

TEXAS CHILDREN'S HOSPITAL
EVIDENCE-BASED OUTCOMES CENTER
Pertussis Infection in Infants
Evidence-Based Practice Course Evidence Summary

Inclusion Criteria

- Infants with known or suspected pertussis

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.

Recommendation	
STRONG	Desirable effects clearly outweigh undesirable effects or vice versa
WEAK	Desirable effects closely balanced with undesirable effects
Quality	Type of Evidence
High	Consistent evidence from well-performed RCTs or exceptionally strong evidence from unbiased observational studies
Moderate	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
Low	Evidence for at least 1 critical outcome from observational studies, from RCTs with serious flaws or indirect evidence
Very Low	Evidence for at least 1 critical outcome from unsystematic clinical observations or very indirect evidence

PICO Question 1: In infants less than 12 months of age, what clinical findings and rapidly available laboratory findings are most suggestive of pertussis infection, rather than viral respiratory infection?

Recommendation(s): Strong recommendation with low quality evidence to strongly suspect pertussis infection in infants with paroxysmal cough, cyanosis, post-tussive emesis, higher WBC count, and/or higher ALC. ⁽¹⁻⁴⁾
Weak recommendation with low quality evidence to consider incorporating the local incidence of positive pertussis tests within the prior 1-2 weeks into decision-making regarding pertussis diagnosis. ⁽¹⁻⁴⁾

The incidence of pertussis has been increasing since the 1980s; the prevalence among U.S. infants <1 year of age is approximately 55 cases per 100,000 population, with an incidence of approximately 98 per 100,000 in infants <6 months of age. ⁽⁵⁾ The Centers for Disease Control, the Global Pertussis Initiative, and other authorities recommend diagnosis and initial management of pertussis based on clinical suspicion. ^(5,6) A case-control study of young infants (<3 months of age) hospitalized with pertussis vs. influenza or RSV found that those with pertussis were more likely to have paroxysmal cough, cyanosis, post-tussive emesis, and seizure or apparent life-threatening event (ALTE) than were those with viral infections. ⁽¹⁾ A retrospective comparison of newborns (age 30 days or less) with pertussis vs. non-pertussis acute respiratory illnesses found that neonates with pertussis were more likely than those with non-pertussis illness to have paroxysmal cough, cyanosis, longer duration of illness before presentation, higher white blood cell (WBC) count and absolute lymphocyte count (ALC), higher median number of days on supplemental oxygen, and less tachypnea. ⁽²⁾ In a retrospective cohort analysis of 443 infants 12 months of age or younger who were tested for pertussis, investigators aimed to improve identification of pertussis cases by incorporating local disease incidence into clinical decision-making. ⁽³⁾ They found that a contextual model combining cyanosis, cough of at least 1 week in duration, and greater than 10% positive pertussis tests locally in the period 8 to 14 days beforehand performed best, showing 100% sensitivity for pertussis. A cohort study attempting to retrospectively identify clinical and laboratory predictors of a positive pertussis test found, by univariate analysis, that pertussis was more likely if the infant was younger, presented between July and October, and had less tachypnea, higher WBC count, and/or higher ALC. ⁽⁴⁾ However, in the logistic regression analysis, ALC was found to be the only independent predictor of a positive pertussis test.

PICO Question 2: In infants with known or suspected pertussis, what clinical findings or characteristics are associated with poorer outcomes, as compared with more favorable outcomes?

Recommendation(s): Strong recommendation with low quality evidence that children with complications from pertussis infection such as apnea, pneumonia, convulsions, or encephalopathy, should be monitored in an intensive care setting. Unvaccinated children <6 months of age are also at a higher risk of developing complications from pertussis. ⁽⁷⁻¹¹⁾

Per CDC data, of infants younger than one year of age presenting with pertussis-related illness, about half are hospitalized. ⁽⁷⁾ Complications of pertussis infection have been identified to include bradycardia, apnea, pneumonia, convulsions, encephalopathy, and death. A prospective cohort study in a German population found a complication rate of 48% (16 of 33 hospitalized patients) and found that there was a 10.33-fold increased risk of hospitalization for unvaccinated children >6 months of age with pertussis infection. ⁽⁸⁾ The same study found a 3.84-fold increased risk of being hospitalized if a child ≤2 years of age with pertussis infection had not received any pertussis vaccine compared to a child who had received at least one dose of any pertussis vaccine. Another study confirmed similar findings that the severity of pertussis was directly related to younger age and vaccine status. Ten deaths were reported in this study, 8 of which were in infants <6 months of age, and all of which were in unvaccinated patients. ⁽⁹⁾ A retrospective chart review from a New Zealand population found that after adjustment for age and immunization status, there was an increased risk of poor outcome associated with the presence of a comorbidity (RR = 5.56) and lymphocytosis (RR = 5.75). ⁽¹⁰⁾ Lastly, in a prospective cohort study conducted in England of children with suspected pertussis, those who were pertussis-positive had a mean duration of hospital stay that was 4.4 days longer than the pertussis-negative group. ⁽¹¹⁾

PICO Question 3: In infants with suspected pertussis, is PCR an accurate method for laboratory diagnosis, as compared with bacterial culture?

Recommendation(s): Strong recommendation with low quality evidence to use PCR for confirmatory testing in infants with suspected pertussis infection, as it has high sensitivity and specificity. ⁽¹²⁻¹⁵⁾

Weak recommendation with low quality evidence for clinicians/hospitals to consider incorporating dual-target or multiplex PCR into testing protocols. ⁽¹²⁻¹⁵⁾

Polymerase chain reaction (PCR) yields rapid results for the diagnosis of pertussis, and is accepted by many authorities in the U.S., and by health systems in many other countries, as proof of infection. ⁽¹⁶⁾ PCR is noted to be far more sensitive than culture, with reported sensitivities >90%. ⁽¹²⁻¹⁴⁾ Furthermore, it shows favorable specificity characteristics, with specificity reported as 95% or greater in multiple studies. ⁽¹³⁻¹⁵⁾ In one study of 3,096 infants and children tested for pertussis, younger age was associated with even greater superiority of PCR over culture for confirming pertussis infection. ⁽¹²⁾ Some studies have suggested that PCR targeting two or more sequences in the pertussis genome can have high sensitivity and specificity and can, in a single assay, identify *B. pertussis* and other relevant *Bordetella* species. ⁽¹⁴⁻¹⁵⁾

PICO Question 4: In infants with known or suspected pertussis, is azithromycin an acceptable choice for antibiotic treatment, as compared with erythromycin or clarithromycin?

Recommendation: Weak recommendation with low quality evidence to administer azithromycin to infants with pertussis. ⁽¹⁷⁻²⁰⁾

Azithromycin is an acceptable antibiotic choice. It is well-tolerated and compares well to longer courses of erythromycin ethyl succinate. A case-control study evaluating the compliance with longer courses of treatment for pertussis showed that longer courses of treatment were associated with decreased compliance. ⁽¹⁷⁾ In addition, an equivalence trial found that children treated with azithromycin had increased compliance compared to erythromycin. ⁽¹⁸⁾ Lastly, a systematic review evaluated 13 trials with 2,197 participants. While the trial qualities were variable, a course of azithromycin was found to be equivalent to seven days of clarithromycin or erythromycin, but with fewer side effects. ⁽¹⁹⁾

PICO Question 5: How long should an infant with pertussis be observed in the hospital prior to discharge home?

Recommendation: Unable to make a recommendation

After review of the literature, we could not find evidence to determine how long an infant with pertussis infection should be kept in the hospital. We queried large children's hospitals within the U.S., and there seems to be no standard practice regarding how long an infant with pertussis infection should receive inpatient care once the patient is tolerating enteral feeds and is not demonstrating A/B/Ds.

Critical Points of Evidence*

Evidence Supports

- Strongly suspect pertussis infection in infants with paroxysmal cough, cyanosis, post-tussive emesis, higher WBC count, and/or higher ALC. ⁽¹⁻⁴⁾ – Strong recommendation, low quality evidence
- Consider incorporating the local incidence of positive pertussis tests within the prior 1-2 weeks into decision-making regarding pertussis diagnosis. ⁽¹⁻⁴⁾ – Weak recommendation, low quality evidence
- Children with complications from pertussis infection such as apnea, pneumonia, convulsions, or encephalopathy, should be monitored in an intensive care setting. Unvaccinated children <6 months of age are also at a higher risk of developing complications from pertussis. ⁽⁷⁻¹¹⁾ – Strong recommendation, low quality evidence
- Use PCR for confirmatory testing in infants with suspected pertussis infection, as it has high sensitivity and specificity. ⁽¹²⁻¹⁵⁾ – Strong recommendation, low quality evidence

- Clinicians/Hospitals should consider incorporating dual-target or multiplex PCR into testing protocols. (12-15) – Weak recommendation, low quality evidence
- Administer azithromycin to infants with pertussis. (17-20) – Weak recommendation, low quality evidence

Evidence Lacking/Inconclusive

- There is no evidence to guide how long an infant with pertussis should be observed in the hospital prior to discharge. – Unable to make a recommendation

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

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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
 - N/A
3. Literature Review of Relevant Evidence
 - Searched: PubMed, Cochrane, PubMed Academic, Google Scholar, Google
4. Critically Analyze the Evidence
 - 1 meta-analysis and 15 nonrandomized studies
5. Summarize the Evidence
 - Materials used in the development of the clinical standard, literature appraisal, and any order sets are maintained in a Pertussis 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, Stakeholder Involvement, 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

"Evidence Against" provides evidence against an intervention.

"Evidence Lacking/Inconclusive" indicates there is insufficient evidence to support or refute an intervention and no conclusion can be drawn *from the evidence*.

The **GRADE** criteria were utilized to evaluate the body of evidence used to make practice recommendations. The table below defines how the quality of the evidence is rated and how a strong versus weak recommendation is established. The literature appraisal reflects the critical points of evidence.

Recommendation	
STRONG	Desirable effects clearly outweigh undesirable effects or vice versa
WEAK	Desirable effects closely balanced with undesirable effects
Quality	Type of Evidence
High	Consistent evidence from well-performed RCTs or exceptionally strong evidence from unbiased observational studies
Moderate	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
Low	Evidence for at least 1 critical outcome from observational studies, RCTs with serious flaws or indirect evidence
Very Low	Evidence for at least 1 critical outcome from unsystematic clinical observations or very indirect evidence

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 and management of pertussis in infants. 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

Date	Action	Comments
Apr 2014	Originally completed	
Aug 2017	Reaffirmed	