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The Role of Tracheal Aspirate Cultures in Antibiotic Usage in a Level IV Neonatal Intensive Care Unit

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Table 1 and 2 available in the Supplementary Files section

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Abstract

Objective: Determine characteristics of babies with artificial airways in our level IV NICU receiving tracheal aspirate cultures (TAcx) and how they relate to antibiotic utilization.

Study Design and Methods: A four-year retrospective study of illness episodes associated with the collection of a TAcx in patients with an artificial airway at a single level IV NICU.

Result: 196 TAcx were collected from 95 patients. 85% of TAcx were positive and patients received empiric antibiotics 93% of the time. Considering common reasons for TAcx, 33% of patients had improvement within 48 hours of antibiotics. Median duration of therapy was 7 days (IQR 5-9 days).

Conclusion: TAcx in neonates commonly yield bacteria leading to extended antibiotic therapy, but treatment targeting these pathogens does not typically lead to improvement in signs and symptoms that triggered collection of the culture. Diagnostic stewardship interventions to reduce use of TAcx could reduce antibiotic misuse in the NICU.

Introduction

Endotracheal intubation is commonly performed in neonates admitted to the neonatal intensive care unit (NICU), and many remain intubated for prolonged periods of time. Cultures of tracheal aspirates [secretions suctioned from the endotracheal tube (ETT)] (TAcx), are frequently ordered in the NICU as part of the evaluation of a neonate who is exhibiting signs and symptoms of potential infection (fever or hypothermia, tachycardia, hypotension, or elevated inflammatory markers) or changes in respiratory status (tachypnea, worsening gas exchange or other changes in respiratory support requirements). However, cultures of secretions collected through the ETT lack specificity and sensitivity for lower respiratory tract infections due to airway colonization by oropharyngeal, enteric, environmental pathogens, and lack of access to distal portions of the lungs respectively. For example, multiple pediatric and adult studies have shown that there is no association between bacterial growth on TAcx or inflammation with clinical findings of respiratory infection[1-5]. Additionally, TAcx have been shown to consistently yield polymicrobial growth more so than cultures obtained by bronchoscopic techniques[6]. Conversely, TAcx have only a sensitivity of approximately 75% among adult patients with hospital-acquired pneumonia and ventilator associated pneumonia[7]. Thus, treating a patient with signs of infection and/or respiratory compromise based on the results of a TAcx may result in overtreatment or undertreatment, the former being an important source of excessive antibiotic exposure[8].

Through implementation of antimicrobial stewardship programs, U.S. hospitals have been combatting antibiotic overuse for years. Incorporation of diagnostic stewardship (optimizing use of diagnostic studies) principles makes sense, as antibiotic use and diagnostic testing are intimately linked. Successful interventions require buy-in from stakeholders, which

may be accomplished through sharing local and individual data and outcomes[9,10] Further investigation is necessary to optimize recommendations for diagnostic testing and antibiotic use in the setting of clinical respiratory decline. In this study, we set out to quantify the utilization of TAcx, describe the microbiology of TAcx, and effectiveness of TAcx-guided patient management in a level IV NICU as a first step toward a diagnostic and antibiotic stewardship pathway for children with concern for infection and/or respiratory decline in endotracheally intubated NICU babies.

Methods

This is a retrospective chart review of neonates and infants in a level IV NICU with a TAcx collected from an artificial airway between January 2019 and April 2023. Demographics, clinical diagnosis, reasons for TAcx, microbiology results, clinical response to antibiotics targeting cultured pathogens, and antibiotic utilization were recorded. Specifically, we looked for signs and symptoms of lower respiratory tract infection (LRTI) during the event that could be considered reasons for obtaining a TAcx and evaluated for clinical improvement within 48 hours of therapy (i.e. back to baseline clinical signs/symptoms and x-ray findings). Additionally, we evaluated the type and duration of antibiotic treatment and took note of recurrent respiratory and non-respiratory infections.

Definitions

Pathogenic bacteria were any organism isolated and identified to at least the genus level (includes but not limited to *Staphylococcus aureus*, *Haemophilus spp*, *Streptococcus pneumoniae*, enteric Gram-negative bacilli, *Candida spp*.). Non-pathogenic bacteria were reported by the microbiology lab as “normal oral flora” and not subject to identification (including but not limited to Gram-positive cocci like viridans group *Streptococcus*,

Stomatococcus spp, *Gemella spp*, and Gram-negative bacteria like *Prevotella spp*, *Eikenella spp*, non-pathogenic *Hemophilus* and *Neisseria spp*. that comprise the normal flora of the upper respiratory tract.). A TAcx result was polymicrobial if it yielded more than one pathogenic organism. Sterile-site cultures are those collected from a site not expected to have colonizing bacteria (blood, CSF, and other body fluids (pleural, peritoneal, synovial). Any cultures (sterile- and nonsterile-site) or PCRs (e.g. viral respiratory pathogen panel) collected within 48 hours of the TAcx were analyzed as a part of the same infection episode. A TAcx had to be collected more than thirty days after a preceding TAcx to be considered a separate episode.

Reasons for obtaining a TAcx were based off the signs and symptoms described in the progress notes written before the culture was collected. For example, signs of worsening gas exchange were determined by increasing levels of FiO_2, ventilator support, or 2 or greater desaturations. Worsening respiratory status was further characterized by noting worsening trends in abnormal lung findings on physical exam (wheezing, rales, rhonchi, or crackles), changes in airway secretions, new or worsening apnea, new or worsening cough (excluding those documented as being induced by suctioning), tachypnea, nasal flaring, or retractions that were documented in serial assessments. A similar approach was applied to cardiac instability, with 2 or more episodes of tachycardia (>170 bpm) or bradycardia (<100 bpm) being regarded a reason for TAcx collection by the medical team. Lab values for leukopenia (<4000 WBC/μL), leukocytosis (15,000 WBC/μL) with left shift (>10% band forms) and C-reactive protein (CRP) >10 mg/L within 48 hours of TAcx collection were included reasons. Finally, chest x-ray changes were also analyzed, looking for the radiologist's report to explicitly say if it had "worsened" or "improved" compared to other recent images.

Data were collected and managed using REDCap electronic data capture tools hosted at the University of Tennessee Health Science Center (UTHSC) College of Medicine in a deidentified manner and analyzed with t-test or chi-square analysis as appropriate for the data[11,12]. A p-value of ≤ 0.05 was considered statistically significant. The study was approved by the UTHSC Institutional Review Board with a waiver of informed consent.

Results

We identified 196 TAcx events from 95 different patients in our NICU during the study period. Demographic characteristics are shown in Table 1. The study group comprised predominantly, preterm, low-birth weight, African American infants, which is representative of our patient population. At the time of culture, most subjects had chronic cardiac and/or pulmonary conditions (Table 1). The median duration of artificial airway at the time of culture was 42 days (IQR 8-96 days), the median age was 130 days (IQR 65-190 days), and the median length of stay was 195 days (IQR 109-349 days).

85% of the TAcx were positive for at least one potential pathogen, and 71% were polymicrobial; 2.6% of cultures yielded only normal oral flora. Other sterile-site cultures collected at the same time were less frequently positive (Table 2). Patients were started on antimicrobial therapy 93% of the time that a TAcx was collected. The median duration of therapy was seven days. Antibiotics were discontinued within 72 hours only 10% of the time. Among the five most common reasons for obtaining a TAcx, 33% of infants experienced improvement in their initial symptoms within 48 hours of starting antibiotics (Figure 1a). Additionally, infants were restarted on antimicrobial therapy within 30 days of antibiotic discontinuation 40% of the time for a respiratory infection and 23% of the time for a non-respiratory infection. Definitive antibiotic therapies most commonly used were vancomycin,

gentamicin (the standard empiric antibiotic regimen used in the unit for late onset sepsis), and nebulized tobramycin.

Discussion

In this retrospective study of TAcx use and its effect on antibiotic usage in our level IV NICU, we found that most TAcx were positive for at least one potential pathogen. However, most patients did not demonstrate clinical improvement within 48 hours after receiving antibiotics and, despite this, antibiotic therapy was prolonged (median duration seven days).

It is very challenging to diagnose lower respiratory infection in neonates and infants with chronic lung disease. Many of the signs and symptoms lack specificity for infection in this setting, including results of TAcx, as colonization of the artificial airway with potentially pathogenic bacteria is the rule rather than the exception [13-15]. Clinical or microbiologic criteria to distinguish infection from colonization could prevent potentially detrimental antibiotic overexposure in this high-risk population. [9,16-19].

Overuse of antibiotics can cause significant harm in neonates by contributing to dysbiosis, which has been associated with gut inflammation, increased risk of bacterial translocation, NEC, and late-onset sepsis[20-24]. For example, pre-term infants with late-onset sepsis tended to have decreased microbial diversity compared to an uninfected control group, with a higher abundance of bacilli and their fermentation products and a lack of anaerobic bacteria[24]. A case-control study demonstrated that antibiotic exposure of greater than 5 days was associated with a 3.6-fold increase in the risk of developing necrotizing enterocolitis[17]. Antibiotic overexposure has also been linked to increased rates of bronchopulmonary dysplasia and invasive fungal infections[18,19]. Exposure to antibiotics at such a young age has also been linked,

via changes to intestinal flora, to more long-term complications such as asthma, obesity, inflammatory bowel disease, asthma, and later infections[16].

In this study analyzing how TAcx impact antibiotic usage in the NICU, we found that most TAcx yielded a potential pathogen. Additionally, there was little evidence of systemic infection, given that the other cultures rarely yielded the same pathogen(s) as the TAcx. Previous studies examining the utility of TAcx have had similar findings[25,26]. In Slagle *et. al*[25], they performed serial TAcx on 94 intubated neonates, with a mean ventilation of 47 days (range 8 to 276 days) as a way to predict late-onset sepsis. 90% of these cultures obtained during the first week of ventilation were sterile. However, of the 1148 total TAcx that were collected, 73% were positive for pathogenic bacteria. In only 5 of the 26 subsequent cases of sepsis that occurred was the same pathogen found in the blood culture and TAcx. In contrast, in Booth *et al.*[14], 139 intubated patients had a TAcx collected within the first 12 hours of life and pathogenic bacteria grew in just 6.5% of them. Previous studies published in the 1980's showed pathogenic bacteria at rates of 7.8%[27] and 14.5%[28] when TAcx were collected before 8-12 hours of age, suggesting that they are potentially more specific during this early timeframe; however, this is a very brief period in the life of a hospitalized preterm neonate.

Clinicians started antibiotics at the time of collection of the TAcx in most cases. This is not unusual as TAcx is often collected as a part of a full sepsis evaluation; however, these antibiotics were rarely discontinued within 72 hours even if other cultures were negative. In many cases, the positive TAcx was used to justify continuation of antibiotics for a longer period of time. Although use of TAcx varies widely among NICUs, their association with increased antibiotic usage has been established[13,29]. Importantly, despite the high rate of antibiotic exposure seen in this study, most infants did not demonstrate significant clinical improvement within 48

hours of starting antimicrobial therapy as seen in Figure 1a. It is our assumption that those who did not improve within this time frame likely did not have true bacterial infection, but rather an alternative non-infectious etiology to explain the presence of clinical signs and inflammation. In Tamma *et al*[30], they retrospectively reviewed whether duration of antibiotic therapy for ventilator-associated tracheitis impacted progression to hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) in their NICU and PICU. They concluded that a longer duration of antibiotic therapy (7 days or greater) did not protect against progression and that they were at a significantly greater risk for acquiring multi-drug-resistant organisms. Ingolfsland et al. [29] validated these findings in their level IV NICU, concluding that a shorter duration of antibiotic therapy (5-7 days) was adequate for treatment of ventilator-associated tracheitis, a condition that lies on the spectrum of respiratory tract colonization and VAP.

TAcx yield a wide array of organisms as seen in Figure 2 and are often polymicrobial. In our study, only 15% of cultures were negative for pathogenic bacteria. Methicillin-susceptible *S. aureus* (MSSA) and *Klebsiella spp*. were the most commonly isolated organisms at 10.4% and 8.8% respectively (Figure 2). Methicillin-resistant *S. aureus* (MRSA) was also common at 7.8% (Figure 2). This is expected, as we know that almost one-third of healthy adult nares are colonized with *S. aureus*[31] and the acquisition rate of MRSA in the NICU is high[32]. However, the array of organisms that grew on the TAcx in our study coupled with the small number of patients with signs of systemic infection (Table 2) suggests that these pathogens are colonizers rather than infection in these patients. This pattern of bacterial growth is similar to what has been demonstrated in previous studies examining tracheal colonization for mechanically ventilated patients[33,34].

The major limitation of this study is that it is retrospective, relying on the accuracy of clinical documentation reporting the reasons for obtaining a TAcx and clinical response to antibiotic therapy. This is also a single-center study which may limit generalizability to other sites.

In summary, the morbidity with potential LRTI, coupled with the risk of antibiotic resistance, as well as gut dysbiosis and chronic diseases thereof, present challenges to clinical-decision making in the NICU regarding antibiotic duration. However, TAcx have proven to be an unreliable predictor of LRTIs, because colonization of a longstanding artificial airway is very common and cannot easily be differentiated from LRTIs. We have re-affirmed this and showed that their use did not have a clear link with improved clinical outcomes in our population. Therefore, in order to promote antibiotic stewardship, a diagnostic stewardship program also needs to be established. This would require better diagnostic criteria for LRTI in order to make appropriate clinical decisions and not rely on TAcx alone. This involves considering the entire clinical picture, including radiographic findings, change in oxygenation, underlying conditions, and laboratory and culture results[35]. A clear guidance on when to obtain TAcx and how best to use results in clinical context is required. In terms of next steps, we look to establish a set of clinical guidelines with these principles in mind and implement them at our level IV NICU, analyzing their impact on TAcx and antibiotic usage as well as clinical outcomes.

Conflict of Interest

The authors declare no conflict of interest.

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Figures

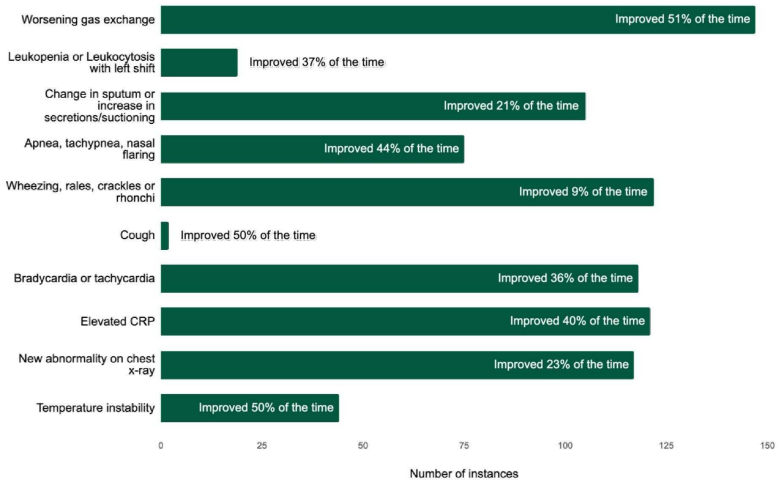


Figure 1a. Number of instances in which each reason for obtaining a TAcx was noted, and how often they improved within 48 hours of starting antimicrobial therapy.

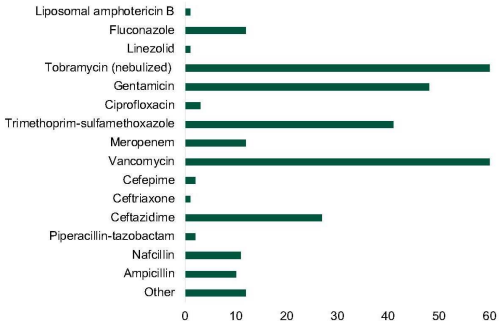


Figure 1b. Definitive antimicrobial therapy.

Figure 1

See image above for figure legend.

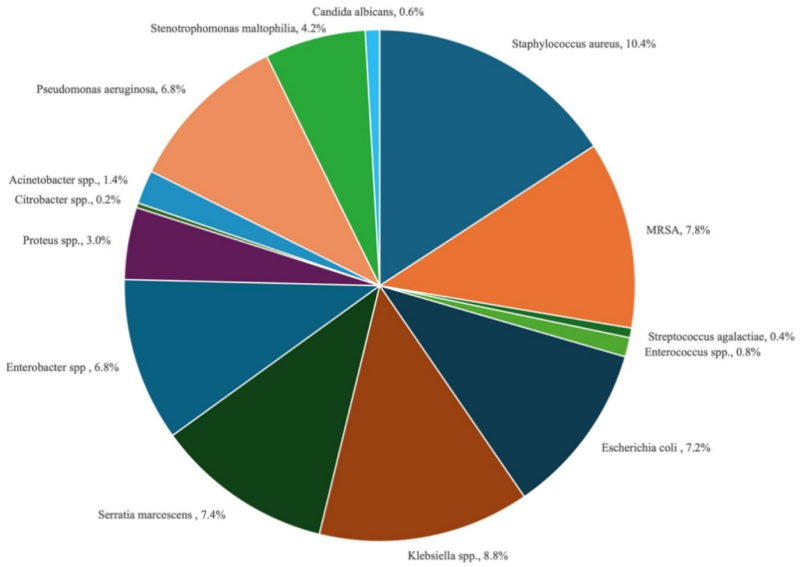


Figure 2. Organisms isolated from TAcx.

Figure 2

See image above for figure legend.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table1TACxManuscript.pdf
- Table2TACxManuscript.pdf