CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

http://doi.org/10.5281/zenodo.2537623

**Available online at: http://www.iajps.com** ***Review Article***

# REVIEW OF THE RECENT UPDATES REGARDING ACUTE ASTHMA EXACERBATION MANAGEMENT IN CHILDREN: A SIMPLE LITERATURE REVIEW

**Zainab Ibrahim Albahouth[1], Alaa Ahmed Algodsi[2], Altaf Mohammed Almoallem[3], Fatimah Sharif Modawi[4], Abdulrahman Muteb Almehaid[5], Naif Abdulaziz Alshenaifi[6], Abdullah Mohammed Almanea[6], Amer Hamoud Al Harbi[7], Alrashdi Faisal Saad S[8], Ibrahim Sulaiman Alduraywish[9], Mutlag Jaual Alqahtani[10], Besma sinan Bukhamsin[11]**

[1]Riyadh Elm University, [2]Ibn Sina National College, [3]Princess Nourah University, [4]King Khalid University, [5]King Saud University, [6]Muzahemiyah General Hospital, [7]King Fahd Specialist Hospital, [8]Jordan University of Science and Technology, [9]King Abdulaziz Naval Base Hospital, 10- Jubail General Hospital, 11-Arabian Gulf University

**Abstract:**

***Background:*** *Asthma is a chronic airway disease characterized by inflammation of the airway, bronchospasm, and hypersensitivity to various stimuli. The standard treatment of asthma exacerbation is the use of inhaled short-acting β-2 agonists, systemic corticosteroids and supplemental oxygen. Nevertheless, every step of treatment is under debate and the search for the most effective management plan continue.*

***Objective:*** *To review the recent literature discussed the different ways of acute asthma exacerbation management in children.*

***Method:*** *A lot of literature have been done in order to provide better outcomes for patients presented with asthma, in our review we aim to discuss the recent literature that discussed asthma management in children.*

***Conclusion:*** *Oxygen should be used as carrier gas for intermittent or continuous nebulization. Frequent nebulization with β-2 agonist at the onset of an asthma exacerbation has been reported to be effective but some cases may require combination of salbutamol along with ipratropium for relief of obstruction. Also, nebulized MgSO4 is a well-tolerated bronchodilator for acutely ill asthmatic patients, and can be administered safely. Dexamethasone can be the preferred oral corticosteroid in the emergency management of pediatric patients with acute asthma exacerbations as an alternative of multi-day regimen of prednisolone in order to avoid non-compliance.*

**Corresponding author:**
**Zainab Ibrahim Albahouth,**
Riyadh Elm University.

QR code

*Please cite this article in press Zainab Ibrahim Albahouth et al.,* ***Review of The Recent Updates Regarding Acute Asthma Exacerbation Management In Children: A Simple Literature Review.,*** *Indo Am. J. P. Sci, 2019; 06(01).*

## INTRODUCTION:

Asthma is a chronic airway disease characterized by inflammation of the airway, bronchospasm, and hypersensitivity to various stimuli. It is estimated that the lifetime prevalence of asthma is 15.6% in United Kingdom (1). In Saudi Arabia, the prevalence of asthma in the general population is 4.05% (2). Among schoolchildren between the ages of 8 and 16 years, it reaches 23% (3).

Asthma exacerbation, also termed asthma "attack" or "episode", is a very common condition in pediatric practice (4). Despite advances in asthma management and the introduction of guidelines specifically for pediatric asthma, acute exacerbations continue to occur and impose considerable morbidity on pediatric patients, thereby placing a considerable strain on health care resources as well as on the lives of affected children and their families (4,5).

Every step of treatment is under debate and the search for the most effective management plan continue. Therefore, in this review, we aim to discuss the different ways of acute asthma exacerbation treatment mentioned in the recent literature.

## METHODOLOGY:

***Sample***

We performed comprehensive search using biomedical databases; Medline, and PubMed, for studies concerned with asthma management in children published in English language. Keywords used in our search through the databases were as {Asthma, Asthma Exacerbation, Asthma Management, Children}. More relevant articles were recruited from references lists scanning of each included study.

***Analysis***

No software was used, the data were extracted based on specific form that contain (Title of the study, name of the author, Objective, Summary, Results, and Outcomes). Double revision of each author outcomes was applied to ensure the validity and minimize the errors.

## DISCUSSION:

Asthma exacerbations pathophysiology is complex. Exposure to a trigger can cause a complex interplay of factors like eosinophil and mast cell degranulation and epithelial damage. These lead to the release of histamine prostaglandin and leukotriene. This cascade will be supported by T cell and B cell differentiation and proliferation along with the promotion by cytokines. Subsequent inflammation, bronchoconstriction and mucus production cause airway obstruction and impairment of gas exchange (6). As the degree of airway obstruction progresses, expiration becomes active and inspiration starts before termination of the previous expiration. This will lead to air trapping and hyperinflation. Areas of obstruction and premature airway closure cause ventilation/perfusion mismatch, leading to hypoxemia (7).

Poor asthma control can lead to severe asthma exacerbations (8). Poor adherence to medicine is an important contributing factor to poor asthma control (4). A recent study showed that children with poor adherence to inhaled corticosteroids had a 21% increase in emergency department visits and a 70% increase in hospitalization (9). Exacerbations in the past year is also a factor associated with future risk according to GINA guidelines (10).

There are more than one contributing factor in most cases. This is true especially for severe exacerbations (11). Viral infections are of special importance because they contribute to up to 90% of exacerbations, especially during the fall and spring in temperate climates, when viral respiratory tract infections are most common. Furthermore, viral infections play a major role in seasonal peaks of exacerbations that occur simultaneously with the return of children to schools after summer and spring breaks (11,12).

Rhinovirus has been the most commonly identified virus in proven viral-induced asthma exacerbations in children and adolescents, although several viruses have been found in asthmatics. Other viruses detected and associated with asthma exacerbation included respiratory syncytial virus, enteroviruses, coronavirus, and human metapneumovirus (4,13).

Wheezing is the most specific sign of airflow obstruction. Occurring predominantly during expiration, with increasing airflow obstruction, wheezing can be heard during inspiration until it becomes absent with severely diminished airflow. It is most reliably documented by a trained health care practitioner using a stethoscope (preferred diagnostic method), but can be audible sometimes without a stethoscope. When parents report 'wheezing', it is important to verify what is meant because the term is often used nonspecifically to describe nasal or otherwise noisy or troubled breathing sounds unrelated to asthma.

## MANAGEMENT:

In summary, the standard treatment of asthma exacerbation is the use of inhaled short-acting β-2 agonists (salbutamol), systemic corticosteroids and supplemental oxygen (14). Oxygen should be used as carrier gas for intermittent or continuous nebulization (15). Current guidelines recommend the use of a

combination of β-2 agonists and anticholinergics (ipratropium) for asthma exacerbation. Frequent nebulization with β-2 agonist at the onset of an asthma exacerbation has been reported to be effective but some cases may require combination of salbutamol along with ipratropium for relief of obstruction. This may result in significantly longer bronchodilation in asthma exacerbation (16).

Available data shows a response rate of 88.5% with the use of salbutamol alone, whereas response was found to be 100% when salbutamol was used in combination with ipratropium bromide. Thus combination therapy may reduce the asthma exacerbation burden and emergency room visits (16,17). Moreover, (Kirkland et al.)(18) cochrane meta analysis of 23 studies confirmed that adding short-acting anticholinergics to short-acting β-2 agonists reduces hospitalizations and relapses but however, increases adverse events in patients who present to the emergency department with asthma exacerbations. Nevertheless, this combination reduced hospitalizations in patients with severe exacerbations (FEV1 or peak expiratory flow <50% predicted) but not in those with mild or moderate exacerbations (19). Another review assessed the combination and they found that the addition of inhaled anticholinergic agents to β-2 agonists reduced hospitalization and improved pulmonary function testing, but was also associated with increased rates of mild adverse events such as dry mouth, tremor, and anxiety (20). Moreover, (Memon et al.)(21) RCT did not find any superiority for the combination of nebulized salbutamol along with ipratropium bromide over salbutamol alone in the treatment of acute asthma exacerbation.

Some studies suggest Magnesium sulfate ($MgSO_4$) as an additional bronchodilator treatment option in patients resistant to standard therapy (22). $MgSO_4$ has been assessed in intravenous and nebulized forms. The nebulized route offers the potential advantage of a quick onset of action and reduced incidence of side effects. Its disadvantages include a reduced dose of drug delivered compared with the intravenous form, and increased respiratory effort of the patient to enhance the drug's effectiveness. The intravenous route provides direct access to the venous system, allowing the delivery of high drug concentrations. Disadvantages include the need for intravenous access and drug administration by infusion lasting for around 20 minutes (23). (Sarhan et al.)(22)'s recent double blind randomized controlled trial (RCT) results suggested that a combination of $MgSO_4$ and salbutamol may be the best choice for the management of acute exacerbations of asthma. Nebulized $MgSO_4$ is a well-tolerated bronchodilator for acutely ill asthmatic patients, and can be administered safely. Being cheap and readily available, it can be commonly used.

Since the anti-immunoglobulin (IgE) humanized monoclonal antibody omalizumab became the first biological treatment approved for treating allergic asthma, many small molecules and monoclonal antibodies targeting biomolecular specificities have been investigated for treating symptomatic asthma. Eosinophilic inflammatory infiltration is a central event in asthma pathogenesis. Interleukin-5 (IL-5) is the chief cytokine responsible for eosinophil production, survival, maturation and recruitment and activation at allergic inflammation sites (24). (Wang et al.)(25) conducted a meta-analysis of RCTs to assess the safety and efficacy of anti-IL-5 monoclonal antibodies therapy in patients with asthma. Their results showed that anti-IL-5 monoclonal therapies were associated with a significant reduction in asthmatic exacerbation compared with placebo. It also reduced blood and sputum eosinophils and improved quality of life along with lung functionality.

Patients with severe acute asthma are often dehydrated because of poor oral intake and increased insensible fluid losses. Appropriate fluid resuscitation and maintenance fluids are indicated. The key is to avoid over-hydration because of the increased risk of trans-pulmonary edema in children with severe asthma associated with large fluctuations in intrathoracic pressures. The use of half normal saline or isotonic solution in dextrose is preferred in the pediatric population (26).

Although most children improve after inhaled bronchodilator by nebulizer or spacer, some require intravenous treatment. For exacerbations that are refractory to initial treatments with inhaled and oral therapies, there is still doubt about which intravenous therapies are most likely to be helpful. β-2 agonists and aminophylline have different mechanisms of action that also affect their adverse effects profiles. Salbutamol and aminophylline cause bronchodilation in airways of children with exacerbations of asthma. Both agents probably work by inducing the c-AMP pathway. This pathway reduces intracellular calcium concentrations which relaxes airway smooth muscle. (Neame et al.)(27) published a review compared intravenous salbutamol and intravenous aminophylline in treating refractory asthma exacerbation. The evidence from RCTs for the

intravenous administration of either drug to children during an asthma exacerbation is minimal and inconsistent. A bolus of intravenous salbutamol may reduce symptoms and hasten recovery. Aminophylline infusions may improve lung function and in some studies have been shown to improve symptoms but this finding is not replicated in all studies. Despite the minimal evidence of benefits from RCTs, intravenous therapy probably does have a role in managing certain children with either refractory or severe exacerbations of asthma, or those who have previously required pediatric intensive care unit admission.

A cochrane review of 15 studies on intravenous β-2 agonists in asthma concluded that neither intravenous salbutamol nor intravenous terbutaline were any more effective in improving peak expiratory flow rate than inhaled salbutamol (28,29). International guidelines recommend the use of systemic corticosteroids in children under 6 years old with severe asthma exacerbations that do not respond to short-acting β-2 agonists and thus up to 38% of wheezing infants receive oral corticosteroids during their first year of life. This practice is based on the general belief that episodes of wheeze in young children are likely early manifestations of asthma caused by the same pathophysiologic process of airway inflammation and narrowing.

(Castro-Rodriguez et al.)(30) meta analysis evaluated the effectiveness of oral corticosteroids compared to placebo in preschoolers presenting with acute asthma exacerbations. They found that treatment with oral corticosteroids in the emergency department or hospital may be beneficial in toddlers and preschoolers with frequent asthma exacerbations as it was associated with lower risk of hospitalization. However, oral corticosteroids did not show any superiority over placebo among either inpatient or outpatient studies. Therefore, the use of oral corticosteroids in the treatment of recurrent wheezing in infants, toddlers and preschoolers remains controversial and needs further research. However, corticosteroid prescriptions such as prednisolone are filled in fewer than 45% of instances after emergency department discharge. This multi-day regimens of prednisone or prednisolone can lead to non-compliance in some patients. Nevertheless, single-dose dexamethasone can circumvent this non-compliance and the need for this multi-day regimens of prednisone or prednisolone. Small randomized controlled trials have suggested that dexamethasone works as well as prednisone and prednisolone in emergency department settings (31,32). (Watnick et al.)(33) paper results indicated that single-dose oral dexamethasone is associated with a decrease of emergency department relapse for pediatric patients with acute asthma exacerbations. They suggested that dexamethasone may be the preferred oral corticosteroid in the emergency management of pediatric patients with acute asthma exacerbations.

## CONCLUSION:

Oxygen should be used as carrier gas for intermittent or continuous nebulization. Frequent nebulization with β-2 agonist at the onset of an asthma exacerbation has been reported to be effective but some cases may require combination of salbutamol along with ipratropium for relief of obstruction. Also, nebulized MgSO4 is a well-tolerated bronchodilator for acutely ill asthmatic patients, and can be administered safely. Dexamethasone can be the preferred oral corticosteroid in the emergency management of pediatric patients with acute asthma exacerbations as an alternative of multi-day regimen of prednisolone in order to avoid non-compliance.

## REFERENCES:

1. Mukherjee, Mome, Andrew Stoddart, Ramyani P. Gupta, Bright I. Nwaru, Angela Farr, Martin Heaven, Deborah Fitzsimmons, Amrita Bandyopadhyay, Chantelle Aftab, Colin R. Simpson, Ronan A. Lyons, Colin Fischbacher, Christopher Dibben, Michael D. Shields, Ceri J. Phillips, David P. Strachan, Gwyneth A. Davies, Brian Mckinstry, and Aziz Sheikh. "The Epidemiology, Healthcare and Societal Burden and Costs of Asthma in the UK and Its Member Nations: Analyses of Standalone and Linked National Databases." BMC Medicine 14, no. 1 (2016). doi:10.1186/s12916-016-0657-8.
2. Moradi-Lakeh, Maziar, Charbel El Bcheraoui, Farah Daoud, Marwa Tuffaha, Hannah Kravitz, Mohammad Al Saeedi, Mohammed Basulaiman, Ziad A. Memish, Mohammad A. Almazroa, Abdullah A. Al Rabeeah, and Ali H. Mokdad. "Prevalence of Asthma in Saudi Adults: Findings from a National Household Survey, 2013." BMC Pulmonary Medicine 15, no. 1 (2015). doi:10.1186/s12890-015-0080-5.
3. Al Frayh R, Shakoor Z, Gad El Rab MO, Hasnain SM. Increased prevalence of asthma in Saudi Arabia. Ann Allergy Asthma Immunol. 2001;86(3):292–6.
4. Fu, Lin-Shien, and Ming-Chin Tsai. "Asthma Exacerbation in Children: A Practical Review." Pediatrics & Neonatology 55, no. 2 (2014): 83-91. doi:10.1016/j.pedneo.2013.07.004.
5. Jackson, David J., Annemarie Sykes, Patrick Mallia, and Sebastian L. Johnston. "Asthma Exacerbations: Origin, Effect, and Prevention." Journal of Allergy and Clinical Immunology

128, no. 6 (2011): 1165-174. doi:10.1016/j.jaci.2011.10.024.
6. Holgate, Stephen T. "Pathogenesis of Asthma." Allergy and Allergic Diseases: 1608-631. doi:10.1002/9781444300918.ch78.
7. Rodriguez-Roisin, Robert, Eugeni Ballester, Josep Roca, Antoni Torres, and Peter D. Wagner. "Mechanisms of Hypoxemia in Patients with Status Asthmaticus Requiring Mechanical Ventilation." American Review of Respiratory Disease 139, no. 3 (1989): 732-39. doi:10.1164/ajrccm/139.3.732.
8. Haselkorn, Tmirah, James E. Fish, Robert S. Zeiger, Stanley J. Szefler, Dave P. Miller, Bradley E. Chipps, F. Estelle R. Simons, Scott T. Weiss, Sally E. Wenzel, Larry Borish, and Eugene R. Bleecker. "Consistently Very Poorly Controlled Asthma, as Defined by the Impairment Domain of the Expert Panel Report 3 Guidelines, Increases Risk for Future Severe Asthma Exacerbations in The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) Study." Journal of Allergy and Clinical Immunology 124, no. 5 (2009). doi:10.1016/j.jaci.2009.07.035.
9. Rust, George, Shun Zhang, and Joshua Reynolds. "Inhaled Corticosteroid Adherence and Emergency Department Utilization among Medicaid-enrolled Children with Asthma." Journal of Asthma 50, no. 7 (2013): 769-75. doi:10.3109/02770903.2013.799687.
10. "2018 GINA Report: Global Strategy for Asthma Management and Prevention." Global Initiative for Asthma - GINA. https://ginasthma.org/2018-gina-report-global-strategy-for-asthma-management-and-prevention/.
11. Jartti, Tuomas, and James E. Gern. "Role of Viral Infections in the Development and Exacerbation of Asthma in Children." Journal of Allergy and Clinical Immunology 140, no. 4 (2017): 895-906. doi:10.1016/j.jaci.2017.08.003.
12. Johnston, Neil W., Sebastian L. Johnston, Geoff R. Norman, Jennifer Dai, and Malcolm R. Sears. "The September Epidemic of Asthma Hospitalization: School Children as Disease Vectors." Journal of Allergy and Clinical Immunology 117, no. 3 (2006): 557-62. doi:10.1016/j.jaci.2005.11.034.
13. Papadopoulos, N. G., I. Christodoulou, G. Rohde, I. Agache, C. Almqvist, A. Bruno, S. Bonini, L. Bont, A. Bossios, J. Bousquet, F. Braido, G. Brusselle, G. W. Canonica, K. H. Carlsen, P. Chanez, W. J. Fokkens, M. Garcia-Garcia, M. Gjomarkaj, T. Haahtela, S. T. Holgate, S. L. Johnston, G. Konstantinou, M. Kowalski, A. Lewandowska-Polak, K. Lødrup-Carlsen, M. Mäkelä, I. Malkusova, J. Mullol, A. Nieto, E. Eller, C. Ozdemir, P. Panzner, T. Popov, S. Psarras, E. Roumpedaki, M. Rukhadze, A. Stipic-Markovic, A. Todo Bom, E. Toskala, P. Van Cauwenberge, C. Van Drunen, J. B. Watelet, M. Xatzipsalti, P. Xepapadaki, and T. Zuberbier. "Viruses and Bacteria in Acute Asthma Exacerbations - A GA2LEN-DARE* Systematic Review." Allergy 66, no. 4 (2010): 458-68. doi:10.1111/j.1398-9995.2010.02505.x.
14. Rodrigo, Gustavo J., Carlos Rodrigo, and Jesse B. Hall. "Acute Asthma in Adults." Chest 125, no. 3 (2004): 1081-102. doi:10.1378/chest.125.3.1081.
15. Gleeson, J. G., S. Green, and J. F. Price. "Air or Oxygen as Driving Gas for Nebulised Salbutamol." Archives of Disease in Childhood 63, no. 8 (1988): 900-04. doi:10.1136/adc.63.8.900.
16. Rodrigo, G. J., and J. A. Castro-Rodriguez. "Anticholinergics in the Treatment of Children and Adults with Acute Asthma: A Systematic Review with Meta-analysis." Thorax 60, no. 9 (2005): 740-46. doi:10.1136/thx.2005.047803.
17. Rodrigo, Gustavo J., and Carlos Rodrigo. "First-Line Therapy for Adult Patients with Acute Asthma Receiving a Multiple-Dose Protocol of Ipratropium Bromide Plus Albuterol in the Emergency Department." American Journal of Respiratory and Critical Care Medicine 161, no. 6 (2000): 1862-868. doi:10.1164/ajrccm.161.6.9908115.
18. Kirkland, Scott W., Christine Vandenberghe, Britt Voaklander, Taylor Nikel, Sandra Campbell, and Brian H. Rowe. "Combined Inhaled Beta-agonist and Anticholinergic Agents for Emergency Management in Adults with Asthma." Cochrane Database of Systematic Reviews, 2017. doi:10.1002/14651858.cd001284.pub2.
19. Haydel, Micelle. "Review: Adding Anticholinergics to β2-agonists for Asthma Exacerbations Reduces Hospitalizations." Annals of Internal Medicine 166, no. 8 (2017). doi:10.7326/acpjc-2017-166-8-045.
20. Gottlieb, Michael, and Matthew J. Kuhns. "Do Inhaled Anticholinergic Agents in Addition to β-Agonists Improve Outcomes in Acute Asthma Exacerbations?" Annals of Emergency Medicine 70, no. 3 (2017): 421-22. doi:10.1016/j.annemergmed.2017.02.026.
21. Memon BN, Parkash A, Ahmed Khan KM, Gowa MA, Bai C. "Response to nebulized salbutamol versus combination with ipratropium

bromide in children with acute severe asthma." J Pak Med Assoc. 2016 Mar;66(3):243-6.
22. Sarhan HA, El-Garhy OH, Ali MA, Youssef NA. "The efficacy of nebulized magnesium sulfate alone and in combination with salbutamol in acute asthma." Drug Des Devel Ther. 2016;10:1927-33. doi:10.2147/DDDT.S103147.
23. Goodacre, Steve, Judith Cohen, Mike Bradburn, John Stevens, Alasdair Gray, Jonathan Benger, and Tim Coats. "The 3Mg Trial: A Randomised Controlled Trial of Intravenous or Nebulised Magnesium Sulphate versus Placebo in Adults with Acute Severe Asthma." Health Technology Assessment 18, no. 22 (2014). doi:10.3310/hta18220.
24. Cardet, Juan Carlos, and Elliot Israel. "Update on Reslizumab for Eosinophilic Asthma." Expert Opinion on Biological Therapy 15, no. 10 (2015): 1531-539. doi:10.1517/14712598.2015.1090972.
25. Wang, Fa-Ping, Ting Liu, Zhu Lan, Su-Yun Li, and Hui Mao. "Efficacy and Safety of Anti-Interleukin-5 Therapy in Patients with Asthma: A Systematic Review and Meta-Analysis." Plos One 11, no. 11 (2016). doi:10.1371/journal.pone.0166833.
26. Nievas, I. Federico Fernandez, and Kanwaljeet J. S. Anand. "Severe Acute Asthma Exacerbation in Children: A Stepwise Approach for Escalating Therapy in a Pediatric Intensive Care Unit." The Journal of Pediatric Pharmacology and Therapeutics 18, no. 2 (2013): 88-104. doi:10.5863/1551-6776-18.2.88.
27. Neame, Matthew, Octavio Aragon, Ricardo M. Fernandes, and Ian Sinha. "Salbutamol or Aminophylline for Acute Severe Asthma: How to Choose Which One, When and Why?" Archives of Disease in Childhood - Education & Practice Edition 100, no. 4 (2015): 215-22. doi:10.1136/archdischild-2014-306186.
28. Travers, Andrew A., Arthur P. Jones, Karen D. Kelly, Carlos A Jr Camargo, Samantha J. Barker, and Brian H. Rowe. "Intravenous Beta2-agonists for Acute Asthma in the Emergency Department." Cochrane Database of Systematic Reviews, 2001. doi:10.1002/14651858.cd002988.
29. Starkey, E. S., H. Mulla, H. M. Sammons, and H. C. Pandya. "Intravenous Salbutamol for Childhood Asthma: Evidence-based Medicine?" Archives of Disease in Childhood 99, no. 9 (2014): 873-77. doi:10.1136/archdischild-2013-304467.
30. Castro-Rodriguez, Jose A., Andrea A. Beckhaus, and Erick Forno. "Efficacy of Oral Corticosteroids in the Treatment of Acute Wheezing Episodes in Asthmatic Preschoolers: Systematic Review with Meta-analysis." Pediatric Pulmonology 51, no. 8 (2016): 868-76. doi:10.1002/ppul.23429.
31. Cooper, William O., and Gerald B. Hickson. "Corticosteroid Prescription Filling for Children Covered by Medicaid Following an Emergency Department Visit or a Hospitalization for Asthma." Archives of Pediatrics & Adolescent Medicine 155, no. 10 (2001): 1111. doi:10.1001/archpedi.155.10.1111.
32. Keeney, G. E., M. P. Gray, A. K. Morrison, M. N. Levas, E. A. Kessler, G. D. Hill, M. H. Gorelick, and J. L. Jackson. "Dexamethasone for Acute Asthma Exacerbations in Children: A Meta-analysis." Pediatrics 133, no. 3 (2014): 493-99. doi:10.1542/peds.2013-2273.
33. Watnick, Caroline S., Daniel Fabbri, and Donald H. Arnold. "Single-dose Oral Dexamethasone Is Effective in Preventing Relapse after Acute Asthma Exacerbations." Annals of Allergy, Asthma & Immunology 116, no. 2 (2016): 171-72. doi:10.1016/j.anai.2015.11.015.