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Outpatient Medications Deimplemented by the AAP Bronchiolitis Guidelines: An Umbrella Review of Meta-analyses

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Table S1: PICOS Framework

P.I.C.O.S.	Patient/Population	Intervention	Comparator	Outcome	Study Designs
Inclusion Criteria	Infants and children diagnosed with bronchiolitis treated in the outpatient or emergency department setting	Study Drugs: Albuterol, Epinephrine, and Hypertonic Saline	Placebo or standard treatment or comparisons of other treatments	Clinical response and rate of hospitalization	Meta-analyses and network meta-analyses with outpatient sub-analyses
Exclusion Criteria	Hospitalized infants and children diagnosed with bronchiolitis	Non-study drugs or other treatment interventions	Not performed	Any other outcome such as oxygen saturation, or duration of hospitalization or treatment	Systematic review only or mixed inpatient and outpatient sub-analyses or inpatient sub-analyses only

Table S1: The PICOS framework defining the inclusion and exclusion criteria for our umbrella review of meta-analyses and network meta-analyses.

Table S2: Epinephrine Excluded Studies with Explanation

Study ID	Exclusion Reason	Study Design	Notes
Gadomski et al.[1]	Wrong Drug	Meta-analysis	Albuterol Cochrane Review
Fernandes et al.[2]	Wrong Drug	Meta-analysis	Glucocorticoids Cochrane Review
Kirolos et al.[3]	Wrong Study Design	Systematic Review	Review of Bronchiolitis Guidelines
Bourke et al.[4]	Wrong Study Design	Systematic Review	Bronchiolitis Review
Kua et al.[5]	Wrong Drug	Meta-analysis	Epinephrine and Glucocorticoids
Lozano et al.[6]	Wrong Study Design	Systematic Review	Bronchiolitis Review
Pereira et al.[7]	Wrong Drug	Meta-analysis	Epinephrine plus Hypertonic Saline
Gadomski et al.[8]	Wrong Drug	Meta-analysis	Albuterol Cochrane Review
Heikkilä et al.[9]	Wrong Drug	Meta-analysis	Hypertonic Saline
Gadomski et al.[10]	Wrong Drug	Meta-analysis	Albuterol Cochrane Review
King et al.[11]	Wrong Study Design	Systematic Review	Systematic Review
Fernandes et al.[12]	Wrong Drug	Meta-analysis	Glucocorticoids Cochrane Review
Chandelia et al.[13]	Wrong Drug	Meta-analysis	Magnesium Sulfate
Castro-Rodriguez et al.[14]	Wrong Study Design	Review Article	Review of systematic reviews
Kellner et al.[15]	Wrong Drug	Meta-analysis	Albuterol
Veerappan et al.[16]	Wrong Study Design	Review Article	Croup and Corticosteroids
Tsygankov et al.[17]	Wrong Study Design	Systematic Review	ICU Patients
Zhang et al.[18]	Wrong Drug	Meta-analysis	Hypertonic Saline Cochrane Review
Zhang et al.[19]	Wrong Drug	Meta-analysis	Hypertonic Saline Cochrane Review
Gonzalez et al.[20]	Publication Type	Consensus Article	Consensus Conference
House et al.[21]	Wrong Drug	Meta-analysis	Nebulized Normal Saline
Hartling et al.[22]	Duplicate Data	Meta-analysis	Same Data as Cochrane Review
Hartling et al.	Missing Article	Meta-analysis	Cochrane Review 2009 not found
Guo et al.[23]	Wrong Population	NW Meta-analysis	Mixed Inpatient and Outpatient

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Table S3: 3% NaCl Excluded Studies with Explanation

Study ID	Exclusion Reason	Study Design	Notes
Heikkilä et al.[1]	Wrong Population	Meta-analysis	Update with inpatient focus
Maguire et al.[2]	Wrong Population	Meta-analysis	Inpatient population focus
Harrison et al.[3]	Background Article	Review Article	Trial Sequential Analysis
Brooks et al.[4]	Wrong Population	Meta-analysis	Inpatient
Heikkilä et al.[5]	Background Article	Review Article	Cost Effectiveness
Lin et al.[6]	Wrong Outcome	Meta-analysis	Studying Dose Effect of HTS
Pereira et al.[7]	Wrong Population	Meta-analysis	Inpatient
Heikkilä et al.[8]	Wrong Population	Meta-analysis	Inpatient
Chandelia et al.[9]	Wrong Drug	Meta-analysis	MgSO4 Cochrane Review
Guo et al.[10]	Wrong Population	NW Meta-analysis	Mixed Inpatient and Outpatient
Dalziel et al.[11]	Wrong Publication Type	Review Article	Comparison of Guidelines
Tsygankov et al.[12]	Wrong Study Design	Systematic Review	ICU Patients
Kirolos et al.[13]	Wrong Study Design	Systematic Review	SR of Bronchiolitis Guidelines
Axelsson et al.[14]	Wrong Study Design	Review Article	Inpatients, Swedish Article
Chang et al.[15]	Wrong Population	Expert Panel Report	Chronic Cough
Caballaro et al.[16]	Wrong Study Design	Systematic Review	Clinical Treatment Review
Everard et al.[17]	Wrong Study Design	Systematic Review	RCT and Systematic Review
Badgett et al.[18]	Wrong Study Design	Systematic Review	Living Systematic Review

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Table S4: Albuterol/Salbutamol Excluded Studies with Explanation

Study ID	Exclusion Reason	Study Design	Notes
Roque et al.[1]	Wrong Drug	Meta-analysis	Chest Physiotherapy
Cai et al.[2]	Wrong Population	Meta-analysis	Mixed inpatient and outpatient
Bourke et al.[3]	Wrong Study Design	Systematic Review	Not a meta-analysis
Lozano et al.[4]	Wrong Study Design	Systematic Review	Not a meta-analysis
Roque et al.[5]	Wrong Drug	Meta-analysis	Chest Physiotherapy
Hartling et al.[6]	Wrong Drug	Meta-analysis	Epinephrine Cochrane Review
Gomez et al.[7]	Foreign language	Meta-analysis	Derivative study
Hartling et al.[8]	Wrong Drug	Meta-analysis	Epinephrine Cochrane Review
Chandelia et al.[9]	Wrong Drug	Meta-analysis	Magnesium Sulfate
Enriquez et al.[10]	Wrong Drug	Meta-analysis	Nebulized deoxyribonuclease
Umoren et al.[11]	Wrong Drug	Meta-analysis	Steam or humidified oxygen
Castro-Rodriguez et al.[12]	Wrong Study Design	Review Article	Review of systematic reviews
Hartling et al.[13]	Wrong Drug	Meta-analysis	Epinephrine
Korppi et al.[14]	Wrong Study Design	Review Article	Not a meta-analysis
AAP Committee[15]	Publication type	Guidelines	2006 Bronchiolitis Guidelines
King et al.[16]	Wrong Study Design	Systematic Review	Not a Meta-analysis
Kellner et al.[17]	Wrong Population	Meta-analysis	Mixed inpatient and outpatient
Kellner et al.[18]	Wrong Population	Meta-analysis	Mixed inpatient and outpatient

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Table S5

Variable*	Epinephrine	Hypertonic Saline	Albuterol
Studies Identified *Plus* Citation Search	28	29	24
Studies Included	4	11	6
No. of Meta-analyses	2	10	4
No. of Network Meta-analyses	2	1	2
Studies Showing Clinical Improvement	4	11	5
Improved Clinical Score	3	7	4
Decreased Admissions	3	9	1

*Data reported as number of studies.

TABLE S5: Summary of study search and clinical results for the three deimplemented drugs.

Table S6: Epinephrine and Hospital Admission Data

Name	agents	Year	N	admit_point	admit_lb	admit_ub	p_value
Elliott SA	Epi Placebo	2021	1587	0.64	0.44	0.93	0.02
Hartling L	Epi Placebo	2011	995	0.67	0.50	0.89	0.01
Hartling L	Epi Placebo	2004	105	0.51	0.18	1.42	0.20
Hartling L	Epi Placebo	2011	920	0.67	0.50	0.89	0.01

Table S7: Epinephrine and Clinical Scores Data

studyname	year	drug1	drug2	totaln	pointestimate	lowerbound	upperbound	p_value_c
Hartling CR	2011	Epinephrine	Placebo	975	-0.40	-0.58	-0.28	0.00
Hartling CR	2004	Epinephrine	Placebo	105	-0.55	-1.11	0.02	0.06
Hartling CR	2004	Epinephrine	Placebo	30	-0.81	-1.56	-0.07	0.03
Hartling NMA	2011	Epinephrine	Placebo	900	-0.45	-0.66	-0.23	0.00
Hartling NMA	2011	Epinephrine	Placebo	30	-0.83	-1.58	-0.08	0.03

Table S8: Hypertonic Saline and Hospital Admissions Data

Name	year	comb2	admit_point	admit_lb	admit_ub	p_value
Zhang L, Mendoza-Sas	2015	HS only v NS only	0.85	0.52	1.40	0.5201
Zhang L, Gunther CB, F	2018	HS only v NS only	0.87	0.68	1.11	0.2653
Elliott SA, Gaudet LA, F	2021	HS only v NS only	0.84	0.56	1.26	0.3993
Zhang L, Mendoza-Sas	2023	HS only v NS only	0.87	0.69	1.08	0.2230
Zhang L, Mendoza-Sas	2015	HS+ ALB v NS +ALB	0.76	0.55	1.06	0.1011
Zhang L, Gunther CB, F	2018	HS+ ALB v NS +ALB	0.72	0.52	0.99	0.0455
Zhang L, Mendoza-Sas	2023	HS+ ALB v NS +ALB	0.78	0.55	1.10	0.1600
Elliott SA, Gaudet LA, F	2021	HS+ALB v NS	0.44	0.23	0.84	0.0130
Elliott SA, Gaudet LA, F	2021	HS +EPI v NS	0.58	0.32	1.06	0.0746
Zhang L, Mendoza-Sas	2017	HS v NS with other agents	0.86	0.76	0.98	0.0200
Hsieh CW, Chen C, Su	2020	HS v NS with other agents	0.85	0.74	0.98	0.0233
Chen YJ, Lee WL, Wan	2014	HS v NS with other agents	0.59	0.37	0.93	0.0248
Zhang L, Mendoza-Sas	2013	HS v NS with other agents	0.63	0.37	1.07	0.0881
Heikkilä P, Renko M, Kc	2018	HS v NS with other agents	0.77	0.62	0.96	0.0199
Zhang L, Mendoza-Sas	2008	HS v NS with other agents	0.63	0.34	1.17	0.1428
Yu JF, Zhang Y, Liu ZB	2022	HS v NS with other agents	0.74	0.59	0.91	0.0065

Appendix S1: PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	See page 1.
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	See page 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	See page 4.
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	See page 4.
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	See pages 5-7.
Information sources	6	Specify all databases, registers, websites, organizations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	See page 5-7.
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	See page 5-7.
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	See page 5-7.
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	See page 5-7.
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	See page 5-7.
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	N/A
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	N/A
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	See Albatross charts.
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	N/A
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	N/A
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	See figures, tables and Albatross charts.
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	N/A
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	N/A
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	N/A
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	N/A

Appendix S1: PRISMA 2020 Checklist

Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	N/A

Section and Topic	Item #	Checklist item	Location where item is reported
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	See combined PRISMA flow chart.
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	See supplemental data.
Study characteristics	17	Cite each included study and present its characteristics.	See Table 1.
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	See Table 1.
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	N/A
Results of syntheses	20a	For each synthesis, briefly summarize the characteristics and risk of bias among contributing studies.	N/A
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	N/A
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	N/A
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	N/A
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	N/A
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	See Table 1.
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	See pages 16-20.
	23b	Discuss any limitations of the evidence included in the review.	See page 20-21.
	23c	Discuss any limitations of the review processes used.	See page 20-21.
	23d	Discuss implications of the results for practice, policy, and future research.	See page 22.
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	N/A
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	N/A
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	See title page
Competing interests	26	Declare any competing interests of review authors.	See title page.
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	See methods section and supplemental data.

Appendix S1: PRISMA 2020 Checklist

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

Appendix S2: Search Strategies

PubMed:

Albuterol and bronchiolitis: (("levalbuterol"[MeSH Terms] OR "levalbuterol"[All Fields] OR "albuterol"[All Fields] OR "albuterol"[MeSH Terms] OR "salbutamol"[All Fields]) AND ("bronchiolitis"[MeSH Terms] OR "bronchiolitis"[All Fields] OR "bronchiolitides"[All Fields])) AND (meta-analysis[Filter] OR systematicreview[Filter])

Racemic epinephrine and bronchiolitis: (("racepinephrine"[MeSH Terms] OR "racepinephrine"[All Fields] OR (("racemate"[All Fields] OR "racemates"[All Fields] OR "racemic"[All Fields] OR "racemically"[All Fields] OR "racemization"[All Fields] OR "racemizations"[All Fields] OR "racemize"[All Fields] OR "racemized"[All Fields] OR "racemizes"[All Fields] OR "racemizing"[All Fields]) AND "ephinephrine"[All Fields]) OR ("epinephrine"[MeSH Terms] OR "epinephrine"[All Fields] OR "adrenalin"[All Fields] OR "adrenaline"[All Fields] OR "epinephrin"[All Fields] OR "epinephrines"[All Fields])) AND ("bronchiolitis"[MeSH Terms] OR "bronchiolitis"[All Fields] OR "bronchiolitides"[All Fields])) AND (meta-analysis[Filter] OR systematicreview[Filter])

Hypertonic saline and bronchiolitis: (("saline solution, hypertonic"[MeSH Terms] OR ("saline"[All Fields] AND "solution"[All Fields] AND "hypertonic"[All Fields]) OR "hypertonic saline solution"[All Fields] OR ("hypertonic"[All Fields] AND "saline"[All Fields]) OR "hypertonic saline"[All Fields]) AND ("bronchiolitis"[MeSH Terms] OR "bronchiolitis"[All Fields] OR "bronchiolitides"[All Fields])) AND (meta-analysis[Filter] OR systematicreview[Filter])

Scopus:

Albuterol and bronchiolitis: TITLE-ABS-KEY (albuterol) OR TITLE-ABS-KEY (salbuterol) OR TITLE-ABS-KEY (levalbuterol) AND TITLE-ABS-KEY (bronchiolitis) OR TITLE-ABS-KEY (bronchiolitides) AND TITLE-ABS-KEY (systematic AND review) OR TITLE-ABS-KEY (meta-analysis) OR TITLE-ABS-KEY (network AND meta-analysis)

Racemic epinephrine and bronchiolitis: TITLE-ABS-KEY (racepinephrine) OR TITLE-ABS-KEY (racemic AND epinephrine) OR TITLE-ABS-KEY (epinephrine) AND TITLE-ABS-KEY (bronchiolitis) OR TITLE-ABS-KEY (bronchiolitides) AND TITLE-ABS-KEY (systematic AND review) OR TITLE-ABS-KEY (meta-analysis) OR TITLE-ABS-KEY (network AND meta-analysis)

Hypertonic saline and bronchiolitis: TITLE-ABS-KEY (hypertonic AND saline AND solution) OR TITLE-ABS-KEY (saline AND solution) OR TITLE-ABS-KEY (hypertonic) AND TITLE-ABS-KEY (bronchiolitis) OR TITLE-ABS-KEY (bronchiolitides) AND TITLE-ABS-KEY (systematic AND review) OR TITLE-ABS-KEY (meta-analysis) OR TITLE-ABS-KEY (network AND meta-analysis)