ISSN 2379-4046

EMERGENCY MEDICINE
OpenJournal

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Editorial

Forty-Four Questions I Would Like to Ask Bronchiolitis Guideline Writers and Researchers

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Article information
Received: June 11th, 2022; **Accepted:** July 6th, 2022; **Published:** July 8th, 2022

Cite this article
Melick LB. Forty-four questions I would like to ask bronchiolitis guideline writers and researchers. *Emerg Med Open J*. 2022; 8(1): e1-e6.
doi: 10.17140/EMOJ-8-e007

INTRODUCTION

As a clinician and academician with front-line experience in the management of the bronchiolitis syndrome, I have previously published opinions about the bronchiolitis guidelines.[1,2]

It is obvious that the de-implementation movement initiated by the bronchiolitis guidelines has not gone as planned. In the United States substantial elements of the bronchiolitis guidelines are generally not being followed in outpatient settings, emergency departments and pediatric intensive care units.[3-6] Guideline non-compliance is also a conspicuous international problem.[7-11] Studies attempting to understand the factors behind and to mitigate apparent resistance to the guidelines have been published.[4,12,13] Other published studies have focused on strategies to maximize de-implementation.[14-21]

Unfortunately, the bronchiolitis guidelines were challenged from the start by inpatient *versus* outpatient bias, lack of clarity or confusion over the disease definition, failure to address clinical distinctions between undifferentiated outpatients *versus* inpatients, the failure to provide management recommendations for bronchodilator responsive bronchiolitis look-a-like conditions and the de-implementation recommendations based on incomplete research of the only therapeutic tools available to the front-line provider.

The diagnosis of bronchiolitis is a central issue and the international lack of agreement and clarity in defining the disease syndrome called bronchiolitis attests to the difficulty of the task.[22-26] In the face of definition imprecision combined with disease heterogeneity and undifferentiated patients sharing bronchiolitis syndrome signs and symptoms, it is not surprising that the busy clinician would lack clarity in their target for treating wheezing infants.[27]

The 2014 American Academy of Pediatrics (AAP) bronchiolitis guidelines and multiple international bronchiolitis guidelines seem to have caused a troublesome phenomenon in healthcare. A distinct division, an "us against them" mentality, now exists between inpatient and outpatient services as well as between academicians and clinically dedicated non-academicians. Meanwhile various publications tout improvements or trends in compliance with the guidelines.[6,20,28] Decreased corticosteroid use, radiographs and viral testing are relatively low clinical value de-implementations and easy wins. On the other hand, de-implementation of albuterol, racemic epinephrine and hypertonic saline, the only potentially therapeutic options available, appear to remain a "line in the sand" for clinicians.

Clarity can sometimes come to a problem by asking the right questions. In this article I provide a list of questions I would rhetorically request to be answered by the bronchiolitis guideline writers and researchers.

NON-COMPLIANCE WITH THE GUIDELINES

1. What is your explanation for the wide-spread non-compliance with bronchiolitis guidelines?
2. When a child arrives to the emergency department with signs and symptoms of the bronchiolitis syndrome and severe respiratory distress, do you suggest that the clinician simply accept guideline recommendations and not use any of the de-implemented therapies?[29]
3. Is there any potential benefit from therapeutic trials of bronchodilators (albuterol, racemic epinephrine, or hypertonic saline) to determine which bronchiolitis syndrome patients may be responders or non-responders?
4. How would you defend your specific guidelines against criticisms leveled by the recent meta-analysis of bronchiolitis guidelines describing major flaws in their development?[30]

BRONCHIOLITIS

5. Do you agree that bronchiolitis is a syndrome?[31]
6. Are there any presentations of viral illnesses in children under 2 years of age that will present with the examination elements of the bronchiolitis syndrome and not be considered bronchiolitis?
7. Is it possible to confidently and consistently discern if the one-year-old child in respiratory distress with wheezing for the first time is bronchiolitis or wheezing from another etiology that may benefit from bronchodilators?
8. Can one easily differentiate bronchiolitis from other first time febrile viral illnesses with wheezing, adventitial sounds, and an upper respiratory tract infection?
9. If a wheezing bronchiolitis syndrome patient responds to albuterol, racemic epinephrine, or hypertonic saline, does that technically negate the diagnosis of bronchiolitis?
10. If a febrile wheezing child under two years of age fails to respond to bronchodilator medications does that suggest bronchiolitis or does it suggest the need for additional bronchodilator therapy and steroids?
11. Do you believe that infants with viral bronchiolitis exhibit a high degree of heterogeneity and that heterogeneity could have an impact on response to therapeutic interventions?[24,31,32]
12. Are respiratory syncytial virus (RSV) bronchiolitis patients under one-year of age clinically different from one- to two-year-old patients infected with rhinovirus, parainfluenza virus or adenovirus?
13. Can children infected with RSV be diagnosed with bronchiolitis if there is only wheezing along with other upper respiratory infections (URI) signs and symptoms but an absence of crackles?
14. Can children with other viral causes of bronchiolitis (rhinovirus, parainfluenza, adenovirus, influenza, human metapneumovirus, coronavirus) be diagnosed with bronchiolitis with absence of crackles and only wheezing with other URI signs and symptoms?
15. Is it possible that the clinical stage (early or late) of the viral illness in bronchiolitis might affect the therapeutic response to bronchodilators, hypertonic saline, or racemic epinephrine?
16. Does the current literature describing bronchiolitis subtypes, phenotypes and genotypes which appear to impact illness severity and potential therapeutic responsiveness, change your recommendations advising against trials of medications?[25,33-38]
17. If there is evidence that some phenotypes of bronchiolitis are more strongly associated with asthma features and are linked to higher risk for asthma development, would that influence your opinion about trials of albuterol, racemic epinephrine, or corticosteroid therapy?[39]

GENERAL THERAPY QUESTIONS

18. Do you believe that the wheezing bronchiolitis syndrome patient presenting to an emergency department should never receive a therapeutic trial of albuterol, racemic epinephrine, or hypertonic saline?
19. Do you believe that the wheezing bronchiolitis syndrome patient presenting to an emergency department will never have a significant therapeutic response to albuterol, racemic epinephrine, or hypertonic saline?
20. If your own child developed severe bronchiolitis, what therapeutic interventions would you allow his/her treating physician to use?
21. If your own child developed severe bronchiolitis, would you forbid the emergency physician from treating your child with albuterol, racemic epinephrine, or hypertonic saline?
22. Are you aware of the number of patients seen in the outpatient settings with the bronchiolitis syndrome who receive treatments with albuterol, racemic epinephrine or hypertonic saline; clinically improve and are discharged home?
23. Do your bronchiolitis guidelines acknowledge the clinical relevance of patients who partially respond to bronchodilators or hypertonic saline but do not avoid admission?
24. If a medication provides a positive clinical response, but does not decrease the frequency of hospital admission, is that an adequate justification for not using the medication?
25. Do your bronchiolitis guidelines acknowledge the clinical relevance of patients who have a therapeutic response to bronchodilators or hypertonic saline and were able to be admitted to the floor instead of the pediatric intensive care unit?

ALBUTEROL

26. Please explain why the 2014 AAP bronchiolitis guidelines recommend total de-implementation of albuterol in treating bronchiolitis when clinical responses to albuterol were reported in multiple guideline references[40-47] and the other referenced systematic reviews acknowledged being limited by the small poor-quality studies available?[48,49]
27. Do you believe that early, mild bronchiolitis in children under one or two-years of age never demonstrate a therapeutic response to bronchodilators such as albuterol?
28. If bronchiolitis is a heterogenous disease with different phenotypes and genotypes, is it possible that some bronchiolitis patients may respond to albuterol?[39]
29. Are the side effects of bronchodilators (tachycardia, tremulousness, ventilation-perfusion mismatch) truly serious enough to outweigh their use and assessment for potential benefit?

RACEMIC EPINEPHRINE

30. Does nebulized racemic epinephrine have any evidence of clinical benefit in the management of asthma or viral induced bronchospasm?[50-55]
31. What is your opinion regarding the use of racemic epinephrine for treating wheezing children under two years of age?
32. Are there any clinical presentations of bronchiolitis syndrome patients presenting to the emergency department setting where you think it would be appropriate to do a racemic epinephrine trial?
33. In the face of the 2006 and 2011 Cochrane reviews and a third systematic review showing evidence of racemic epinephrine benefit in the outpatient setting, please provide your strongest argument for continuing to support the 2014 AAP guidelines recommendation against the use of racemic epinephrine in the outpatient setting.[56-58]

"*Given that epinephrine has a transient effect and home administration is not routine practice, discharging an infant after observing a response in a monitored setting raises concerns for subsequent progression of illness*".

34. Is a recommendation based on speculation and unproven "what if" assumptions appropriate for a national guideline?
35. What is the strength of your evidence that bronchiolitis patients treated with racemic epinephrine and discharged will not have continued benefit?
36. Why would an early or mild bronchiolitis patient with a good clinical response to racemic epinephrine not be safe for discharge home?
37. Are you aware of any epinephrine or racemic epinephrine delivery options available for home treatments?[59,60]

HYPERTONIC SALINE

38. If hypertonic saline is recognized as beneficial in inpatients and is considered a safe intervention, why would de-implementation of its use in the outpatient setting be an appropriate recommendation?[1]
39. Since the publication of the bronchiolitis guidelines, has the pendulum of evidence supporting hypertonic saline use in bronchiolitis expanded and now benefit has been demonstrated in both inpatient and outpatient settings?[61-68]
40. If guideline writers and researchers continue to believe that hypertonic saline should not be used for treating outpatients, what is your basis for this recommendation?
41. Are you aware of any research that indicates poorer outcomes after hypertonic saline was stopped in a pediatric intensive care unit (PICU) setting?[69]

SUMMARY QUESTIONS

42. Should national and international organizations have delayed making full de-implementation recommendations for the only therapies available (albuterol, racemic epinephrine, hypertonic saline) for a heterogenous disease with a controversial definition and millions of undifferentiated patients with overlapping clinical presentations until better evidence had evolved?
43. Why have intensive care unit (ICU) admissions and use of non-invasive ventilation significantly increased since implementation of the bronchiolitis guidelines?[70-75]
44. Do you agree that evolving research on the most important de-implemented therapeutic modalities will provide the definitive evidence and allow a final assessment of the current bronchiolitis guidelines?

ACKNOWLEDGEMENTS

The author would like to thank Drs. Ronald Waldrop and Shane McKinney for their review and editorial advice concerning this paper.

FUNDING SOURCE

No external funding for this manuscript.

FINANCIAL DISCLOSURE

The author has financial relationships relevant to this article to disclose.

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