylase as a diagnostic biomarker in patients with clinically suspected VAP. Prior studies have demonstrated that alpha-amylase can be measured in tracheal aspirates of patients with tracheostomies and laryngectomies (8, 9); that alpha-amylase can be used to quantify the magnitude of microaspiration in both pediatric (10) and mechanically ventilated adult patients (11, 12); and, in retrospective data, that patients with VAP have higher levels of alpha-amylase in BAL fluid.(13) This study extends prior research to show that, among prospectively identified patients at high risk for VAP, alpha-amylase levels are strongly associated with VAP diagnosis based on positive culture results. This suggests that alpha-amylase may be a useful biomarker for early VAP diagnosis.

Before alpha-amylase measurement can be recommended for routine practice, however, additional work is needed. The study by Samanta *et al* included 151 patients from a single center (14). Mortality was higher than other studies of VAP with similar APACHE II scores (15, 16). 95% of the pathogens identified were gram-negative, whereas prior epidemiological studies suggest gram-positive organisms typically account for at least 30% of culture isolates.(1) In addition, all patients had early-onset VAP, as mini-BAL samples were collected within 72 hours of intubation. Future studies are needed to confirm these results extend to other patient populations, for example in patients with gram-positive or late-onset VAP.

In addition to confirming external generalizability, it is also important to consider the best way for BAL alpha-amylase to assist clinical decision-making. 163 units/L was identified as the cut-point that optimized both sensitivity and specificity. However, in clinical practice, it may be better to use a cut-point with high sensitivity, such that a low value could confidently exclude VAP, and clinicians could be comfortable withholding antibiotics. The incremental benefit of alpha-amylase over clinical factors must also be confirmed, as this study and prior studies show that alpha-amylase level is strongly correlated with clinical risk factors for aspiration.(13) Finally, the selected threshold should be evaluated in a separate population of patients because biomarker performance (e.g. sensitivity) is overly-optimistic when tested on the same patients who were used to determine the cut-point.(17)

In conclusion, alpha-amylase is a readily measured biomarker in BAL fluid that may be able to rule out VAP several days before culture results are available. VAP remains a significant cause of morbidity and mortality in the ICU setting, and there is increasing pressure to minimize unnecessary antibiotic exposure. Current guidelines from the Infectious Diseases Society of America recommend using clinical criteria alone when deciding to initiate

antibiotics.(18) However, alpha-amylase is a promising biomarker that may prove to be a useful adjunct to clinical criteria and facilitate antimicrobial stewardship efforts.

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References

1. Kalanuria AA, Ziai W, Mirski M. Ventilator-associated pneumonia in the ICU. *Crit Care*. 2014; 18(2):208. [PubMed: 25029020]
2. Wang Y, Eldridge N, Metersky ML, Verzier NR, Meehan TP, Pandolfi MM, et al. National trends in patient safety for four common conditions, 2005–2011. *N Engl J Med*. 2014; 370(4):341–51. [PubMed: 24450892]
3. Melsen WG, Rovers MM, Groenwold RH, Bergmans DC, Camus C, Bauer TT, et al. Attributable mortality of ventilator-associated pneumonia: a meta-analysis of individual patient data from randomised prevention studies. *Lancet Infect Dis*. 2013; 13(8):665–71. [PubMed: 23622939]
4. Kollef MH, Hamilton CW, Ernst FR. Economic impact of ventilator-associated pneumonia in a large matched cohort. *Infect Control Hosp Epidemiol*. 2012; 33(3):250–6. [PubMed: 22314062]
5. Yu VL, Singh N. Excessive antimicrobial usage causes measurable harm to patients with suspected ventilator-associated pneumonia. *Intensive Care Med*. 2004; 30(5):735–8. [PubMed: 14991088]
6. Metheny NA, Clouse RE, Chang YH, Stewart BJ, Oliver DA, Kollef MH. Tracheobronchial aspiration of gastric contents in critically ill tube-fed patients: frequency, outcomes, and risk factors. *Crit Care Med*. 2006; 34(4):1007–15. [PubMed: 16484901]
7. Bai C, Liu J, Song Y. Amylase in bronchoalveolar lavage fluid: a new marker for pulmonary aspiration. *Crit Care Med*. 2013; 41(3):916–7. [PubMed: 23425826]
8. Nandapalan V, McIlwain JC, England J. Amylase activity in tracheobronchial secretions of laryngectomized patients. *J Laryngol Otol*. 1995; 109(7):637–9. [PubMed: 7561471]
9. Nandapalan V, McIlwain JC, Hamilton J. A study of alpha-amylase activity in tracheobronchial secretions of seriously ill patients with tracheostomies. *J Laryngol Otol*. 1995; 109(7):640–3. [PubMed: 7561472]
10. Abu-Hasan M, Elmallah M, Neal D, Brookes J. Salivary Amylase Level in Bronchoalveolar Fluid as a Marker of Chronic Pulmonary Aspiration in Children. *Pediatr Allergy Immunol Pulmonol*. 2014; 27(3):115–9. [PubMed: 26697264]
11. Dewavrin F, Zerimech F, Boyer A, Maboudou P, Balduyck M, Duhamel A, et al. Accuracy of alpha amylase in diagnosing microaspiration in intubated critically-ill patients. *PloS One*. 2014; 9(6):e90851. [PubMed: 24603906]
12. Filloux B, Bedel A, Nseir S, Mathiaux J, Amadeo B, Clouzeau B, et al. Tracheal amylase dosage as a marker for microaspiration: a pilot study. *Minerva Anesthesiol*. 2013; 79(9):1003–10. [PubMed: 23652170]
13. Weiss CH, Moazed F, DiBardino D, Swaroop M, Wunderink RG. Bronchoalveolar lavage amylase is associated with risk factors for aspiration and predicts bacterial pneumonia. *Crit Care Med*. 2013; 41(3):765–73. [PubMed: 23314582]
14. Samanta S, Poddar B, Azim A, et al. Significance of mini bronchoalveolar lavage fluid amylase level in ventilator associated pneumonia: a prospective observational study. *Crit Care Med*. 2017 in press.
15. Mirsaeidi M, Peyrani P, Ramirez JA. Predicting mortality in patients with ventilator-associated pneumonia: The APACHE II score versus the new IBMP-10 score. *Clin Infect Dis*. 2009; 49(1): 72–7. [PubMed: 19480582]
16. Zhou XY, Ben SQ, Chen HL, Ni SS. A comparison of APACHE II and CPIS scores for the prediction of 30-day mortality in patients with ventilator-associated pneumonia. *Int J Infect Dis*. 2015; 30:144–7. [PubMed: 25461659]

17. Altman DG, Vergouwe Y, Royston P, Moons KG. Prognosis and prognostic research: validating a prognostic model. *BMJ*. 2009; 338:b605. [PubMed: 19477892]
18. Kalil AC, Metersky ML, Klompas M, Muscedere J, Sweeney DA, Palmer LB, et al. Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. *Clin Infect Dis*. 2016; 63(5):e61–e111. [PubMed: 27418577]