

A Systematic Review of Clinical Practice Guidelines for the Diagnosis and Management of Bronchiolitis

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Background. Bronchiolitis is the leading cause of hospital admission for respiratory disease among infants aged <1 year. Clinical practice guidelines can benefit patients by reducing the performance of unnecessary tests, hospital admissions, and treatment with lack of a supportive evidence base. This review aimed to identify current clinical practice guidelines worldwide, appraise their methodological quality, and discuss variability across guidelines for the diagnosis and management of bronchiolitis.

Methods. A systematic literature review of electronic databases EMBASE, Global Health, and Medline was performed. Manual searches of the gray literature, national pediatric society websites, and guideline-focused databases were performed, and select international experts were contacted to identify additional guidelines. The Appraisal of Guidelines for Research and Evaluation assessment tool was used by 2 independent reviewers to appraise each guideline.

Results. Thirty-two clinical practice guidelines met the selection criteria. Quality assessment revealed significant shortcomings in a number of guidelines, including lack of systematic processes in formulating guidelines, failure to state conflicts of interest, and lack of consultation with families of affected children. There was widespread agreement about a number of aspects, such as avoidance of the use of unnecessary diagnostic tests, risk factors for severe disease, indicators for hospital admission, discharge criteria, and nosocomial infection control. However, there was variability, even within areas of consensus, over specific recommendations, such as variable thresholds for oxygen therapy. Guidelines showed significant variability in recommendations for the pharmacological management of bronchiolitis, with conflicting recommendations over whether use of nebulized epinephrine, hypertonic saline, or bronchodilators should be routinely trialed.

Conclusions. Future guidelines should aim to be compliant with international standards for clinical guidelines to improve their quality and clarity and to promote their adoption into practice. Variable recommendations between guidelines may reflect the evolving evidence base for bronchiolitis management, and platforms should be created to understand this variability and promote evidence-based recommendations.

Keywords. bronchiolitis; guidelines; diagnosis; treatment.

Bronchiolitis is the leading cause of hospital admission for respiratory disease among infants <1 year of age and is associated with an estimated 1 of every 13 primary care visits [1]. It most commonly presents in the first 2 years of life, and diagnosis is based on clinical signs. However, the use of these signs and other measures, such as pulse oximetry, within diagnostic criteria is inconsistent, and they significantly overlap with signs of other conditions, such as pneumonia and sepsis.

Many pharmacological interventions have been suggested, including bronchodilators, corticosteroid therapy, and antiviral therapy. The evidence base for the benefit of these therapies,

however, is often poor [2]. There is also significant variation in the management of bronchiolitis between clinicians and hospitals, with therapeutic interventions poorly supported by evidence often performed [3]. Management of bronchiolitis is predominantly supportive, with no specific effective therapies available [4]. Recently, methods of oxygen delivery that focus on flow rate and monitoring, as well as evidence around the thresholds for oxygen use, have emerged as potentially effective interventions to reduce the length of hospital admission [5, 6].

Clinical practice guidelines can help guide clinicians and benefit patients by promoting evidence-based practices [7]. However, guidelines may vary significantly, owing to differing methods of literature review, populations, definitions, interpretations of the evidence, and sponsor purposes. Meanwhile, there remain issues around the implementation and sustained use of guidelines in clinical practice. One study reported that only 56% of physicians used written guidance in managing bronchiolitis [8].

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Identifying differences and similarities between current clinical practice guidelines will allow the opportunity to highlight variations in suggested practice and could guide the future development of standardized guidelines that are based on the best evidence. We aimed to systematically identify current clinical practice guidelines for the diagnosis and management of bronchiolitis in children. We also aimed to appraise their quality and compare recommendations across guidelines.

METHODS

Literature Review

A systematic review of the literature for guidelines published between January 1996 and March 2017 was conducted. Citation and abstract screening of the electronic medical literature databases EMBASE, Global Health, and Medline was conducted by 2 independent reviewers. Manual searches of gray literature and guideline-focused databases/repositories (Web of Science, Google Scholar, National Guidelines Clearinghouse, BMJ Best Practice, TripDatabase, National Institute for Health and Care Excellence, Scottish Intercollegiate Guidelines Network, and World Health Organization) were conducted. Search strategies are detailed in [Appendix 1](#). Select international experts were contacted, and references of included guidelines were searched to identify any other relevant documents for inclusion.

Eligibility Criteria

Clinical practice guidelines and guidance documents with recommendations for the diagnosis or management of bronchiolitis that were produced by national or international clinical bodies were eligible for inclusion. The following items were excluded: withdrawn or superseded guidelines, clinical trials or systematic reviews not part of clinical practice guidelines, articles by a single author, guidelines focusing solely on bronchiolitis in high-risk or single specific subpopulation of children, and guidelines regarding use of monoclonal antibody for prevention of respiratory syncytial virus infection only

Guideline Review

Data extraction was performed by 2 independent reviewers into standard templates. Reviewers noted whether guidelines supported or rejected specific recommendations, made other specific recommendations, or highlighted equivocal evidence. Disagreements were resolved after discussion between reviewers.

Quality Assessment

The AGREE (Appraisal of Guidelines, Research, and Evaluation) II instrument was used to assess the quality of guidelines [9]. This tool is designed to assess the quality and reporting of practice guidelines. Guidelines are assessed under 6 domains: scope

and purpose, stakeholder involvement, rigor of development, clarity of presentation, applicability, and editorial independence. For our systematic review, each domain contains 2–8 specific items. The quality of each item was scored by 2 independent reviewers on a 7-point scale ([Appendix 2](#)). When differences of ≤ 2 were found between reviewers for a specific item, the average of the 2 scores was used as the final score for that item. When differences of ≥ 3 points were recorded for a specific item, the reviewers discussed the criterion and agreed on a final score for that item. In accordance with AGREE II instructions, the overall quality of each domain was calculated as a percentage, as follows: $[\text{total actual domain score} - \text{minimum possible domain score}] / [\text{maximum possible domain score} - \text{minimum possible domain score}] \times 100$.

We report median percentages and interquartile ranges (IQRs) per domain across guidelines. No specific cutoff exists as a measure of high-quality guidelines [10]. However, we report the proportion of guidelines with a score above a threshold of 60%.

RESULTS

A total of 32 bronchiolitis clinical practice guidelines were included in this review [11–42] ([Appendix 3](#)).

Guideline Characteristics

[Appendix 4](#) details the characteristics of the 32 clinical practice guidelines included in the review. Guidelines identified were published between 2000 and 2017. Fourteen were from the World Health Organization European Region, 9 from the Region of the Americas, 8 from the Western Pacific Region, and 1 from the African Region.

Quality Assessment

[Supplementary Table A6.1](#) summarizes the number of guidelines scoring $>60\%$ and the median score across guidelines for each domain of assessment. Guidelines had good descriptions of their scope and purpose and scored well in terms of clarity of presentation. However, most guidelines did not score highly for stakeholder engagement, particularly in terms of consulting with families of affected children. Many guidelines scored poorly in terms of rigor of development, owing to poor descriptions of their development and a lack systematic processes in formulating recommendations. Many guidelines also performed poorly in terms of applicability, because they failed to explicitly consider the financial and technical implications of and barriers to their application. The majority of guidelines also scored poorly regarding editorial independence by failing to adequately state their independence from the funding body or to address any possible competing interests of the authors. [Appendix 5](#) contains the domain scores for each guideline.

Guideline Recommendations

Appendix 6 summarizes the recommendations from all included guidelines.

Diagnosis

Across the majority of guidelines, use of chest radiography, blood culture, full blood count, urea and electrolyte analyses, and urine culture (to exclude urinary tract infection) for diagnosing bronchiolitis were not recommended for routine use (Table 1). However, guidelines varied in stating specific recommendations for subgroups, with a number providing recommendations for severe presentations, cases in which comorbidities were present, or cases in which there was diagnostic uncertainty (Supplementary Table A6.2). Virological testing was not recommended for routine use in diagnosis by the majority of guidelines, but a number of guidelines recommend use of such testing for grouping patients into cohorts or in epidemiological studies.

Pharmacological Management

Thirty-two guidelines provided recommendations for the pharmacological management of bronchiolitis. Table 1 details the number of guidelines that recommended routine use of pharmacological

management, the number that recommended against use of pharmacological management, and the number that suggested considering a trial of use or highlighted equivocal evidence for a number of pharmacological therapies. While most guidelines did not recommend the routine use of inhaled/nebulized bronchodilators in managing bronchiolitis, there were conflicting recommendations across a number of guidelines as to whether they should be trialled (Supplementary Table A6.3).

There were mixed recommendations for the use of nebulized epinephrine. Nineteen guidelines (including most recent guidelines) recommended against nebulized epinephrine use. However, 3 guidelines recommended routine use, and 7 guidelines suggested use or consideration of a trial of use (or highlighted equivocal evidence), particularly for patients with severe symptoms.

Recommendations for the use of hypertonic saline demonstrated considerable variability across the 18 guidelines that discussed its use. Seven guidelines did not recommend use of hypertonic saline, whereas 8 provided recommendations in support of routine use in managing bronchiolitis (Supplementary Table A6.3).

No guidelines recommended the routine use of corticosteroids, with a minority suggesting use in exceptional

Table 1. Guideline Recommendations for Routine Diagnostic Testing for and Pharmacologic Treatment, Supportive Management, and Infection Prevention and Control of Bronchiolitis

Variable	Guidelines Recommending Routine Use, No.	Guidelines Recommending Against Routine Use, No.	Guidelines Stating Equivocal Evidence Or Recommend Considering a Trial of Use, No.
Diagnostic test			
Chest radiography	0	26	-
Blood culture	0	20	-
Complete blood count	0	19	-
Urea and electrolyte analyses	0	11	-
Blood gas analysis	1	14	-
Urine culture	0	6	-
Pharmacologic treatment			
Bronchodilators	3	22	14 ^b
Hypertonic saline ^a	8	7	7 ^b
Nebulized epinephrine	3	19	7 ^b
Corticosteroids	0	29	5 ^b
Antivirals	0	20	4 ^b
Montelukast	0	10	0
Antibiotics	0	26	0
Supportive management			
Chest physiotherapy	1	19	1
Infection prevention and control			
Handwashing	13	0	...
Gloves	8	0	...
Gowns	8 ^d	1	...
Isolation and/or cohorting	14	2	...

^aOne guideline has recommendations both for and against routine use, depending on the setting.

^bA number of these guidelines are also classified as for or against routine use. This is because certain guidelines provide recommendations for or against routine use of particular treatments but also state that the evidence for use is equivocal or suggest considering a trial of use.

^cTwo of these guidelines recommended use of personal protective equipment or reasonable barrier precautions but not gloves explicitly.

^dTwo of these guidelines recommend use of personal protective equipment or reasonable barrier precautions, and 2 recommended physician/white coats but not gowns explicitly.

circumstances, such as severe cases, in outpatient settings, and for asthmatic patients (Supplementary Table A6.3). No guidelines recommended routine use of antivirals, montelukast, or antibiotics in managing bronchiolitis.

General Supportive Management

Twenty-seven guidelines provided recommendations regarding general supportive management for bronchiolitis.

Oxygen and Noninvasive Ventilation. The oxygen saturation level used as a guide for commencing supplemental oxygen therapy varied from <90% to <95% among guidelines (Supplementary Figure A1). However, the most commonly recommended cutoff was <92%.

Fourteen guidelines discussed when to commence continuous positive airway pressure (CPAP). These decisions were mostly based on the severity of symptoms, with 3 guidelines using the presence of apneas or hypercapnia as indications for commencing CPAP (Supplementary Table A6.4).

Airway Clearance. Sixteen of 22 guidelines that discussed suctioning of secretions from the nasopharynx recommended its use when needed. Only 1 of 21 guidelines recommended the routine use of chest physiotherapy in treating children with bronchiolitis.

Hydration and Nutritional Support. Guidelines recommended nasogastric feeding for patients who cannot tolerate oral feeding and intravenous fluids for patients who are unable to tolerate oral or nasogastric feeding. Nasogastric feeding was also recommended in a number of guidelines for patients with severe disease.

Nosocomial Infection Control

Seventeen guidelines provided recommendations involving infection and prevention control measures for bronchiolitis. Hand washing was recommended by all 13 guidelines that mentioned it. Use of gloves was suggested by all 6 guidelines that discussed their use. Of 9 guidelines, 4 recommended the use of aprons, 2 recommended the use of white/physician's coats, 2 recommended barrier procedures/appropriate personal protective equipment, and 1 did not recommend use. Fourteen of 16 guidelines recommended isolating or cohorting patients admitted to the hospital (Supplementary Table A6.5).

Risk Factors for Severe Disease

Twenty-nine guidelines considered the risk factors for developing severe disease. While guidelines agreed that prematurity is a risk factor for severe disease, there was variation in the gestational age below which children are considered at high risk for severe disease, ranging from <34 to <37 weeks of gestation, and the gestational age was undefined in several guidelines.

Guidelines also agreed that a younger age at presentation increases the risk of severe disease. However, the definition of this age in guidelines varied from <1 month to <12 months, with an age of <3 months most commonly used (Supplementary Table A6.6).

Guidelines agreed on congenital heart disease, chronic lung disease, immunodeficiency, neurological disorders, and exposure to tobacco smoke as risk factors for severe disease. Five guidelines reported exposure to environmental air pollution, and 6 reported poverty as risk factors for severe disease.

Indications for Hospital Admission

Twenty-seven guidelines provided recommendations on indications for hospital admission. Signs of moderate-to-severe respiratory distress, including nasal flaring, tachypnea, chest recessions/retractions, and accessory muscle use, were mentioned in 25 guidelines as indicators for hospital admission. The threshold for oxygen saturation as a guide for hospital admission in 26 guidelines varied from <88% to <95%. The most commonly specified oxygen saturation threshold ranged from <90% to <92%. There was also variability in the guidelines over the degree of tachypnea that would indicate that hospital admission is required (Supplementary Table A6.7).

Poor feeding or dehydration was recommended as an indication for hospital admission by all 25 guidelines that discussed it, with <50% of the usual intake stated in 5 guidelines as their definition of poor feeding. In all 21 guidelines that discussed the presence of cyanosis or hypoxemia, both were suggested as an indication for hospital admission. Twenty-four guidelines suggested a history of apnea as an indication for admission to hospital. Twenty-three guidelines specified that high risk infants (very young age and/or the presence of a significant medical condition) were indications for considering hospital admission.

Sixteen guidelines suggested considering poor social circumstances as an indication for admission to hospital. Five guidelines suggested severe malnutrition as an indication for hospital admission. Two guidelines suggested uncertainty over the diagnosis of bronchiolitis as an indication for hospital admission.

Discharge Criteria

Sixteen guidelines provided recommendations on criteria for discharge. Eleven guidelines suggested an improved respiratory effort as a criterion for discharge. Among guidelines that suggested oxygen saturation as a criterion for discharge, the level varied from >90% to >94%. Four guidelines stated "improved saturations" as a criterion without specifying a specific value (Supplementary Table A6.8).

All 16 guidelines that discussed adequate oral feeding recommended using it as a guide for discharge. Fifteen guidelines that discussed carer ability recommend considering the ability of the child's carer to cope at home and providing adequate

parental education as criteria for discharge. Thirteen guidelines recommended considering the need for follow-up to be arranged.

DISCUSSION

We identified 32 clinical practice guidelines providing recommendations for the diagnosis and management of bronchiolitis in children. There were a number of areas where there was general agreement between guidelines regarding the diagnosis of bronchiolitis, risk factors for severe disease, indicators for hospital admission, and discharge criteria. However, despite consensus within many of these areas, there remained variability over the specifics of different recommendations, often reflecting a paucity of evidence in some areas of commonly accepted practice. The comparison between guidelines highlighted variation and sometimes conflicting recommendations, particularly with regard to the pharmacological management of bronchiolitis. Some of this variability may be related to the capability of guideline teams to synthesize data, the purpose of the guidelines (particularly if a health economic perspective is included) and the change in available evidence with time. Many clinical practice guidelines were lacking in a number of key areas when evaluated using AGREE II criteria.

An important limitation in some of the reviewed guidelines is the lack of their consideration (by systematic literature review) of relevant evidence, with many scoring poorly in terms of rigor of development. Other guidelines failed to describe a systematic process for appraisal of evidence and development of recommendations. Common deficiencies included a failure to declare conflicts of interest, poor stakeholder involvement (reflecting a failure to consult with affected families), and a failure to consider the implementation of the recommendations. Clinical practice guidelines for bronchiolitis should ensure that they use appropriate development and reporting frameworks, such as the AGREE II criteria or the RIGHT (Essential Reporting Items for Practice Guidelines in Health) checklist, in formulating guidelines [9, 43]. By adhering to these standards, guidelines can improve their quality and promote their applicability and adoption in practice.

There was agreement in the majority of guidelines for the avoidance of unnecessary routine diagnostic investigations that did not alter treatment. Only when there was diagnostic uncertainty, complications were suspected, or there was a severe presentation did a number of guidelines suggest additional investigations.

Guidelines largely agreed in recommending against the routine use of adrenaline, corticosteroids, montelukast, antibiotics, and antivirals. However, guidelines differed in recommendations for use of these therapies in certain subsets of children presenting with bronchiolitis, such as those with severe disease. Use of alternative therapies, such as xylometazoline, helium, or immunomodulants, with a poor evidence base were mentioned by few guidelines.

The use of bronchodilators in managing bronchiolitis has been contentious. The most recent guidelines tended to concur with the most recent evidence against their routine use [44]. However, several guidelines still recommended a trial of bronchodilators in managing bronchiolitis. Another area of mixed recommendations in guidelines is the routine use of nebulized hypertonic saline. This variability may reflect the equivocal evidence for its effectiveness in treating bronchiolitis. For example, a number of systematic reviews have proposed that hypertonic saline is a safe and effective intervention [45, 46], while other recent clinical trials have provided no evidence to suggest that hypertonic saline improves outcomes in the management of bronchiolitis [47, 48]. Different oxygen saturation thresholds were recommended for guiding hospital admission and discharge and for commencing oxygen therapy. The evolving evidence around differences in outcomes with use of oxygen therapy, along with other context-specific factors, may be a key reason for the differences between guidelines. However, a recent trial suggested that outcomes may not differ significantly when an oxygen saturation target of $\geq 90\%$ is used [6]. In general, differing recommendations over the management of bronchiolitis may also in part reflect the change in the evidence base over time, and this evidence and other research should be incorporated into new guidance in future.

This review only included guidelines published from 1996 onward. Despite this, there have been significant developments in the evidence base of treatment for bronchiolitis over the past 2 decades. It is therefore likely that older guidelines included in this review were based on evidence that has since been outdated. For example, a number of more recent guidelines provided recommendations on high-flow nasal cannula, which this review did not investigate, in addition to use of CPAP. This review, notably, did not identify any guidelines from the World Health Organization East Mediterranean or South-East Asian regions and only identified 1 from the African Region. This may reflect limitations in search methods, which may not have identified non-English language guidelines published in certain regions. This limits the application of many of these recommendations for low-income countries.

Given that bronchiolitis is a leading cause of hospital admission among children, improving clinical practice by establishing high-quality, evidence-based guidelines has significant potential to improve health outcomes and health service efficiency. This review has highlighted variation and sometimes conflicting recommendations in guidelines for the diagnosis and management of bronchiolitis. The variability in guideline recommendations in a number of areas of bronchiolitis treatment highlights the need for standards that account for the most-recent evidence and are supported by an international consensus. We suggest that agencies publishing bronchiolitis clinical practice guidelines should adopt consensus standards

for clinical practice guidelines during their formulation or when they are updated, so that the presentation of the evidence base for decisions is improved and proper management of interests is promoted. Platforms should be created to promote greater understanding of the reasons for differences in national guidelines and, where appropriate, to promote greater uniformity of policies. We recommend conducting audits of adherence to existing national guidelines, to improve understanding of the current use of guidelines and to identify areas in which guideline implementation could be improved and thereby improve clinical practice among clinicians. This may in turn inform postgraduate programs of clinical training and continuing professional development on management of bronchiolitis.

RESCEU INVESTIGATORS

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SUPPLEMENTARY DATA

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Foundation during the conduct of the study and receiving grants and personal fees from the World Health Organization and Sanofi and grants from the Innovative Medicines Initiative (Horizon 2020) and the National Institute of Health Research outside the submitted work. S. C. is chair of the NICE panel, which wrote one of the guidelines assessed in this manuscript but was not involved in the quality assessment of guidelines, and reports receiving fees from Janssen, Ablynx, ReViral, and Pulmocide outside of the submitted work. H. C. reports receiving grants and personal fees from the World Health Organization, the Bill and Melinda Gates Foundations, and Sanofi during the conduct of the study. R. M. F. is an author in one of the included guidelines (Portugal). All other authors: No reported conflicts.

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