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Is α -Amylase an Important Biomarker to Detect Aspiration of Oral Secretions in Ventilated Patients?

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Abstract: Alpha-amylase has emerged as a biomarker of interest in detecting aspiration of oral secretions. In several studies, most ventilated patients have α -amylase values detected in pulmonary secretions. Values of α -amylase are high (as expected) in oral secretions and lowest in bronchoalveolar lavage samples. Around 5–7% of oral α -amylase is detectable in tracheal secretions. Once secretions are aspirated, the duration of detection of α -amylase in pulmonary secretions is unknown. Evidence varies on the relationship between α -amylase and clinical outcomes. Although detection of α -amylase in pulmonary secretions is useful to identify that aspiration has occurred, the lack of standardized reference values, the lack of knowledge regarding duration of detection following aspiration, and mixed findings related to clinical outcomes, limit its usefulness as a measurement tool. If α -amylase is to be used in research and/or clinical practice, additional data are needed to assist in interpretation and application of findings.

Key Words: alpha-amylase; aspiration; biomarkers; infection; intubation; mechanical ventilation

Aspiration of oral and gastric secretions is a well-known complication of intubation and mechanical ventilation. Aspiration can lead to complications, such as ventilator-associated pneumonia (VAP), pneumonitis, and other aspiration syndromes (1–4). Colonization of oropharyngeal secretions that accumulate above the cuff of the endotracheal tube (ETT), and bacterial translocation from the stomach contribute to the pathogenesis of VAP and pulmonary complications associated with aspiration (5, 6).

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It is challenging to accurately detect when aspiration occurs, source of aspiration (oral or gastric), and the degree of aspiration. Detection of pepsin in tracheal or bronchoalveolar lavage (BAL) secretions is often considered the gold standard for identifying aspiration of gastric secretions (7, 8). Researchers have assessed levels of salivary (alpha) amylase in pulmonary secretions to detect aspiration of oral secretions. Alpha-amylase is a digestive enzyme that is present in saliva. If oral secretions are aspirated, α -amylase should be detectable in pulmonary secretions, but data related to interpretation of α -amylase values are limited. This brief article summarizes what is known about α -amylase values and discusses issues associated with its use as a biomarker for detection of aspiration of oral secretions.

ALPHA-AMYLASE VALUES FOR DIFFERENT SPECIMEN SOURCES

Alpha-amylase values are highest in the mouth (normal expected finding) and decrease depending on proximity of sample collection from the mouth. **Table 1** compares α -amylase values reported for oral, subglottic, tracheal, and BAL specimens. Because of extremes in values, median levels provide more meaningful comparative data. Median values for “oral” samples ranged between 195,029 to 307,606 U/L (9, 10). “Subglottic” secretions were assessed in only one study, and the median α -amylase value was 130,750 U/L (9). Median values of α -amylase in “tracheal” secretions varied widely from 0 in a small pilot study to over 22,000 U/L in patients with documented aspiration or VAP (10, 11, 15). Median values for “BAL” specimens ranged from 134 U/L to 927 U/L; a mean value of 1,722 U/L was reported in those at high risk for aspiration (17–20).

It has been suggested that the ratio of tracheal values to oral α -amylase values (T/O ratio) is an indicator of the degree of aspiration (9). T/O ratios in recent studies have ranged from 0.055 (5.5%) in a sample of 26 patients to 0.07 (7.0%) in a sample of 410 patients (9, 16). Although one study showed a higher rate of pulmonary infection in patients with a higher T/O ratio (14), another found no differences in clinical outcomes (16).

SENSITIVITY AND SPECIFICITY OF VALUES

Sensitivity and specificity of α -amylase values are limited. Filloux et al (9) reported a tracheal α -amylase cutoff value of 1,832 U/L had an 88.0% sensitivity and 100.0% specificity. Dewavrin et al (11)

TABLE 1. Levels of Alpha-Amylase Based Upon Type of Specimen

Method of Specimen Collection	References	Mean (SD) Amylase U/L	Median (IQR) Amylase U/L
Oral secretions	Filloux et al (9)		
	Intubated group:	NR	307,606 (200,725–461,300)
	Sole et al (10)		
	Baseline:	542,312 (820,745)	195,029 (47,767–773,358)
	Post 1–4 hr:	696,578 (1,263,022)	273,305 (104,617–627,628)
Subglottic secretions	Filloux et al (9)	NR	130,750 (55,257–157,717)
Tracheal secretions	Dewavrin et al (11)		
	No aspiration:	NR	3,075 (1,526–12,796)
	Aspiration:		22,190 (4,799–81,443)
	Abundant aspiration:		9,771 (2,100–60,672)
	Filloux et al (9)		
	Control:	NR	191 (10–917)
	Intubated:		6,661 (2,774–19,358)
	Jaillette et al (12)		
	Tapered ETT cuff:	NR	4,591 IU/mL (24,720–268,028 IU/mL)
	Standard ETT cuff:		3,516 IU/mL (14,097–218,989 IU/mL)
	Millot et al (13)		
	Control:	NR	4,279 (1,564–55,572)
	Subglottic secretion drainage:		10,675 (2,293–79,705)
	Nandapalan et al (14)		
	Control:	NR	295 (NR)
	Severe infection (day 2):		4,866 (NR)
	Severe infection (day 3):		8,017 (NR)
	Qu et al (15)		
	VAP:	NR	23,596 (3,983–66,329)
	Non-VAP:		3,321 (263–10,291)
Sole et al (10)			
Baseline:	3,294 (5,786)	0 (0–6,115)	
Post 1–4 hr:	2,437 (4,415)	0 (0–5,240)	
Sole et al (16)			
Control:	15,298 (36,643)	6,664 (NR)	
Intervention:	13,086 (25,288)	5,918 (NR)	
Bronchoalveolar lavage fluid	Abu-Hasan et al (17)		
	No risk for aspiration:	307	NR
	Risks for aspiration:	1,722	
	Samanta et al (18) ^a	NR	210 (91–562)
	Tripathi et al (19)	NR	927 (118–5,300)
	Weiss et al (20)	NR	134 (38–557)

ETT = endotracheal tube, IQR = interquartile range, IU = international units, NR = not reported, VAP = ventilator-associated pneumonia.

^aMini bronchoalveolar lavage used as technique for specimen collection.

reported a similar sensitivity of 87.0% using a tracheal α -amylase value of 1,685 U/L, but the specificity was only 29.0%. Methods for determining sensitivity and specificity varied between the two studies, and Dewavrin et al (11) classified aspiration of oral secretions using pepsin biomarkers, which is likely the reason for the difference in specificity between the two studies (9). With the emergence of using α -amylase as a biomarker, researchers have begun to use a cut-point of 1,685 U/L or higher to classify aspiration.

APPLICATION OF ALPHA-AMYLASE RESULTS

Incidence of Aspiration

Alpha-amylase has been used to assess frequency of aspiration of oral secretions (Table 2). Sample sizes and frequency of measures of α -amylase vary widely across studies. Studies used varying cut-off values of α -amylase to report the occurrence of aspiration, and many reports did not list values at all. With the exception of a pilot study, aspiration of oral secretions exceeded 75%, validating that the majority of intubated patients aspirate secretions around the cuff of the ETT.

Duration of Alpha-Amylase in Secretions After Aspiration

Once oral secretions are aspirated, it is unknown how long α -amylase is detectable in pulmonary secretions. Studies with

multiple measures detected α -amylase up to 14 days after intubation (11, 12, 16), and no changes in either the α -amylase values or T/O ratio over time (16). Reported values may reflect ongoing aspiration around the ETT cuff and/or stability of α -amylase in the pulmonary system once aspiration occurs.

CLINICAL SIGNIFICANCE

Alpha-Amylase Levels and Pulmonary Complications

Several researchers assessed the relationship between α -amylase and development of pulmonary complications, including VAP and ventilator-associated events (VAEs). In some studies, α -amylase in tracheal or BAL specimens was significantly higher in those with VAP (15, 18, 20). An α -amylase of 4,681 U/L had a 90% sensitivity and 79% specificity for identifying VAP (15), whereas a value of 163 U/L in mini-BAL specimens had a reported sensitivity of 73.0% and specificity of 68.6% (18). Another study reported that an α -amylase value less than 125 U/L in BAL fluid reduced the odds for developing VAP after adjusting for gender, chest radiography, and preintubation risk factors (odds ratio, 0.39; 95% CI, 0.21–0.71; $p = 0.002$) (20). In contrast, other researchers used α -amylase to evaluate outcomes of interventions and reported data related to VAE. In these studies, no relationships were observed between α -amylase levels and development of VAE (12, 16).

TABLE 2. Estimates of Aspiration

References	Design	Population	Aspiration Estimates/Total No. of Patients (Incidence)	Aspiration Estimates Amylase Cutoff Value (U/L)	Amylase Collection Day(s)
Tracheal aspirates					
Dewavrin et al (11)	Retrospective observational from RCT	Adult; intubated	82/109 (75.2%)	> 1,688 U/L	Multiple
Filloux et al (9)	Prospective pilot	Adult; intubated	34/37 (91.9%)	1,932 U/L	Single
Jaillette et al (12)	Prospective RCT	Adult; intubated	299/326 (91.7%)	> 1,685 U/mL in > 30% samples	Multiple
Millot et al (13)	Prospective observational	Adult; intubated	83/100 (83.0%)	> 1,685 U/L	Single
Nseir et al (21)	Prospective RCT	Adult; intubated	Enteral nutrition: 48/78 (75.0%) Parenteral nutrition: 33/73 (54.0%)	> 1,685 U/mL in > 30% samples	Multiple
Sole et al (10)	Prospective pilot	Adult; intubated	5/13 (38.5%)	1,305 U/L	Single
Sole et al (16)	Prospective RCT	Adult; intubated	315/410 (76.8%)	392 U/L	Multiple
Bronchoalveolar lavage specimens					
Abu-Hasan et al (17)	Retrospective observational	Pediatric with chronic respiratory illness; nonintubated	51/64 (79.7%)	250 U/L	Single
Samanta et al (18)	Prospective observational	Adult	88/151 (58.3%)	163 U/L	Single
Tripathi et al (19)	Prospective observational	Adult; intubated, tracheostomy, unprotected airway	98/100 (98.0%)	Not reported	Single

RCT = randomized controlled trial.

Aspiration Risk Factors and Alpha-Amylase

Having risk factors for aspiration prior to and after intubation was associated with higher α -amylase levels in tracheal and/or BAL specimens (15, 17, 18, 20). Risk factors include altered consciousness, swallowing dysfunction, cardiac arrest, preintubation vomiting, and/or difficulty with intubation (20).

ETT Type Impact on Aspiration

Specialized ETTs with subglottic suction ports and different cuff configurations have been developed and tested. Although some devices have been shown to reduce VAP, findings vary when using α -amylase as an outcome measure (12, 13, 19). No differences were noted in the percentage of patients with aspiration between a tapered-cuff versus a standard-cuff ETT (90.1% vs 93.3%; $p = 0.095$) (12). Additionally, no differences were found in the proportion of tracheal specimens positive for α -amylase between those with a subglottic secretion drainage tube compared with a standard tracheal tube (88.0% vs 100.0%; $p = 0.859$) (13). It is not known if the lack of differences is attributed to the devices or if α -amylase was unable to detect differences.

DISCUSSION

Several researchers have used α -amylase as a biomarker to assess for aspiration of oral secretions. As expected, values of α -amylase decreased depending on the proximity of specimen collection from the mouth. Approximately 5–7% of oral α -amylase is detectable in tracheal samples calculating a T/O ratio (9, 16). The majority of subjects across studies had aspiration as indicated by positive levels of α -amylase in pulmonary specimens. Aspiration was noted with different ETT cuff configurations and with subglottic suction tubes (12, 22).

Challenges in Interpretation of Values

Several challenges in interpretation of study findings exist including lack of standardization. Studies reported different cutoff points of α -amylase to identify aspiration. Alpha-amylase values that indicate microaspiration or macroaspiration are unknown. Some researchers classified patients as having aspirated if α -amylase was detected at a minimal level detectable by laboratory methods (10, 16–18). Other studies used a higher value based on sensitivity and specificity analysis, requiring values of 1,685 U/L or higher to indicate aspiration (11, 13). Some studies classified aspiration only if a percentage of the samples (e.g., 30% or more) were higher than a predetermined cutoff point (12, 21).

Clinical Significance

The clinical significance of aspiration of oral secretions remains unknown. Some, but not all, researchers identified higher α -amylase levels in those with pulmonary complications, such as infection or VAP (14–16). Macroaspiration of secretions is a risk factor for aspiration pneumonia, secondary to the bacterial load that is introduced from either the oral cavity or upper gastrointestinal tract (4). Therefore, colonization of the oral secretions may be a more important factor in identifying complications than α -amylase levels.

Studies will likely be more meaningful if aspiration is measured by both pepsin and α -amylase biomarkers. Since aspiration of gastric contents can result in an inflammatory reaction and chemical pneumonitis (2), assessment of pepsin in pulmonary secretions may be more important in assessing risk for complications.

It is unknown how stable α -amylase is in pulmonary secretions as research has found no differences in values over time after intubation (16). Therefore, detection of α -amylase only indicates that aspiration of oral secretions occurred, but not when.

Despite the recent increase in measurement of α -amylase in detecting aspiration, many questions remain unanswered: 1) what is the duration of detecting α -amylase in the lungs following aspiration; 2) what values which are considered “positive for aspiration;” 3) what values indicate microaspiration versus macroaspiration; and 4) what is the clinical significance of values?

CONCLUSIONS

Although α -amylase is detected in most intubated patients, many unknowns exist about interpretation and usefulness of values. A lack of standardization in measurement and interpretation suggest that overall usefulness of α -amylase, even as a research outcome, has many limitations.

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