Commentary

Detecting Infection in Neonates: Promises and Challenges of a Salivary Approach

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ABSTRACT

Premature newborns present unique challenges for the caregiver. Their clinical fragility and immature immune system places them at increased risk for bacterial and viral infections. Current clinical standard of care mandates invasive phlebotomy to assess an infant for an infection. However, serial blood draws can lead to blood transfusions and the infliction of noxious stimuli to this vulnerable population. Salivary screening for common neonatal morbidities, such as infections, could vastly improve the care for these infants and positively affect their long-term clinical outcomes. Recent technological advancements have improved our ability to detect thousands of proteins and/or microbes from a single salivary sample, making noninvasive assessment in neonates a possibility. This article reviews the clinical applications and challenges associated with integrating salivary analysis for infectious surveillance into the neonatal population. (*Clin Ther*. 2015;37:523–528)

Key words: infection, inflammation, neonates, saliva, sepsis.

INTRODUCTION

Neonatologists have long championed the use of saliva as a noninvasive biofluid for clinical assessment. Saliva is an easily obtained, slightly acidic exocrine secretion that contains electrolytes, immunoglobulins, enzymes, hormones, proteins, nucleic acids, mucins, and nitrogenous products.[1] It is produced by the major (parotid, submandibular, and sublingual) and minor (labial, buccal, lingual, and palatal) salivary glands and, depending on its origin, may be classified as serous, mucous, or mixed. Most salivary constituents enter saliva via passive diffusion, active transport, or extracellular filtration.[2–6] Thus, salivary components are reflective of the status of health in the body and can be used to assess for neonatal well-being and systemic disease.

Critically ill neonates often require serial monitoring of their infection risk throughout their prolonged hospitalization. Blood sampling, however, confers additional risk to the unique neonatal physiology, which, at baseline, is at higher risk for anemia and cardiorespiratory instability. Thus, salivary testing is ideal in this fragile population, where blood volumes are limited. In addition, salivary testing could represent an alternative to universal serum screening for a variety of infectious processes. Although historically neonatal salivary analyses have been limited to a single protein or microbe, recent technologic advances have revealed the feasibility of high-throughput salivary analysis for thousands of analytes (proteins and microbes) from a single sample.[7–9] Thus, saliva represents an ideal biofluid for the assessment of infection in the neonate and could represent an alternative to serum testing, especially in the intensive care unit and resource-poor areas where universal serum testing is clinically detrimental and neither technically or financially feasible. This article aims to highlight previous and future applications of infectious screening using salivary analyses as a substitute to serum testing in newborns.

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CLINICAL DILEMMA: NEONATAL INFECTION

Because of altered innate and adaptive immune responses, premature neonates represent a highly vulnerable patient population who are at an increased risk for infection compared with older children.[10] Early- and late-onset viral or bacterial sepsis in the newborn confers significant morbidity and mortality.[11] Because clinical symptoms of sepsis in the neonate are often subtle, infants are commonly empirically treated even when they are not truly infected.[12] This limitation has resulted in "rule out sepsis" becoming one of the most common discharge diagnoses and antibiotics being the most prescribed drugs in neonatal intensive care units.[13–15] However, empirical administration of antibiotics in newborns results in manipulation of their microbiome, exposure to drug toxic effects, nosocomial infections, and the emergence of resistant strains of bacteria.[16] Thus, there is an urgent need to correctly identify truly infected newborns while limiting unnecessary antibiotic exposure to healthy infants.

Screening for infection in neonates currently depends on serial blood assessments that confer added procedural risks and blood loss. These limitations are especially detrimental to the preterm neonate, who has limited blood volumes and is at risk for complications such as apnea, bradycardia, and intraventricular hemorrhage when exposed to noxious stimuli. Although some diagnostic hurdles can be overcome by microscale techniques, many large-volume hematologic tests cannot be avoided, presenting a challenge to clinicians caring for this unique patient population. Furthermore, most of these hematologic tests necessitate a painful percutaneous procedure. Cumulative painful procedures negatively affect neurologic development in key cortical brain areas linked to behavior and cognitive outcomes.[17,18] Seeking an alternative means by which to noninvasively monitor the vulnerable newborn for both bacterial and viral infections could greatly improve clinical care and long-term developmental outcomes.

CLINICAL APPLICATIONS

Detection of Infectious Microorganisms

In 1965, Stern and Tucker[19] published the first report of the use of saliva as a biofluid for detecting pathological microbial infection in neonates. In this original article, the authors reported that cytomegalovirus (CMV) was readily detectable in the saliva of newborns and children. This work had important clinical implications because perinatally acquired CMV is the most common congenital infection and the most frequent cause of nonhereditary hearing loss. Current standard of care does not dictate universal screening of newborns because of technical and economic limitations. Rather, detection of the virus is performed on urine samples only in those infants who have potential clinical sequelae of the disease (eg, intrauterine growth restriction and thrombocytopenia). However, CMV infections are largely asymptomatic and can confer significant morbidity. Recently, Yamamoto et al[20] and Boppana et al[21,22] reported that quantitative polymerase chain reaction (PCR) amplification of CMV DNA in neonatal saliva is as accurate as PCR amplification of CMV in neonatal urine. These studies revealed excellent sensitivity and specificity of both liquid and dried salivary PCR assays for CMV and superiority over dried blood spot PCR assays in this population. Furthermore, the negative and positive predictive values of liquid salivary PCR assays were 100% and 91.4%, respectively, illustrating the accuracy and reliability of routine salivary PCR screening in the newborn.[21] Universal newborn screening for CMV in saliva could have a significant public health effect and warrants further consideration. This noninvasive assessment of CMV infection holds great promise for early identification of newborns whose conditions may otherwise go undiagnosed, providing caregivers an important opportunity to provide timely interventions to improve outcomes.

Direct microbial detection in saliva is not limited to CMV. Recent advancements in DNA amplification and quantification, along with cell culture techniques, have made the identification of an array of pathologic microbes in saliva feasible. Quantitative PCR has been used to assess the effect of antiretroviral therapy on periodic shedding of varicella and herpes viruses in immunologically compromised adults.[23,24] This technique provides a noninvasive and relatively rapid means to monitor the effectiveness of drug therapy and could be extrapolated to the newborn when duration of therapy, particularly in the setting of viral infections, may be unclear. Furthermore, in the past decade, salivary ELISAs for hepatitis B surface and E antigens have effectively detected hepatitis B viral infections in adults.[25–27] Although similar studies have not been conducted in the neonate, this research lays the foundation for surveillance of viral infections in this vulnerable population.

An alternative to direct microbial detection in neonatal saliva is the assessment of salivary antibodies to