Inclusion Criteria
- All infants who have failed a hearing screening (ABER)

**Background**
Over 3,000 hearing screens are completed annually at Texas Children’s Hospital. Based on internal audiology data, over a 9 month period, approximately 1% of patients were referred for a final screen. Of those that were referred, 38% passed a follow-up exam, 33% received a diagnosis of hearing loss, 26% were lost to follow-up, and 3% were discharged to home hospice.

**Critically Analyze the Evidence**
The GRADE criteria were used to evaluate the quality of evidence presented in research articles reviewed during the development of this guideline. The table below defines how the quality of evidence is rated and how a strong versus a weak recommendation is established.

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Type of Evidence</th>
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<tbody>
<tr>
<td>STRONG</td>
<td>Desirable effects clearly outweigh undesirable effects or vice versa</td>
</tr>
<tr>
<td>WEAK</td>
<td>Desirable effects closely balanced with undesirable effects</td>
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<table>
<thead>
<tr>
<th>Quality</th>
<th>Type of Evidence</th>
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<tr>
<td>High</td>
<td>Consistent evidence from well-performed RCTs or exceptionally strong evidence from unbiased observational studies</td>
</tr>
<tr>
<td>Moderate</td>
<td>Evidence from RCTs with important limitations (e.g., inconsistent results, methodological flaws, indirect evidence, or imprecise results) or unusually strong evidence from unbiased observational studies</td>
</tr>
<tr>
<td>Low</td>
<td>Evidence for at least 1 critical outcome from observational studies, from RCTs with serious flaws or indirect evidence</td>
</tr>
<tr>
<td>Very Low</td>
<td>Evidence for at least 1 critical outcome from unsystematic clinical observations or very indirect evidence</td>
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**PICO Question 1:** In infants who fail their hearing screen, when should CMV testing be completed?

**Recommendation:** Strong recommendation, low quality evidence to send saliva and urine CMV cultures with a failed unilateral ABER.

A review of the literature revealed one study that looked at CMV testing on infants who failed a hearing screen. A retrospective chart review was completed on 79,047 infants who had abnormal hearing screen results and positive urine cytomegalovirus culture results. Out of the 79,047 infants enrolled, 572 (0.7%) did not pass the inpatient ABR screening tests and 483 (84%) out of the 572 had urine cultures performed for CMV. The CMV cultures were positive on 24 (5%) of the 483 patients. Sixteen out of the 24 patients had both congenital CMV infection and confirmed hearing deficits in follow-up testing. Of the 16 patients with confirmed hearing impairment, 4 (25%) had clinical signs suggesting a congenital infection that prompted testing for CMV, whereas 12 (75%) were identified as being infected with CMV only because they did not pass the hearing screening tests.

Other studies reviewed focused on the initiation of a universal protocol for CMV screening. A study looked at a cohort of 388 children born between 1980 and 1996 that were identified during the newborn period as having CMV infection received repeated hearing evaluations to assess whether hearing loss occurred. Only 17% of the infants had screening of hearing before being discharged from the hospital nurseries. Hearing loss of >20 dB thresholds was detected in 5.2% of all newborns with congenital CMV infection within the first month of life. Approximately 6.5% of infants had SNHL detected by 3 months of age. By the age of 72 months, approximately 15% of children with congenital CMV infection had documented SNHL. Children with clinically apparent disease at birth had significantly more SNHL than children without any apparent disease (22.8% vs. 4.0% at 3 months and 36.4% vs. 11.3% at 72 months).

In another study, a cohort of 76 infants with congenital CMV infection, identified by means of newborn virologic screening, was monitored for outcome. The amount of infectious CMV was analyzed in urine specimens obtained during the first week of life. Infants with clinical abnormalities at birth (symptomatic congenital CMV infection) had higher amounts of CMV in urine than infants with no symptoms. Eight children with and four children without symptoms had hearing loss. Among children without symptoms, those with hearing loss had a significantly greater amount of CMV in urine (p = 0.03) and PB virus burden (p = 0.02) during infancy than those with normal hearing. Infants with <5 \(10^3\) pfu/mL of urine CMV and infants with <1 \(10^4\) copies/mL of viral DNA in PB were at a lower risk for hearing loss.
PICO Question 2: In infants who fail their hearing screen, what is the safest antiviral treatment to improve outcomes?

Recommendation: Strong recommendation with low quality evidence to give valganciclovir 15-18 mg/kg/dose twice daily and started as soon as possible after birth, after confirmation of congenital CMV infection and confirmation of hearing loss or other CNS disease caused by congenital CMV. (2)

There are a few studies that address antiviral treatment for CMV and its outcomes. One retrospective case series and one observational study that looked at the pharmacokinetics of oral valganciclovir were evaluated. The retrospective case series looked at 13 cases where infants with congenital CMV infection and CNS involvement who started antiviral treatment beyond the neonatal period in Spain between 2008 and 2010. All patients received oral valganciclovir, 32 mg/kg/day (b.i.d.) and 4 received intravenous ganciclovir, 12 mg/kg/day (b.i.d.) prior to valganciclovir. Median valganciclovir treatment duration was 6 months and it was well tolerated. Six patients developed neutropenia, none requiring granulocyte colony-stimulating factor. Eleven children (85%) had hearing defects at baseline, compared to 50% at 12 months. By ears, 18 ears showed hearing loss at baseline (7 mild, 3 moderate, 8 severe). At 12 months, 9 remained stable, 7 had improved and none had worsened. In 8 normal ears at baseline, no deterioration was found at 12 months. (2)

Additionally, in the observational study that looked at the pharmacokinetics of oral valganciclovir, 24 subjects were placed into 2 protocols and received antiviral therapy for 6 weeks. In protocol version 1.0, subjects received intravenous ganciclovir therapy for 6 weeks; therapy was interrupted on days 5-6 and 35-36 for administration of oral valganciclovir. In protocol version 2.0, subjects received 1 dose of oral valganciclovir and twelve hours later intravenous ganciclovir was initiated. All 5 subjects enrolled in version 1.0 received valganciclovir at a dose of 14 mg/kg. Nine of the 19 subjects enrolled in version 2.0 initially received valganciclovir at a dose of 14 mg/kg, 4 subjects initially received ganciclovir at a dose of 20 mg/kg and 6 subjects initially received ganciclovir at a dose of 16 mg/kg. At the time of re-initiation of oral valganciclovir after administration of intravenous ganciclovir in version 2.0 of the study, 15 study subjects restarted valganciclovir treatment at the same dose per kilogram of body weight that was used for dose 1. Of the 18 subjects who had detectable CMV in whole blood at baseline or during therapy, 11 had <4 log viral DNA copies/mL at baseline, and 7 had ≥4 log viral DNA copies at baseline. The median decrease in viral load among all subjects was 0.7 log viral DNA copies/mL, with those subjects who started the study with higher viral burden experiencing greater decreases in viral load than subjects who started the study with a lower viral burden. Of the 18 subjects with detectable CMV at or after the beginning of viral therapy, 6 were PCR negative at the completion of 42 days of antiviral therapy and 12 remained PCR positive; of the 6 subjects who were PCR negative, 2 remained PCR negative at day 56 and 4 were PCR positive. Oral valganciclovir was well tolerated by study subjects, with no vomiting or other indicators of dosing intolerance. Neutropenia of grade 3 or 4 developed in nine of the twenty four (38%) subjects.

Critical Points of Evidence*

Evidence Supports
- If an infant fails a unilateral ABER, send saliva and urine CMV cultures. (1-5) – Strong recommendation, low quality evidence
- After confirmation of hearing loss or other CNS disease caused by congenital CMV, give valganciclovir, 15-18 mg/kg/dose twice daily started as soon as possible after birth. (2) – Strong recommendation, low quality evidence

*NOTE: The references cited represent the entire body of evidence reviewed to make each recommendation.

Apply the Evidence

Currently, Guidelines for the Acute Care of the Neonate, recommend urine CMV culture for babies who bilaterally fail the ABER. A team consisting of representatives from neonatology, pediatrics, infectious diseases, audiology and nursing recommended the following:
- After a failed ABER unilaterally, saliva and urine (if possible) cultures should be sent for CMV testing before discharge. A failed ABER occurs after two “referred” OAE screens.
- CMV culture results should be routed to the primary care physician for follow-up.
- Antiviral treatment should be initiated and monitored by a physician experienced in antiviral treatment, such as a pediatric infectious disease specialist.
- Complete blood counts, clinical assessments and dosage adjustments should be performed every 4 weeks.
- Diagnostic ABER testing performed as soon as possible following the referred ABER screening.
- Further diagnostic ABER testing should be performed 3 months following the initial diagnostic ABER or as recommended by audiology.

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References


Clinical Standards Preparation
This clinical standard was prepared by the Evidence-Based Outcomes Center (EBOC) team in collaboration with content experts at Texas Children’s Hospital. Development of this clinical standard supports the TCH Quality and Patient Safety Program initiative to promote clinical standards and outcomes that build a culture of quality and safety within the organization.

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Development Process
This clinical standard was developed using the process outlined in the EBOC Manual. The literature appraisal documents the following steps:
1. Review Preparation
   - PICO questions established
   - Evidence search confirmed with content experts
2. Review of Existing External Guidelines
   - Guidelines for the Acute Care of the Neonate
3. Literature Review of Relevant Evidence
   - Searched: PubMed
4. Critically Analyze the Evidence
   - 4 nonrandomized studies and 1 case report
5. Summarize the Evidence
   - Materials used in the development of the clinical standard, literature appraisal, and any order sets are maintained in a Cytomegalovirus (CMV) Testing for Newborns evidence-based review manual within EBOC.

Evaluating the Quality of the Evidence
Published clinical guidelines were evaluated for this review using the AGREE II criteria. The summary of these guidelines are included in the literature appraisal. AGREE II criteria evaluate Guideline Scope and Purpose, Rigor of Development, Clarity and Presentation, Applicability, and Editorial Independence using a 4-point Likert scale. The higher the score, the more comprehensive the guideline.

This clinical standard specifically summarizes the evidence in support of or against specific interventions and identifies where evidence is lacking/inconclusive. The following categories describe how research findings provide support for treatment interventions. “Evidence Supports” provides evidence to support an intervention.

Recommendations
Practice recommendations were directed by the existing evidence and consensus amongst the content experts. Patient and family preferences were included when possible. The Content Expert Team and EBOC team remain aware of the controversies in the diagnosis/management of cytomegalovirus (CMV) in newborns. When evidence is lacking, options in care are provided in the clinical standard and the accompanying order sets (if applicable).

Approval Process
Clinical standards are reviewed and approved by hospital committees as deemed appropriate for its intended use. Clinical standards are reviewed as necessary within EBOC at Texas Children’s Hospital. Content Expert Teams are involved with every review and update.

Disclaimer
Practice recommendations are based upon the evidence available at the time the clinical standard was developed. Clinical standards (guidelines, summaries, or pathways) do not set out the standard of care and are not intended to be used to dictate a course of care. Each physician/practitioner must use his or her independent judgment in the management of any specific patient and is responsible, in consultation with the patient and/or the patient’s family, to make the ultimate judgment regarding care.

Version History

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<th>Date</th>
<th>Action</th>
<th>Comments</th>
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<tbody>
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<td>Aug 2013</td>
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