

Improving the management of infants with bronchiolitis presenting to the emergency department

Ed Oakley

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DECLARATION

This is to certify that:

1. This thesis comprises only my original work towards the Doctor of Medical Science except where indicated in the preface.
2. This work has not been submitted previously, in whole or in part, to qualify for any other higher academic degree except as part of advanced trainee project of the Royal Australasian College of Physicians or the Australasian College for Emergency Medicine.
3. Due acknowledgement has been made in the text to all other material used.
4. Any editorial work, paid or unpaid, carried out by a third party is acknowledged.
5. Ethics procedures and guidelines have been followed.
6. The thesis is less than 100,000 words in length, exclusive of tables, bibliographies and appendices.

Signature

Ed Oakley

Date 20/03/2020

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Medical Students:

Ms Nisa Sheriff

Fellows and trainees:

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Professor David Johnson

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PREFACE

Chapter 1:

Management of Bronchiolitis in Australasian Emergency Departments

Paper 1-1:

Babl, Franz E, Sheriff, Nisa, Neutze, Jocelyn, Borland, Meredith, Oakley, Ed.
Bronchiolitis Management in Pediatric Emergency Departments in Australia and New Zealand: A PREDICT Study.

Pediatric Emergency Care 2008;24(10), 656-658

I assisted with the development of the protocol. I assisted in the analysis and led the interpretation of the outcomes. This study formed part of the thesis for a Bachelor of Medical Science submitted by Ms Sheriff to the University of Melbourne.

Chapter 2:

Exploration of methods of hydration in patients with bronchiolitis in the emergency department and admitted to hospital in Australia and New Zealand

Paper 2-1:

Ed Oakley, Franz E Babl, Jason Acworth, Meredith Borland, David Kreiser, Jocelyn Neutze, Theane Theofilos, Susan Donath, Mike South and Andrew Davidson. The Paediatric Research in Emergency Departments International Collaborative (PREDICT).

A prospective randomised trial comparing nasogastric with intravenous hydration in children with bronchiolitis (protocol). The comparative rehydration in bronchiolitis study (CRIB).

BMC Pediatrics; 2010;10:37 (<http://www.biomedcentral.com/1471-2431/10/37>)

I developed the protocol and obtained ethics approval with Professor Babl, and Associate Professor Donath. I coordinated the recruitment of sites for the study and led the application for funding from the National Health and Medical Research Council. I wrote the paper.

Paper 2-2:

Ed Oakley, Meredith Borland, Jocelyn Neutze, Jason Acworth, David Krieser, Stuart Dalziel, Andrew Davidson, Susan Donath, Kim Jachno, Mike South, Theane

Theophilos, Franz E Babl, for the Paediatric Research in Emergency Departments International Collaborative (PREDICT).

Nasogastric hydration versus intravenous hydration for infants with bronchiolitis: a randomised trial.

Lancet Respiratory Medicine 2013;1(2), 113 – 120 IF:23.0

I developed the protocol together with Professor Babl and Associate Professor Donath. I obtained the multi-site ethics approval with Ms Theophilos. I obtained funding for the study with a project grant from the National Health and Medical Research Council. I recruited the sites for the study and led the Trial Steering Committee and Data Monitoring Committee. I oversaw recruitment of patients. I assisted the analysis of the data with Associate Professor Donath and Ms Kim Jachno. I wrote the paper.

Paper 2-3:

Oakley E; Carter R; Murphy B; Borland M; Neutze J; Acworth J; Krieser D; Dalziel S; Davidson A; Donath S; Jachno K; South M; Babl FE; Paediatric Research in Emergency Departments International Collaborative (PREDICT).

Economic evaluation of nasogastric versus intravenous hydration in infants with bronchiolitis.

Emergency Medicine Australasia. 2017;29(3):324-329.

I developed the protocol with Ms Murphy. I collected the cost data and supervised the collection of the outcome data. I analysed the data with Professor Carter. I wrote the paper with Professor Carter.

Chapter 3:

Exploring Hydration Methods Used for Infants Under 2 Months of Age with Bronchiolitis

Paper 3-1:

Ed Oakley, Sonny Bata, Sharmila Rengasamy, David Krieser, John Cheek, Kim Jachno, Franz E. Babl,

Nasogastric Hydration in Infants with Bronchiolitis Less Than 2 Months of Age.

The Journal of Pediatrics. November 2016;178, 241–245.e1

I developed the protocol together with Professor Babl, and obtained ethics approval. The data were collected by Drs Bata and Rengasamy under my direct supervision. I

assisted in the analysis with Ms Jachno and Dr Bata. I supervised the writing of the paper. This study formed part of an advanced trainee project submitted by Dr Bata to the Royal Australasian College of Physicians.

Chapter 4:

Paper 4-1:

Bronchiolitis management in Australian and New Zealand Intensive Care Units

Oakley E; Chong V; Borland M; Neutze J; Phillips N; Krieser D; Dalziel S; Davidson A; Donath S; Jachno K; South M; Fry A; Babl FE.

Intensive care unit admissions and ventilation support in infants with bronchiolitis.

Emergency Medicine Australasia. 2017;29(4), 421-428

I developed the protocol and obtained ethics approval. The data were obtained by Dr Chong under my direct supervision. I directly supervised the analysis. I wrote the paper. This study formed part of an advanced trainee project submitted by Dr Chong to the Royal Australasian College of Physicians.

Chapter 5:

Exploring low value care in bronchiolitis in Australia and New Zealand

Paper 5-1:

Oakley E; Brys T; Borland M; Neutze J; Phillips N; Krieser D; Dalziel SR; Davidson A; Donath S; Jachno K; South M; Williams A; Babl FE; Paediatric Research in Emergency Departments International Collaborative (PREDICT).

Medication use in infants admitted with bronchiolitis. *Emergency Medicine Australasia*. 2018;30(3), 389-397

I developed the protocol. I obtained ethics approval with Ms Williams. I supervised collection of the data under my direct supervision. I directly supervised and assisted in the analysis. I wrote the paper. This study formed part of an advanced trainee project submitted by Dr Brys to the Royal Australasian College of Physicians.

Chapter 6:

Providing evidence for the use of high flow nasal cannula in bronchiolitis

Paper 6-1:

O'Brien S; Craig S; Babl FE; Borland ML; Oakley E; Dalziel SR; Paediatric Research in Emergency Departments International Collaborative (PREDICT) Network, Australasia. 'Rational use of high-flow therapy in infants with bronchiolitis. What do the latest trials tell us?' A Paediatric Research in Emergency Departments International Collaborative perspective.

Journal of Paediatrics & Child Health. 55(7):746-752, 2019 Jul

I was the senior Australian author on this paper. I assisted with the search strategy and with the assistance of Ms O'Brien and Professor Dalziel reviewed the papers. I assisted with the analysis and writing of the paper.

Chapter 7

Improving bronchiolitis care - Knowledge mobilisation and translation

Paper 7-1:

Catherine L Wilson, David Johnson, and Ed Oakley on behalf of the Paediatric Research in Emergency Departments International Collaborative (PREDICT) network. Knowledge translation studies in paediatric emergency medicine: A systematic review of the literature.

Journal of Paediatrics and Child Health 52 (2016) 112–125

I was the senior author on this paper and developed the protocol with Ms Wilson. I performed the study with the assistance of Ms Wilson who performed the data search under my direct supervision. I directly supervised and assisted in the analysis and writing of the paper.

ETHICS APPROVAL, FUNDING AND STUDY SITE

Ethics

Ethics approval for all studies was obtained at the Human Research and Ethics Committee at all study hospitals, with multi institutional ethics agreements obtained at The Royal Children's Hospital, Melbourne, Australia.

Papers 1-1, 2-1, 2-2, 2-3, required prospective written informed consent; papers 3-1, 4-1, 5-1, 6-1 and 6-2 received a waiver of consent.

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Papers 2-1, 2-2, 2-3, 3-1 4-1, 5-1, 6-1

The Samuel Nissen Charitable Foundation Melbourne, Australia

2-1, 2-2, 2-3, 4-1, 5-1

Murdoch Children's Research Institute, Melbourne, Australia

1-1, 2-1, 2-2, 2-3, 4-1, 5-1

All papers drew on in kind support from the Murdoch Childrens Research Institute, Melbourne, Australia, and infrastructure support from the Victorian Government's Operational Infrastructure Support Program, Melbourne, Victoria.

The funders had no influence on study design, protocol development, data collection, analysis or the writing of the papers.

Study Sites

Multicentre studies included the following institutions:

Paper 1-1: The Royal Children's Hospital Melbourne,, Monash children's Hospital Melbourne, Sunshine Hospital Melbourne, The Royal Children's Hospital Brisbane, Mater Children's Hospital Brisbane, Princess Margaret Hospital Perth, Women's and Children's Hospital Adelaide, Sydney Children's Hospital Sydney, Westmead

Children's Hospital Sydney, KidzFirst Hospital Middlemore NZ, Starship Children's Hospital Auckland NZ.

Papers 2-1, 2-2, 2-3, 4-1,5-1: The Royal Children's Hospital Melbourne, Monash Children's Hospital Melbourne, Sunshine Hospital Melbourne, The Royal Children's Hospital Brisbane, Princess Margaret Hospital Perth, KidzFirst Hospital Middlemore NZ, Starship Hospital Auckland NZ.

Paper 3-1: Royal Children's Hospital, Monash Children's Hospital, and Sunshine Hospital in Melbourne.

All studies were conducted in the Emergency Department at the Royal Children's Hospital, Melbourne, Australia. The Royal Children's Hospital is a 320 bed free-standing publicly-funded tertiary children's hospital. The Murdoch Children's Research Institute, the largest child health research institute in the Southern hemisphere, and the Department of Paediatrics of the University of Melbourne are co-located at the Royal Children's Hospital Campus. I hold appointments with all three institutions. The Emergency Department at Royal Children's Hospital currently has an annual census of 90,000 attendances. It is the only designated paediatric trauma centre for the state of Victoria (population of 5 million). Major trauma patients are seen to age 16, minor trauma and medical patients to 18 years of age. Older medical patients are only seen in the Emergency Department at Royal Children's Hospital if they have not been transitioned to an adult service.

Some studies make reference to the Paediatric Research in Emergency Departments International Collaborative (PREDICT) network. The Emergency Department at Royal Children's Hospital is a member of PREDICT, a collaboration of 15 major paediatric emergency departments in Australia and New Zealand. I was a founding member of PREDICT, Chair from 2009-2014, and remain a member of the executive.

SUMMARY

This thesis represents a compilation of peer-reviewed papers addressing the care for children presenting to emergency departments with bronchiolitis. After an introductory chapter, papers related to one of several themes are briefly introduced and placed in context with each other.

The papers, and their compilation in this thesis, aim to provide guidance for paediatricians and emergency physicians caring for children on how to bronchiolitis in hospital, with specific attention paid to hydration methods, reducing low value care and high flow nasal cannula use. Many aspects of this work, including certain research findings, are being used by, or have been implemented in, the Emergency Department at Royal Children's Hospital and other emergency departments across Victoria, Australia, as well as interstate and overseas.

I take primary responsibility for the initial concept, design, protocol development and successful execution of all projects used for this thesis. To my knowledge, no other co-author has presented papers from this compilation for submission as part of a degree. Exceptions are the use of parts of the projects in the fulfilment of Advanced Trainee requirements for the Royal Australasian College of Physicians or the Australasian College for Emergency Medicine, or for advanced medical students in the fulfilment of a Bachelor of Science through the University of Melbourne.

THESIS OUTLINE

This thesis is divided into six chapters or themes which are linked by the ultimate goal of improving care for infants presenting with bronchiolitis to emergency departments in Australia and New Zealand

In **Chapter 1** of this thesis, I present data from a survey of paediatric emergency regarding management strategies for children presenting to emergency departments with bronchiolitis. This is compared with international literature. Some opportunities for learning are outlined.

In **Chapters 2** I present the protocol, study results and economic analysis of a seven centre randomised controlled trial (RCT) of two hydration methods commonly in use in Australia and New Zealand in children 2 months to 1 year of age with bronchiolitis. Best practice from these results is discussed.

In **Chapter 3**, I present a three site, single state review of hydration practices in children under 2 months of age with bronchiolitis, and compare outcomes with those from the study presented in Chapter 2. I also discuss how the study results from chapter 2 have influenced management.

In **Chapters 4 and 5**, I present data from two observational studies using the cohort of all infants presenting to the emergency department during the period of recruitment for, and at all sites involved in the study in chapter 2. The first study reports admission to the intensive care unit and ventilation strategies used (**Chapter 4**) assessing changes in respiratory support used. The second study looks at medication use in bronchiolitis (**Chapter 5**). In addition to describing the use of these interventions these studies shine light on practice change in emergency department care of bronchiolitis.

In **Chapter 6**, I present efforts made to improve the care of infants presenting with bronchiolitis. I describe further efforts by our research team including development of a bi-national clinical practice guideline, and a randomised controlled trial of high flow nasal cannula use. Finally I present a systematic review of high flow nasal cannula and recommendations for its use in infants with bronchiolitis.

In **Chapter 7** I present work to determine the best way to ensure research evidence is taken up into practice by the treating clinicians. I describe a systematic review of the

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literature to determine intervention strategies that have been shown to be useful in changing practice.

The appendices include some key papers on bronchiolitis management that are referred to in the text of the thesis but not used for this compilation.

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PAPERS USED IN BODY OF THESIS

Chapter 1:

Assessing bronchiolitis management in Australia and New Zealand

Paper 1-1:

Babl, Franz E, Sheriff, Nisa, Neutze, Jocelyn, Borland, Meredith, Oakley, Ed.
Bronchiolitis Management in Pediatric Emergency Departments in Australia and New Zealand: A PREDICT Study.
Pediatric Emergency Care 2008;24(10):656-658.

Chapter 2:

Hydration in infants presenting to hospital with bronchiolitis - options and evidence

Paper 2-1:

Ed Oakley, Franz E Babl, Jason Acworth, Meredith Borland, David Kreiser, Jocelyn Neutze, Theane Theophilos, Susan Donath, Mike South and Andrew Davidson. The Paediatric Research in Emergency Departments International Collaborative (PREDICT).
A prospective randomised trial comparing nasogastric with intravenous hydration in children with bronchiolitis (protocol). The comparative rehydration in bronchiolitis study (CRIB).
BMC Pediatrics; 2010;10:37 <http://www.biomedcentral.com/1471-2431/10/37>

Paper 2-2:

Ed Oakley, Meredith Borland, Jocelyn Neutze, Jason Acworth, David Krieser, Stuart Dalziel, Andrew Davidson, Susan Donath, Kim Jachno, Mike South, Theane Theophilos, Franz E Babl, for the Paediatric Research in Emergency Departments International Collaborative (PREDICT).
Nasogastric hydration versus intravenous hydration for infants with bronchiolitis: a randomised trial.
Lancet Respiratory Medicine 2013;1(2):113–120

Paper 2-3

Oakley E; Carter R; Murphy B; Borland M; Neutze J; Acworth J; Krieser D; Dalziel S; Davidson A; Donath S; Jachno K; South M; Babl FE; Paediatric Research in Emergency Departments International Collaborative (PREDICT).
Economic evaluation of nasogastric versus intravenous hydration in infants with bronchiolitis.
Emergency Medicine Australasia. 2017;29(3):324-329. doi: 10.1111/1742-6723.12713

Chapter 3:

Exploring Hydration Methods Used for Infants Under 2 Months of Age with Bronchiolitis

Paper 3-1:

Ed Oakley, Sonny Bata, Sharmila Rengasamy, David Krieser, John Cheek, Kim Jachno, Franz E. Babl,
Nasogastric Hydration in Infants with Bronchiolitis Less Than 2 Months of Age.
The Journal of Pediatrics. November 2016;178:241–245.e1

Chapter 4:

Bronchiolitis management in Australian and New Zealand Intensive Care Units

Paper 4-1:

Oakley E; Chong V; Borland M; Neutze J; Phillips N; Krieser D; Dalziel S; Davidson A; Donath S; Jachno K; South M; Fry A; Babl FE.
Intensive care unit admissions and ventilation support in infants with bronchiolitis.
Emergency Medicine Australasia. 2017 Aug;29(4):421-428.

Chapter 5:

Exploring low value care in bronchiolitis in Australia and New Zealand

Paper 5-1:

Oakley E; Brys T; Borland M; Neutze J; Phillips N; Krieser D; Dalziel SR; Davidson A; Donath S; Jachno K; South M; Williams A; Babl FE; Paediatric Research in Emergency Departments International Collaborative (PREDICT).
Medication use in infants admitted with bronchiolitis.
Emergency Medicine Australasia. 2018;30(3):389-397

Chapter 6:

Providing evidence for the use of high flow nasal cannula in bronchiolitis

Paper 6-1:

O'Brien S; Craig S; Babl FE; Borland ML; Oakley E; Dalziel SR; Paediatric Research in Emergency Departments International Collaborative (PREDICT) Network.

Rational use of high-flow therapy in infants with bronchiolitis. What do the latest trials tell us? A Paediatric Research in Emergency Departments International Collaborative perspective.

Journal of Paediatrics & Child Health. 2019;55(7):746-752

Chapter 7:

Improving bronchiolitis care - Knowledge mobilisation and translation

Paper 7-1:

Catherine L Wilson, David Johnson, and Ed Oakley on behalf of the Paediatric Research in Emergency Departments International Collaborative (PREDICT) network. Knowledge translation studies in paediatric emergency medicine: A systematic review of the literature.

Journal of Paediatrics and Child Health. 2016;52:112–125

In keeping with Journal copyright manuscripts are presented as PDF versions of the final submitted and approved manuscript. Exceptions are Chapter 1 (Paper 1-1) where the final submitted manuscript was not available, and Chapter 2 (Paper 2-1) which is published free open access, and the final journal article PDF has been included.

Introduction

Bronchiolitis is a disease of the lower respiratory tract caused by a number of different viruses, with peak incidence in winter. It is the leading cause of hospitalisation during the first year of life, accounting for 21% of all hospital admissions for children younger than 1 year in the US. Bronchiolitis is also a major cause of morbidity and mortality[1-5]

Viral bronchiolitis is a clinical diagnosis based on typical features on history and examination, including rhinorrhoea, cough, crackles and wheeze. Peak severity is usually around day two or three of the illness with resolution over 7-10 days. The associated cough may last for weeks.[6] While bronchiolitis most commonly occurs in the winter months, it can be seen all year round.

Bronchiolitis typically begins with an acute upper respiratory tract infection, followed by the onset of respiratory distress with fever and one or more of cough, tachypnoea, retractions, widespread crackles or wheeze. It is usually self-limiting, often requiring no treatments or interventions. [4]

Known risk factors for more serious illness include gestational age less than 37 weeks, chronological age at presentation less than 10 weeks, post-natal exposure to cigarette smoke, breast fed for less than 2 months, failure to thrive, chronic lung disease, congenital heart disease, chronic neurological conditions, and indigenous ethnicity.[7, 8]

There are no clearly effective drug treatments of infants with bronchiolitis. Pharmacological interventions including corticosteroids, bronchodilators, inhaled hypertonic saline and inhaled adrenaline have been extensively investigated with meta-analyses failing to show improvement in outcome. Individual studies use a variety of different diagnostic criteria, age ranges, scoring system and outcome measure, leading to multiple studies being undertaken on each intervention. So treatment is currently limited to oxygen, supportive care of breathing, and fluid replacement therapy.[6, 9-14]

Maintaining hydration is an important component of the care of infants with bronchiolitis. Fluid replacement therapy is required in about 30% of children admitted with bronchiolitis, due to reduced oral intake and evaporative losses from increased respiratory effort and fever. [15]

There are two methods of fluid replacement available – intravenous and nasogastric - and there is a lack of agreement on which method of fluid replacement is most beneficial for patients with bronchiolitis.[6, 10] They both have theoretical grounds for superiority, but both also have a range of possible complications. [16-21]

Nasogastric fluid replacement provides the physiological benefit of enteral hydration, which allows the body to absorb the required amounts of water and solute. In children with dehydration due to gastroenteritis, nasogastric fluid replacement provides faster recovery, shortens hospital stay and lowers the cost compared with IV fluid replacement. [22, 23] However, concerns have been raised that there may be an increased risk of aspiration in patients with bronchiolitis having nasogastric fluid replacement,[18] and the partial obstruction of the upper airway may further compromise respiratory function.[20, 21] However these studies have been mostly in young or preterm infants with diseases other than bronchiolitis. Whilst intravenous hydration has commonly been used for infants with bronchiolitis iatrogenic water intoxication and electrolyte imbalances have been reported.[6] With up to 30% of infants with bronchiolitis reported to have hyponatraemia vigilance (and repeat checking of electrolyte levels) is required with iv fluid therapy.[24] Delaying enteral nutrition has been postulated to delay recovery due to persistent irritability of the hungry infant and a loss of nutritional status.

The mode of rehydration therapy (intravenous vs nasogastric) has not been evaluated in randomised controlled trials. It has also been suggested that evidence-based clinical practice guidelines can improve treatment for infants with bronchiolitis by reducing variation in practice, avoiding hospitalisations and reducing length of hospital stay.[6]

Bronchiolitis is therefore an ideal disease to investigate as it is a high volume emergency department presentation, has a variety of clinical severities, has some management strategies that lack an evidence base, and some management strategies that have been shown to have no benefit but are still used; including routine chest xray, bronchodilators, antibiotics, and steroids.[11, 12, 25-28]

As a first step to understanding local emergency department practice and practice differences in the management of bronchiolitis a survey of emergency physicians[29] (**Oakley senior Author**) was undertaken to inform areas of research need. Hydration was shown to be an area of practice variation. Little literature was

available to guide clinicians in the use of intravenous or nasogastric hydration. So, I led a multi-site team in developing, funding and undertaking a 3 year randomised controlled trial at seven hospitals to determine the best hydration option.[30] (**Oakley lead author**) I collaborated with health economists from Deakin University to lead a formal health economic analysis of the results of this trial to further inform practice change.[31] (**Oakley lead author**)

The data from this randomised controlled trial prospectively identified nearly 4000 children admitted to hospital with bronchiolitis. There were limited recent local data on intensive care admissions, or on medication use for bronchiolitis. I led a group of researchers, including advanced paediatric trainees, to undertake a review of all the histories of these 4000 infants to examine medication use, and intensive care admission rates and ventilation strategies.[32, 33] (**Oakley lead author**)

The research group questioned whether the results of this study might be applicable to infants under 2 months of age (who were excluded from the randomised trial), and what the current practice in this younger population was. I led a study, supporting an advanced paediatric trainee, investigating the hydration methods of infants under 2 months of age with bronchiolitis admitted to two hospitals in Melbourne, Victoria.[34] (**Oakley lead author**)

The results of these studies identified the need for two further pieces of research – a randomised controlled trial on the use of high flow nasal cannula in bronchiolitis, and the development of an evidence based Australasian Bronchiolitis Guideline. The randomised controlled trial on high flow nasal cannula use was performed in conjunction with the Queensland Paediatric Critical Care research Group.[35] (**Oakley co-author, Appendix 1**) A systematic review of the literature on high flow nasal cannula use was then conducted and is presented, accompanied by recommendations for use of high flow nasal cannula in children with bronchiolitis.[36] (**Oakey senior Australian author**).

A means of mobilising the evidence for clinical management of bronchiolitis for Australasian clinicians was identified. I was the Australian lead for the systematic review and development of the bi-national bronchiolitis guideline.[37, 38] (**Oakley senior Australian author, Appendix 2 and 3**). I describe these studies. While our ability to undertake clinical trials to produce the evidence, and to summarise the results into guidelines to mobilise the evidence have improved, our understanding of how to

effectively implement evidence into clinical practice is limited.[39] [40] [41] The emergency department presents unique challenges to the effective translation of knowledge into practice.[42] Large patient volumes, time pressures to meet demand, frequent staff rotations and substantial child and parent anxiety, all contribute to a dynamic and demanding environment. The challenges are made even greater for paediatric emergency medicine as most children are cared for in mixed emergency departments that are focussed primarily on adult care and may not have specific paediatric emergency medicine expertise. A systematic review of the literature to describe the implementation literature in paediatric emergency medicine and to determine the best means of implementing evidence was undertaken[43] (**Oakley senior author**) A cluster randomised controlled trial of implementation strategies for the bi-national bronchiolitis guideline, aiming to address the lack of evidence for local successful knowledge implementation strategies is planned and outlined.[44] (**Oakley senior Australian author, Appendix 4**).

Many of the studies presented in this thesis refer to and were conducted with the approval of the Paediatric Research in Emergency Departments International Collaborative (PREDICT). This research collaborative was established in 2004 with 11 institutions involving large paediatric emergency departments in Australia and New Zealand, including all tertiary paediatric emergency departments. The aim of this research network was to provide evidence for the care of children in emergency departments through multicentre research. The goal was to improve the care for all children presenting to emergency departments in Australia and New Zealand. Much of the research presented used the PREDICT research network to identify and engage sites for the research.

CHAPTER 1

Assessing bronchiolitis management in Australia and New Zealand

Problem

Bronchiolitis care across the world has been shown to be variable.[6, 45-47] Mainstays of treatment are oxygen, hydration, and in a small proportion breathing assistance in the intensive care unit. While pharmacologic interventions have in general not been shown to improve outcome,[25, 26, 48-50] they are not infrequently used.[51] While rehydration is needed in about 30% of children presenting to hospital with bronchiolitis, the mode of intravenous therapy (intravenous vs nasogastric) has not been assessed in high quality, well powered clinical trials.

As it is a frequent cause of presentation to the emergency department and the most common cause for admission to hospital for infants under one year of age, management of bronchiolitis is important for all emergency department clinicians caring for children. Understanding local clinical practice, guideline use and conformity and variations in care between sites is necessary to be able to focus improvement efforts where the need lies.

In this first chapter I present the results of a survey of doctors who work in emergency departments and provide clinical care to children. The survey was aimed at assessing availability and uniformity of guidelines for bronchiolitis, clinicians use of medication, and hydration methods used when managing infants with bronchiolitis.

Questions

What bronchiolitis specific clinical practice guidelines are available for use at the survey sites?

What is the clinicians reported management of infants with bronchiolitis with mild, moderate and severe disease (based on case studies presented)?

Answers

What bronchiolitis specific clinical practice guidelines are available for use at the survey sites?

What is the clinicians reported management of infants with bronchiolitis with mild, moderate and severe disease (based on case studies presented)?

Paper 1-1:

Babl, Franz E, Sheriff, Nisa, Neutze, Jocelyn, Borland, Meredith, Oakley, Ed.

Bronchiolitis Management in Pediatric Emergency Departments in Australia and New Zealand: A PREDICT Study.

Pediatric Emergency Care 2008;24(10):656-658

A standardised anonymous survey was undertaken for senior medical staff involved in clinical care of children in the emergency department of 11 hospitals in Australia and New Zealand (comprising all 8 tertiary children's hospitals and 3 large mixed hospitals) with an annual census of over 350,000 children. Senior medical staff are equivalent grade to physicians, consultants or attendings in other health systems. The survey was in two parts. First, we asked each emergency department to identify and provide to the research team all bronchiolitis specific clinical practice guidelines used in their department. Secondly, we provided the clinicians with brief clinical scenarios followed by multiple choice responses for drug management and a series of questions allowing open ended responses.

Bronchiolitis severity was defined in the questionnaire as:

Mild bronchiolitis: wheezing. No accessory muscle use/recession. Oxygen saturation more than 95% on air. Feeding well.

Moderate bronchiolitis: wheezing. Accessory muscle use/recession. Oxygen saturation more than 95% on air. Feeding less but not dehydrated.

Severe bronchiolitis: agitated/distressed. Marked accessory muscle use/recession. Oxygen saturation less than 92% on air. Tachycardia. Marked limitation of ability to feed.

The severity definitions were derived from the most common definitions used in existing bronchiolitis guidelines in Australia and New Zealand.

Surveys were completed by 78/83 (94%) senior medical staff. Ten of the 11 sites had a specific bronchiolitis guideline, with eight different CPGs used across those 10 sites.

All guidelines addressed medication use, all recommending no medication in younger infants with bronchiolitis, and all permitting β -agonist (salbutamol) or corticosteroid use in older infants who might be thought to have asthma. Seven guidelines addressed fluid management (at nine sites), with five (seven sites) recommending intravenous hydration primarily. In five guidelines nasogastric hydration was allowed, but was reserved for the recovery phase or for difficult intravenous access, and two guidelines recommended nasogastric hydration primarily.

The management approaches used by clinicians revealed 82% would not use β -agonist for any severity of disease, 4% would prefer adrenaline to salbutamol and 97% would not use corticosteroids. For hydration 45% used intravenous and 49% used nasogastric hydration, with 4% using both depending on the severity of disease.

Limitations

The limitations in this study include: the difficulty in determining whether the survey responses correlate to clinical practice; that this is a snap shot of clinician practice at a single point in time and may not reflect future management; and that the survey reports the results of senior clinicians at mainly tertiary paediatric institutions which may not reflect broader management.

Table 1-1: Senior Physician Management Strategies for Bronchiolitis (n = 78)*

Severity^f	Inhaled Beta		Supplemental	Antibiotics
	Agonist	Steroids	Oxygen	
Mild	1 (1%)	0 (0%)	0 (0%)	0 (0%)
Moderate	4 (5%)	0 (0%)	5 (6%)	0 (0%)
Severe	14 (18%)	2 (3%)	75 (96%)	1 (1%)

*Based on a 3 month-old child.

^fDefinition of severity - see Above.

Implications

Implications

Bronchiolitis specific clinical practice guidelines are readily available with small differences only across the sites surveyed. The use of medications, and specifically bronchodilators and corticosteroids, were similar in clinical guideline recommendations and clinician practice. Hydration method was split approximately equally between intravenous and nasogastric in clinician practice, while guideline recommendations favoured the intravenous route. Evidence to guide clinician decision making for hydration method is lacking and there are theoretical risks of each method, with accidental water intoxication and electrolyte imbalances reported with intravenous hydration,[6] and concerns regarding the risk of aspiration and worsening breathing difficulties raised with nasogastric hydration.[18, 20, 21] The question of optimal mode of hydration should be addressed through multicentre comparative randomised controlled trials.

PDFs of Papers Chapter 1

Paper 1-1

Babl, Franz E, Sheriff, Nisa, Neutze, Jocelyn, Borland, Meredith, Oakley, Ed.

Bronchiolitis Management in Pediatric Emergency Departments in Australia and New Zealand: A PREDICT Study.

Pediatric Emergency Care 2008;**24**(10):656-658

The Paper associated with this chapter is not available due to copyright

CHAPTER 2

Hydration in infants presenting to hospital with bronchiolitis - options and evidence

Problem

Bronchiolitis is the most common reason for children under 1 year of age to be admitted to hospital. There was an annual cost in Victoria in 2006 of \$8.1 million (data supplied at personal request from Victorian Admitted Episodes Dataset, Performance Reporting & Analysis Unit, Department of Human Services Victoria), and in United States of America the annual cost in 2004 was \$US390 million. Around 30% of admitted infants needing non-oral hydration, meaning a large number of infants are receiving non-oral hydration during their treatment for bronchiolitis.[52] As described in **Chapter 1** there is equipoise in the use of nasogastric and intravenous hydration for infants admitted to hospital who fail oral hydration in Australia and New Zealand, indicating that it is not known which is the better hydration method.[29] Both nasogastric and intravenous hydration methods have theoretical grounds for superiority and both have possible complications.

Nasogastric hydration is the treatment of choice for children with gastroenteritis,[22, 53] as it allows enteral nutrition and may be able to be inserted more easily in young or dehydrated infants. Concerns regarding nasogastric use have included further obstruction of a partially obstructed upper airway with compromise of respiratory function and aspiration of gastric contents.[18, 20, 21] Intravenous hydration is commonly used internationally in bronchiolitis however unintentional hyponatraemia has been documented [6, 16, 54], and the delay in nutrition has been postulated to delay recovery.

The variation in hydration practices that is shown in the survey in **Chapter 1** is also shown in a review of hydration practices and in a review of bronchiolitis management in New Zealand hospitals in 1998. [47, 55] There are no published trials directly comparing the hydration methods in bronchiolitis. In a case series of 37 infants with bronchiolitis, Sammartino[56] found nasogastric hydration was tolerated without incident. Whilst two infants deteriorated as the illness progressed removal of the NGT did not help.

A number of authors conducting reviews of bronchiolitis care have highlighted that fluid replacement therapy in bronchiolitis has not been validated in randomised trials, and call for adequately powered trials, with clinically relevant outcomes to determine the best hydration method.[6, 10, 57]

Questions

What is the best method of non-oral hydration for infants admitted to hospital with bronchiolitis?

What is the most cost effective model for non-oral hydration in infants admitted to hospital with bronchiolitis?

Answers

What is the best method of non-oral hydration for infants admitted to hospital with bronchiolitis?

Paper 2-1:

The Paediatric Research in Emergency Departments International Collaborative (PREDICT), Ed Oakley, Franz E Babl, Jason Acworth, Meredith Borland, David Kreiser, Jocelyn Neutze, Theane Theophilos, Susan Donath, Mike South and Andrew Davidson.

A prospective randomised trial comparing nasogastric with intravenous hydration in children with bronchiolitis (protocol) The comparative rehydration in bronchiolitis study (CRIB). *BMC Pediatrics* 2010;10:37

Paper 2-2:

Ed Oakley, Meredith Borland, Jocelyn Neutze, Jason Acworth, David Krieser, Stuart Dalziel, Andrew Davidson, Susan Donath, Kim Jachno, Mike South, Theane Theophilos, Franz E Babl, for the Paediatric Research in Emergency Departments International Collaborative (PREDICT).

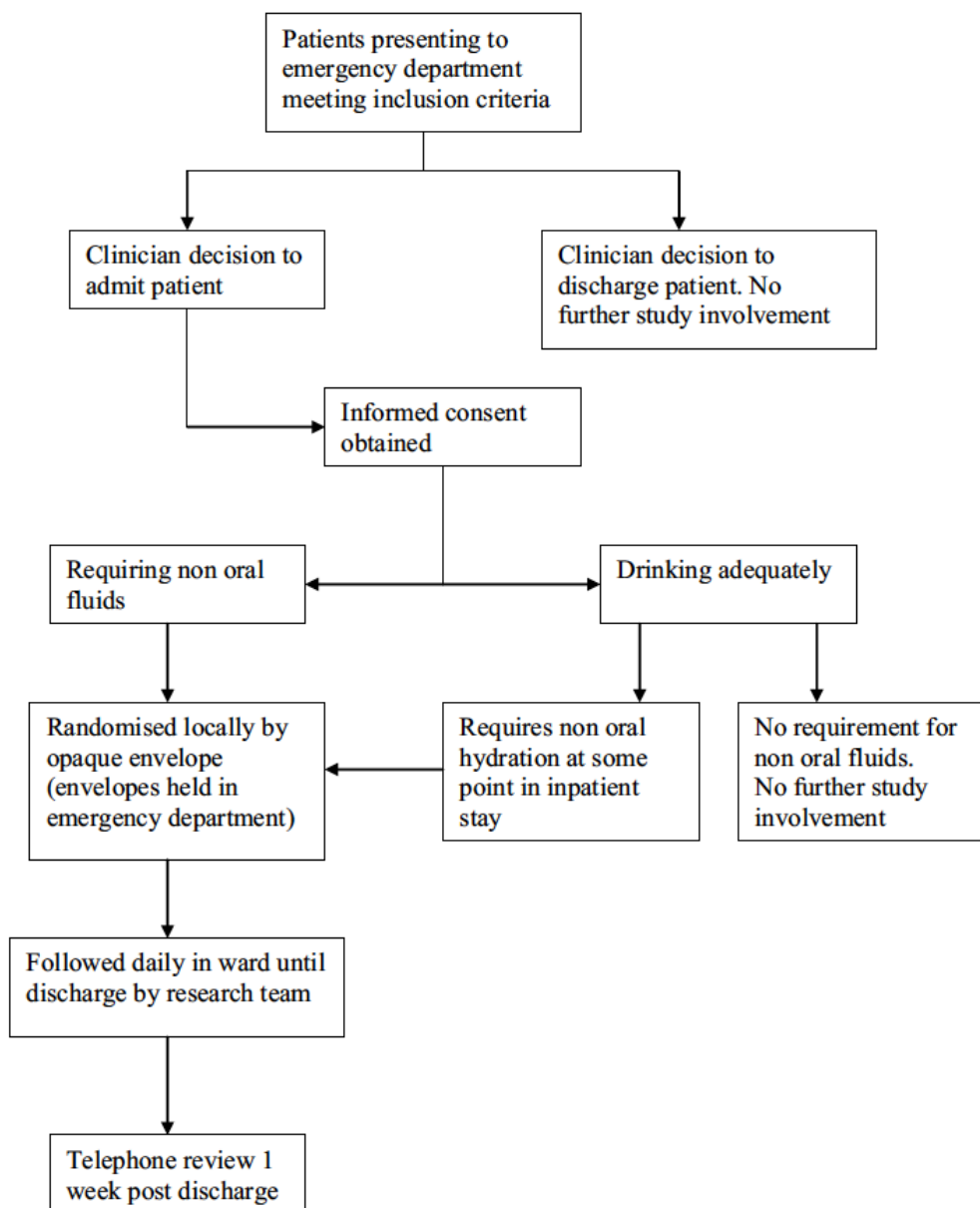
Nasogastric hydration versus intravenous hydration for infants with bronchiolitis: a randomised trial.

Lancet Respir Med 2013;1: 113–20

To inform decision making regarding non-oral hydration in infants with bronchiolitis, a multicentre randomised trial was devised. This trial compared nasogastric hydration with intravenous hydration at seven emergency departments across Australia and New Zealand. The patient population was infants younger than 12 months of age and older than eight weeks of age (corrected for prematurity) who were admitted to hospital with bronchiolitis, and required non-oral hydration (at the treating clinicians discretion). Infants were consented at the time of admission and randomised at the time non-oral hydration was needed. Randomisation was computer generated in a 1:1 ratio, and was stratified by hospital site and age group (2 to <6 months and 6 to 12 months). Assessment of infants and enrolment in the study is outlined in **Figure 2-1**. Primary outcome measure was hospital length of stay - measured as both total length of stay and also as a length of stay

until ready to be discharged (defined as the infant has not received supplemental oxygen for 12 hours, has had stable respiratory status for 4 hours (including slight or nil recession) and is feeding adequately). Important secondary outcomes included ease of insertion of and need for replacement of hydration method, intensive care unit admission and parental satisfaction. A total sample size of 750 infants was determined to allow a detection in difference of length of hospital stay between groups of 0.2 standard deviations. The standard deviation of length of stay was determined by both a retrospective review of 100 bronchiolitis cases and a pilot implementation of the study protocol in 50 patients. We expected to have power to detect a difference in length of stay of 12 hours which was determined to be clinically significant.

The trial was funded by a project grant from the National Health and Medical Research Council and was conducted from April to November (the bronchiolitis season) in years 2009 to 2011 inclusive. Of 3899 infants presenting to the seven emergency departments during the recruiting period 3408 were assessed for inclusion, and after exclusions 1745 were consented to the study. Of these 759 were randomly allocated to the interventions (932 not requiring non-oral fluids and 54 excluded due to severe illness after consent); with 381 infants randomised to nasogastric therapy and 378 to intravenous therapy. Primary outcome data were available for all randomised infants.

Figure 2-1: Patient identification, entry and flow through the CRIB study

CRIB comparative rehydration in bronchiolitis

There was no difference in the mean length of hospital stay (the primary outcome) (86·6 h [SD 58·9] for infants assigned nasogastric hydration vs 82·2 h [SD 58·8] for infants assigned intravenous hydration; difference 4·5 h [95% CI –3·9 to 12·9], $p=0\cdot30$), with similar results for the time ready for discharge. **Table 2-1** summarises the primary outcome and major complication outcomes. A survival analysis curve demonstrates the length of stay outcome in **Figure 2-2**.

Table 2-1 Length of stay, intensive-care unit admission, and adverse events

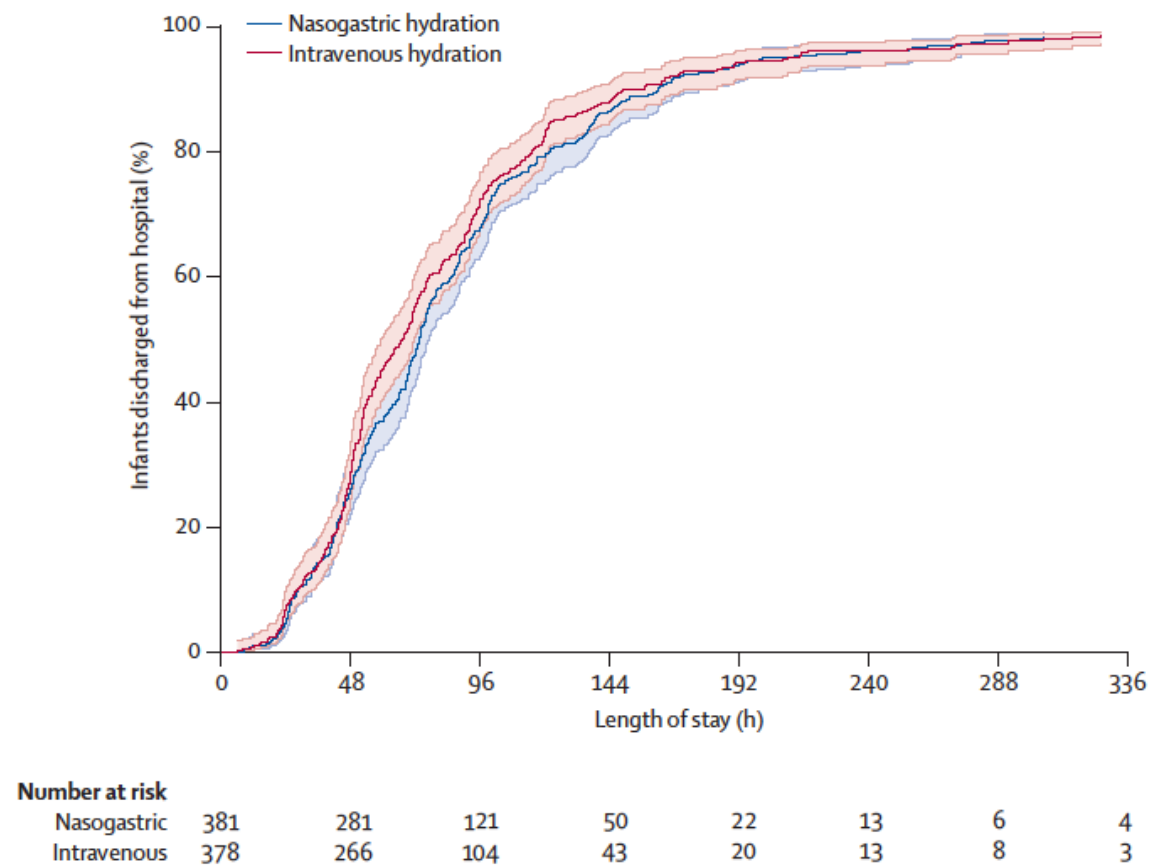
	Nasogastric Hydration (n=381)	Intravenous Hydration (n=378)	Difference (95% CI)	P value
Length of stay, h	86.6 (58.9)	82.2 (58.8)	4.5 (-3.9, 12.9)	0.30
Intensive-care unit admission	21 (6%)	25 (7%)	-1.1% (-4.5 to 2.3)	0.53
Continuous positive airway pressure	12 (3%)	13 (3%)	-0.3% (-2.8 to 2.3)	0.83
Intubated and Ventilated	5 (1%)	5 (1%)	-0.01% (-1.6 to 1.6)	0.99
Oxygen Saturation <90%*	19 (5%)	14 (4%)	1.3% (-1.6 to 4.2)	0.39
Duration of non-oral hydration, h	43.7 (48.6)	41.7 (44.8)	2.1 (-4.6 to 8.8)	0.54
Duration of oxygen therapy, h	45.8 (52.1)	43.6 (51.9)	2.2 (-5.1 to 9.7)	0.55
Bradycardia	6 (2%)	4 (1%)	0.5% (-1.1 to 2.1)	0.53
Apnoea	1 (<1%))	1 (<1%)	0.0% (-0.7 to 0.7)	1.00
Epistaxis	0	1 (<1%)	-0.3% (-0.8 to 0.3)	0.32
Aspiration	0	0	-	-

Data are mean (SD) or n (%), unless otherwise stated. *Oxygen saturation in room air.

Change of therapy to the alternative hydration method was less common in the nasogastric hydration group (50 infants [13%]) than in the intravenous hydration group (95 infants [25%]); absolute difference 12.0% (95% CI 6.5–17.5, $p<0.0001$). Data for number of insertion attempts were recorded for 323 (85%) infants assigned nasogastric hydration and 294 (78%) infants assigned intravenous hydration. The success rate of the first attempt at insertion was higher in the nasogastric hydration group (275 [85%]) than the intravenous hydration group (165 [56%]), $p<0.0001$.

Parental satisfaction and follow up data for readmission and medical visits was similar between the two groups.

Figure 2-2: Kaplan-Meier analysis of length of stay, truncated at 14 days
(Shaded areas show 95% CIs).



What is the most cost effective model for non-oral hydration in infants admitted to hospital with bronchiolitis?

Paper 2-3:

Oakley E; Carter R; Murphy B; Borland M; Neutze J; Acworth J; Krieser D; Dalziel S; Davidson A; Donath S; Jachno K; South M; Babl FE; Paediatric Research in Emergency Departments International Collaborative (PREDICT).

Economic evaluation of nasogastric versus intravenous hydration in infants with bronchiolitis.

Emergency Medicine Australasia. 2017;29(3):324-329.

Using the results from the randomised trial presented earlier in this chapter, an economic evaluation was undertaken with the aim of determining whether intravenous hydration was more cost effective than nasogastric hydration for treating infants admitted to hospital with bronchiolitis, using a cost per child discharged ratio. The economic evaluation was designed to inform which of the treatment methods to use based on cost, and not whether the treatment should be provided. The initial design of this economic analysis was to capture both treatment specific costs as well as costs associated with the length of hospital stay. As there was no statistically significant difference in the length of stay in the primary study between comparator groups, or key secondary outcomes, a cost minimisation analysis was performed, focussing on the cost differences between the arms of the trial. The primary outcome was therefore the cost of each intervention arm and associated treatments. It is worth noting here that the largest individual driver of cost was the bed stay cost (accounting for approximately 90% of the total cost of treatment).

All relevant costs to the hospital for the treatments and interventions associated with each treatment arm were identified and cost data including unit prices for all products, services and activities were collected from study hospitals using a costing template. An average procedure time was calculated from 20 procedures (10 of each intervention) at five different sites allowing the development of an average cost per intervention (including equipment and staff time costs). Costs to the family and community were not included.

Table 2-2 Cost results presented as ‘cost per child treated’ for each arm and by age

	N		Estimated cost of treatment†		Cost difference
	NGH	IVH	NGH	IVH	
Total population	381	378	\$74.30	\$113.31	\$39.01
By age					
<6 months	201	196	\$75.75	\$121.34	\$45.60
6–12 months	180	182	\$72.68	\$104.66	\$31.98

†Costs associated with a patient switching from one intervention to the other and all subsequent treatment costs were assigned to the original randomised treatment group to give the real cost of each treatment arm. Prices are reported in ‘real prices’ for the reference year of the clinical trial (2009). All cost estimates are ‘intention-to-treat’. IVH, intravenous hydration; NGH, nasogastric

Using the ‘cost per child assigned to treatment’ result, there was a cost difference of \$39.01 in favour of nasogastric hydration, with the costs outlined in **Table 2-2**. This benefit was seen for age groups <6 months and 6 to <12 months; and while there were variations in costs across sites, all sites showed a cost benefit for nasogastric hydration.

Limitations

The randomised control trial has a number of limitations. The interventions were not blinded leading to the possibility of bias related to discharge. The use of a “time ready for discharge” surrogate was implemented to assess this. Parental satisfaction was performed using a Likert scale which is not validated for this purpose. We excluded infants under 8 weeks of age limiting the extrapolation of the outcomes to younger infants with bronchiolitis.

The economic analysis had the following limitations: when interventions were switched (eg from nasogastric to intravenous) the number of attempts at insertion were not documented; costs of interventions were estimated on a sub set of patients and extrapolated to the entire cohort (rather than being determined accurately for each patient), and meaning that multiple attempts were not costed. These limitations suggest the estimated cost difference is an underestimate.

Implications

Both the randomised controlled trial and the economic evaluations were the first trials of their type comparing nasogastric and intravenous hydration in bronchiolitis. The randomised trial comparing nasogastric and intravenous hydration was designed to address the lack of an evidence base for non-oral hydration identified in earlier reviews of bronchiolitis management.[6, 10, 57] The trial, found no difference in length of hospital stay between the two arms, and no difference in any safety outcomes assessed. There was a difference in the ease of application of the hydration method with nasogastric hydration having better first attempt success rates and fewer occasions of needing to revert to the alternative hydration method. These outcomes would suggest some patient comfort benefits and some efficiency benefits for hospital staff being associated with nasogastric insertions. This trial confirms the safety and acceptability of both methods of hydration in infants with bronchiolitis, dispelling previously raised concerns.

The economic evaluation (**Paper 2-3**) revealed a small cost benefit, across all age groups and all hospitals, for the use of nasogastric hydration, and is the first such analysis undertaken. While there have been cost analyses of various treatments for bronchiolitis there have been none that included hydration. [2, 58] [59]

These outcomes suggest nasogastric hydration should be considered as the first line hydration option for infants with bronchiolitis as it offers some benefits over intravenous treatment. It must be noted the study included infants eight weeks to 12 months of age only, and excluded those with severe disease and chronic cardiac, neurological or respiratory illnesses.

PDFs of Papers Chapter 2

Paper 2-1

Ed Oakley, Franz E Babl, Jason Acworth, Meredith Borland, David Kreiser, Jocelyn Neutze, Theane Theophilos, Susan Donath, Mike South and Andrew Davidson. The Paediatric Research in Emergency Departments International Collaborative (PREDICT)

A prospective randomised trial comparing nasogastric with intravenous hydration in children with bronchiolitis (protocol). The comparative rehydration in bronchiolitis study (CRIB).

BMC Pediatrics; 2010;**10**:37

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STUDY PROTOCOL

Open Access

A prospective randomised trial comparing nasogastric with intravenous hydration in children with bronchiolitis (protocol) The comparative rehydration in bronchiolitis study (CRIB)

The Paediatric Research in Emergency Departments International Collaborative (PREDICT), Ed Oakley^{*1,2,3}, Franz E Babl^{2,4,5}, Jason Acworth⁶, Meredith Borland⁷, David Kreiser^{8,2}, Jocelyn Neutze⁹, Theane Theophilos^{2,4}, Susan Donath², Mike South^{2,5,10} and Andrew Davidson^{2,5,11}

Abstract

Background: Bronchiolitis is the most common reason for admission of infants to hospital in developed countries. Fluid replacement therapy is required in about 30% of children admitted with bronchiolitis. There are currently two techniques of fluid replacement therapy that are used with the same frequency-intravenous (IV) or nasogastric (NG).

The evidence to determine the optimum route of hydration therapy for infants with bronchiolitis is inadequate. This randomised trial will be the first to provide good quality evidence of whether nasogastric rehydration (NGR) offers benefits over intravenous rehydration (IVR) using the clinically relevant continuous outcome measure of duration of hospital admission.

Methods/Design: A prospective randomised multi-centre trial in Australia and New Zealand where children between 2 and 12 months of age with bronchiolitis, needing non oral fluid replacement, are randomised to receive either intravenous (IV) or nasogastric (NG) rehydration.

750 patients admitted to participating hospitals will be recruited, and will be followed daily during the admission and by telephone 1 week after discharge. Patients with chronic respiratory, cardiac, or neurological disease; choanal atresia; needing IV fluid resuscitation; needing an IV for other reasons, and those requiring CPAP or ventilation are excluded.

The primary endpoint is duration of hospital admission. Secondary outcomes are complications, need for ICU admission, parental satisfaction, and an economic evaluation. Results will be analysed using t-test for continuous data, and chi squared for categorical data. Non parametric data will be log transformed.

Discussion: This trial will define the role of NGR and IVR in bronchiolitis

Trail registration: The trial is registered with the Australian and New Zealand Clinical Trials Registry - ACTRN12605000033640

Background

Bronchiolitis is a disease of the lower respiratory tract with peak incidence in the winter. It is the leading cause of hospitalisation during the first year of life and is a major cause of morbidity and mortality [1-5]. Victorian

state-wide data for the calendar year 2006 reveal 2280 admissions for bronchiolitis, with an average length of stay of 3.2 days. One hundred sixty eight (7.4%) patients were admitted to intensive care. The estimated cost of the Victorian bronchiolitis hospital admissions for 2006 is \$8.1 million dollars (data supplied at personal request from Victorian Admitted Episodes Dataset, Performance Reporting & Analysis Unit, Department of Human Services Victoria). In the United States of America bronchi-

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olitis accounts for 21% of all hospital admissions for children under 1 year of age, with an annual cost of \$390 million dollars [5].

There are no clearly effective chemotherapeutic treatments to improve the outcome of infants with bronchiolitis, so treatment is limited to oxygen, supportive care of breathing, and fluid replacement therapy [1,2,6-10]. Maintaining hydration is an important component of the care of infants with bronchiolitis. Fluid replacement therapy is required in about 30% of children admitted with bronchiolitis, due to reduced oral intake and evaporative losses from increased respiratory effort and fever [11].

There are currently two techniques of fluid replacement therapy, IV or NG. There is a lack of agreement on which method of fluid replacement is most beneficial for patients with bronchiolitis - we do not know which therapy is better. They both have theoretical grounds for superiority, but both also have a range of possible complications. As fluid replacement is such an important aspect of the management of this common disease it is very important that fluid therapy is evidence based.

Nasogastric fluid replacement (NGR) is effective and has few complications. It provides the physiological benefit of enteral hydration, which allows the body to absorb the required amounts of water and solute. In children with dehydration due to gastroenteritis, NGR is the treatment of choice as it provides faster recovery, shorter hospital stay and lowers the cost compared to IV fluid replacement (IVR) [12,13]. A nasogastric tube (NGT) can often be inserted more easily than an IV catheter, especially in infants with poor peripheral circulation due to reduced oral intake. However, concerns have been raised regarding the use of nasogastric tubes (NGT) in infants with bronchiolitis. There may be an increased risk of aspiration in patients with bronchiolitis [14]. The partial obstruction of the upper airway may compromise respiratory function, [15-18] with some studies showing up to a 50% increase in the work of breathing [16]. However these studies have been mostly in young or preterm infants and the ability to extrapolate these findings to older infants with bronchiolitis is questionable.

Intravenous fluid replacement (IVR) is commonly used in bronchiolitis [1]. However, accidental water intoxication and electrolyte imbalances are potential complications [10]. Up to 30% of children admitted with bronchiolitis have been shown to have some degree of hyponatraemia requiring vigilance with IV fluid administration [19,20]. It has also been postulated that delaying enteral nutrition will cause delay in recovery due to loss of nutritional status, and that the persisting hunger may make the children more irritable.

Kennedy et al (2005) [21] reviewed the evidence for fluid replacement in children with bronchiolitis. The authors report a wide variation in practice, with use of

NGR in many units. They conclude that "there is no good quality evidence for or against the use of NGR in infants with bronchiolitis. A randomised controlled trial is needed." Vogel (2003) [22] described the management of bronchiolitis admissions in New Zealand hospitals in 1998. There was a large variation in management between hospitals, with between 6% and 64% of children needing fluid replacement therapy receiving NGR.

We confirmed the wide variation of practice in Australia with a pilot study. As baseline data for our proposed study, a survey of Australasian paediatric emergency physicians was undertaken in 2005, by the Paediatric Research in Emergency Departments International Collaborative (PREDICT), a research collaborative of all tertiary paediatric emergency departments and major mixed emergency departments in Australia and New Zealand). Of the 78 senior doctors surveyed at 11 sites (including all tertiary paediatric emergency departments in Australia and New Zealand), 48% reported using NGR and 52% IVR as initial treatment in acute bronchiolitis. There were no guidelines in any institution to determine which fluid replacement therapy should be used in bronchiolitis [23].

There are no published trials directly comparing NGR and IVR. The research available on NGR in bronchiolitis comes from two small studies. In a case series of 37 infants with bronchiolitis, Sammartino (2002) [24] found NGR was tolerated without incident. Two infants deteriorated as the illness progressed and removal of the NGT did not help.

Smyth and Openshaw [10] in a *Lancet* review article conclude "Neither oxygen therapy, nor fluid replacement strategies have been validated in large randomised controlled trials, although the dangers of hyponatraemic fluid overload are recognised. These treatment options should be addressed in randomised controlled trials." Further Smyth states that "Clinical trials of interventions in bronchiolitis have been criticised for being too small and focusing on short-term outcomes, rather than reporting outcomes of interest to clinicians and parents, such as length of hospital stay."

Davison et al [6] conclude in another recent review: "There is an ongoing need for studies that are adequately powered to identify therapies that may benefit critically ill children with this disease (bronchiolitis). Because the mortality associated with bronchiolitis is low, large multi-centre trials that focus on continuous outcome measures such as duration of mechanical ventilation and ICU or hospital length of stay will provide the best opportunity to demonstrate a clinical benefit with adequate statistical power."

The evidence to determine the optimum route of hydration therapy for infants with bronchiolitis is inadequate. This randomised trial will be the first to provide

good quality evidence of whether NGR offers benefits over IVR.

Methods/Design

Study Aims

The primary aim of this multicentre randomised trial is to investigate whether the type of fluid replacement - NG versus IV - affects the duration of hospital admission, in children aged between 2 and 12 months admitted to hospital with a clinical diagnosis of bronchiolitis. Secondary aims are to undertake an economic appraisal, and to determine the difference in the incidence of complications, duration of treatment and parental satisfaction for the two treatments.

We hypothesise that there will be a difference in the length of hospital stay between the two treatment modalities.

Study Design and setting

This study is an open randomised trial comparing two interventions. This study will take place in 6 paediatric emergency departments and inpatient wards in Australia and New Zealand.

Ethical considerations

The study has ethical approval at all participating sites. All parents/guardians are provided with both verbal and written information about the study and written informed consent is obtained prior to enrolment in the trial.

The trial is overseen by a trial steering committee that is responsible for the ethical and rigorous conduct of the trial.

A data monitoring committee (with membership entirely independent of the conduct of the trial) will monitor adverse events and review outcomes and complications annually. They will report and make recommendations to the trial steering committee. No formal stopping rules are in place.

Subject Selection

Children satisfying the inclusion and exclusion criteria who are admitted to the hospital will be eligible for the study. Patients admitted to the ward with bronchiolitis who deteriorate and need institution of hydration will be eligible for randomisation. Figure 1 outlines the flow of patients through the study.

Definition of Disease State

The eligible patients will be all children younger than 12 months and older than 8 weeks (corrected for prematurity) presenting to the Emergency Department with bronchiolitis requiring hydration. The need for hydration will be defined by a history of oral intake less than 50% in the last 6 hours or signs of dehydration such as reduced urine

output, tachycardia (in the absence of fever), dry mucous membranes, decreased skin turgor or sunken fontanelle.

Inclusion and Exclusion Criteria

Inclusion and exclusion criteria are shown in Additional File 1. In order to keep the study group as homogeneous as possible patients younger than 8 weeks were excluded as the very young often have a different and more severe clinical presentation and course of bronchiolitis. Children older than 12 months were also excluded as other diagnoses, in particular asthma assume an increasing role, impacting on the identification and management of these patients.

Patient randomisation

The patients will be randomised at the time they require non oral fluid replacement. Randomisation will be stratified by 2 age groups (2 months to less than 6 months, 6 months to less than 12 months) and by site. Randomisation will be blocked in 3 randomly allocated block sizes to ensure concealment of allocation. Each site will have its own set of opaque sealed randomisation envelopes. These will have a reminder of inclusion and exclusion criteria to be assessed before the envelope is opened.

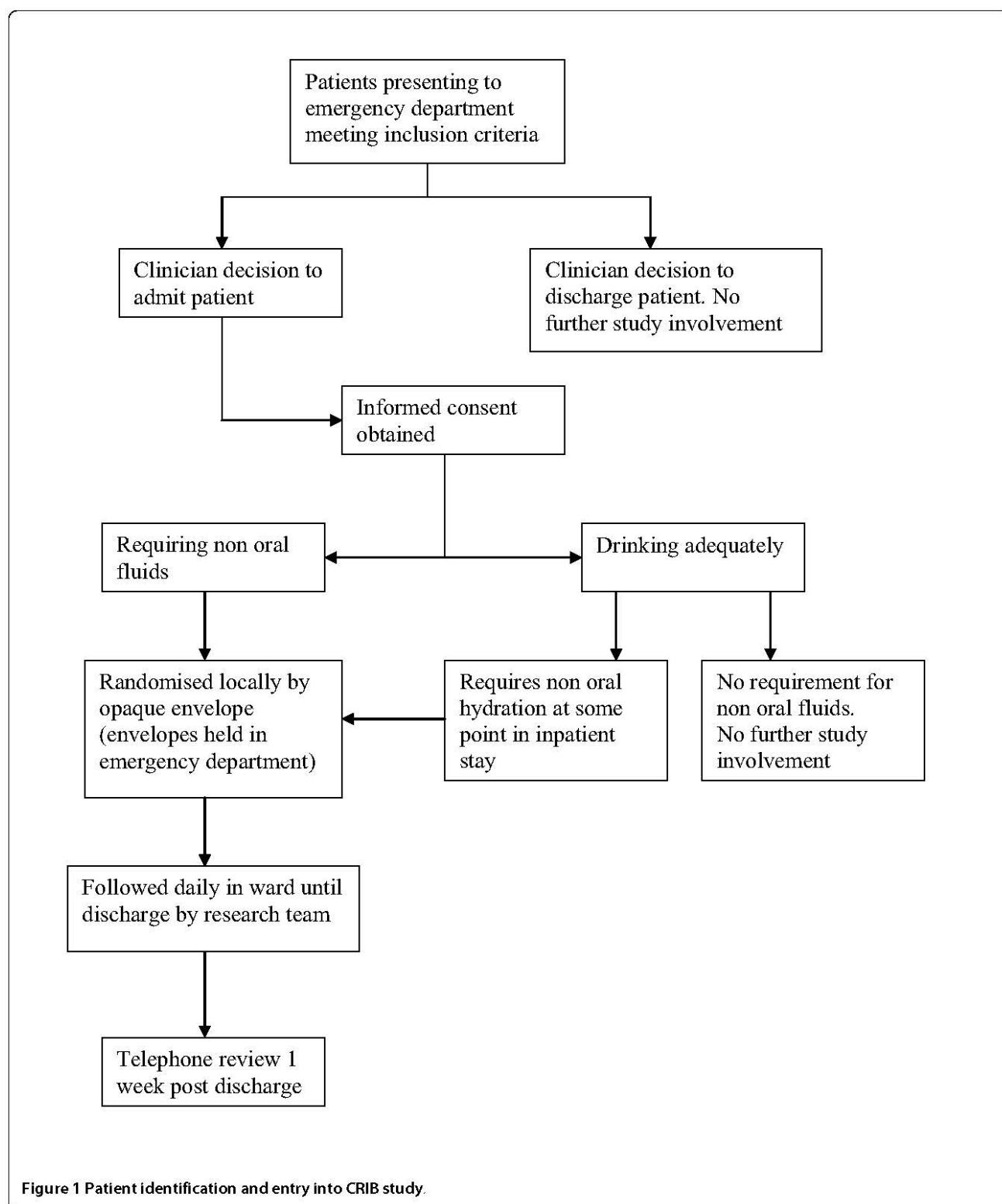
Randomised treatments

Intravenous fluid replacement group

Topical anaesthetic cream will be used in accordance with hospital policy to reduce the pain of IV insertion. Insertion of the IV cannula will be at the site of anaesthetic cream application after 30-60 minutes. Size 22 or 24 gauge cannulae will be used for all cases. The fluid used for hydration will be 0.45% Sodium Chloride with 2.5 or 5% dextrose. Ongoing fluid replacement will be guided by the measured serum electrolytes (see "Data Collection").

Nasogastric fluid replacement group

Insertion of the NGT will be by experienced personnel. The nostril will be sprayed with local anaesthetic spray 2 minutes prior to NGT insertion. The tube will be measured from nares to epigastrium to determine depth of insertion. Post insertion correct tube placement will be confirmed by aspiration of stomach contents with pH < 4. Failed aspiration or pH ≥ 4 should be repeated after 30 minutes. A repeated failure to confirm the presence of the NGT in the stomach by these means requires an abdominal/chest x-ray to be performed to confirm the position of the tube prior to its use. If there is doubt about the position of the tube after this it should be removed and replaced. Tubes will be size: 6 French < 6 months of age, and 8 French 6-12 months of age. NGR will be by continuous infusion with a standard oral electrolyte solution for the first two hours, followed by expressed breast milk or formula.



For both groups All patients will be admitted to the ward under the appropriate unit. Total fluid replacement will not exceed 100% of normal daily requirements. Oral feeds will be at the discretion of the clinical team and the IV or NG fluid rate adjusted accordingly.

A parent satisfaction score will be obtained using a standardised, five point Likert scale. The score will be obtained daily from one parent or by agreement with both parents if they are in attendance. A final "overall"

satisfaction score will be obtained immediately prior to hospital discharge.

All patients will be followed up at 5 to 7 days post discharge with a standard questionnaire to determine the incidence of complications, or need for further medical care.

Study Procedure

All patients will have all clinical observations entered into a Clinical Report Form (CRF) by the nursing staff at the time of performing the observations. All CRFs will be checked daily by research staff while the participant is an inpatient.

Clinical observations from nursing records

SpO₂, respiratory rate, respiratory effort, and heart rate will be measured at enrolment, at hourly intervals for the first 2 hours then 2 hourly. These will allow comparison of groups by severity of disease at enrolment, and ensure any clinically relevant complications are captured.

Oxygen administered (L/min for nasal cannulae or %O₂ for head box) will be documented for each shift. The times oxygen is commenced and ceased will be documented. This will allow accurate capture of the duration of oxygen therapy. Type, route and volume of fluid administered will be recorded, with hourly, shift, and daily totals. This allows assessment of fluid requirements and cross referencing volumes of fluid infused. Hydration status of the patients will be measured using urine output (with shift and daily totals) and weight (measured at the time of admission, and then daily).

Complications recorded will include: episodes of apnoea and bradycardia (lasting more than 20 seconds); all episodes where the SpO₂ was recorded at < 90%; and the need for replacement of, or problems with the IV cannula or NGT.

The need for and duration of ICU admission will be documented. Duration of hospital admission will be documented and checked by calculation from the hospital admissions and discharge system.

Laboratory investigations

Electrolytes, urea and creatinine, and glucose levels will be measured when inserting the IV line. Electrolytes will be repeated 6-8 hours after commencement of therapy in the intravenous therapy group (as an accepted standard in IV fluid management); and daily thereafter. Blood sampling may be by draw back on IV cannulae with discarding of 2 mls of blood or alternatively sampling by IV access or capillary blood sample at the discretion of physician managing patient. All testing of electrolyte levels in patients with iv fluids and non testing in patients with NG fluids are in line with current local recommended practice and represent standard care at the participating hospitals [23]. No additional blood tests will taken for the purpose of this trial.

Other investigations will be at the discretion of the managing physician.

Post discharge phone review

Will be undertaken for all patients 5 to 7 days post discharge. Information collected will include return visits to a hospital, admission to hospital, attendance at local medical officer - planned and unplanned and other complications including difficulty feeding, nasal sores, arm bruising or sores.

Guidelines for oxygen therapy

- Oxygen should be commenced to keep SpO₂ ≥ 92%, or if there is markedly increased work of breathing and respiratory distress.
- The least amount of oxygen needed to keep SpO₂ ≥ 92% should be administered.
- Oxygen should be ceased when SpO₂ is consistently above 92%, and the child is able to feed well. Cease by weaning the flow as tolerated until 1 l/min or less is needed.

Guidelines for non-oral fluid commencement are presented in Table 1.

Guidelines for changing the treatment from one intervention to the other are presented in Additional File 2.

Outcome measures

The primary outcome measure is the inpatient length of stay. This will be recorded in 2 ways: 1) the actual duration of inpatient stay will be determined from the computerised database of patient admission; 2) Given that the length of stay can be affected by many administrative and

Table 1: Guidelines for commencement of non oral fluid therapy.

Weight (Kg)	Fluid rate (mls/hr)	
	Intravenous	Nasogastric
3.0	10	12
4.0	13	18
5.0	16	21
6.0	19	24
7.0	22	27
8.0	26	30
9.0	29	33
10	32	36
12	35	39
15	40	42
20	48	50

Note: total initial hydration rate is determined at about 80% maintenance fluid requirements, and should never exceed 100% of daily fluid requirements

social factors unrelated to the condition of the child, we will record and report also the time until the child is ready for discharge using objective criteria. An infant will be considered ready for discharge if he/she has not received supplemental oxygen for 12 hours, has had stable respiratory status for 4 hours (including slight or nil recession) and is feeding adequately.

The secondary outcome measures are the incidence and type of complications of hydration therapy (complications will include any adverse event related to the method of hydration, including but not limited to electrolyte abnormalities, IV line/NGT needing replacement, infection, thrombosis of the IV site, trauma to the nose from the NGT, pulmonary aspiration, extravasation of IV fluid); the duration of therapy; parental satisfaction (measured daily) and an economic appraisal of each intervention.

Sample size, power and statistical methods

The minimal clinically significant difference in length of hospital stay was thought to be greater than or equal to 12 hours. In order to perform the sample size calculation we determined mean duration of hospital stay and standard deviation (sd) from two available sets of admitted patients with bronchiolitis. Mean (sd) length of inpatient stay in a retrospective review of 36 patients admitted with bronchiolitis and requiring fluid replacement was 84 (49) hours. For the patients who were enrolled and randomised in the pilot study, mean (sd) duration of admission was 98 (70) hours, suggesting that patients who enter the study may have more severe illness.

Recruiting a total of 750 subjects (375 per arm) will give 80% power to detect an effect size of 0.2 (a small effect) using a two group t-test with a 0.05 two-sided significance level. That is a difference of 0.2 standard deviations between the mean length of stay in the 2 groups. If the sd is 70 hours (as in the pilot of the protocol), the study will be able to detect a difference between the groups of 14 hours; if the sd is 50 hours (as in the retrospective review), the study will be able to detect a difference of just over 8 hours. Thus, this study is powered to detect a difference in duration of admission of 14 hours, and possibly much less.

For the secondary outcomes, using this sample size, and knowing that approximately 30% of all intravenous cannulae have been shown to have complications,[25-28] gives 80% power to detect a 30% change in complications (from 30% to 20%) with a 0.05 significance level.

Analysis will be by intention to treat. Data will be analysed descriptively and statistically using the STATA data analysis program. Since this is a RCT and 2 of the outcome measures are measured on a continuous scale (duration of inpatient stay or hours of therapy), t-tests will be used to compare the 2 groups. If necessary due to

skewed data, the data will be log-transformed. Data on parental satisfaction and complications will be treated as categorical and a Chi-squared test will be used.

No interim analysis of the data is planned.

Economic evaluation

A trial-based economic evaluation will be conducted to assess which approach to fluid replacement therapy is the more 'cost-effective', as judged by their 'cost per child ready for discharge' ratio. The appraisal will be a cost-effectiveness analysis (i.e. outcomes measured with clinically meaningful indicators) using decision tree analysis. The choice of Cost Effective Analysis reflects the research question - one of 'technical efficiency' (i.e. which treatment approach to use) rather than 'allocative efficiency' (i.e. whether treatment should be provided). The appraisal will be conducted from a 'health sector perspective', but with a primary focus on the 'hospital as provider' and 'government as 3rd party funder' perspectives.

Data collection for the economic appraisal is integrated in the resource monitoring, process and outcome measures described above. On the cost side, pathway analysis and patient flowcharts will be used to fully specify all treatment activities (i.e. activity; probability of occurrence; no of times activity occurs; unit price). Resource costs to be included in the study (e.g. ICU bed occupation, general hospital bed occupation, complications & adverse events, tests & procedures, etc) will be fully specified in the economic evaluation protocol before the study commences. The appraisal will include sensitivity and uncertainty analysis (using the @Risk software) to explore the impact on cost-effectiveness results of uncertainty in cost and outcome data. Discounting will not be relevant to this study as the time horizon is less than one year.

Adverse experiences

All adverse experiences either observed by the investigator or one of the clinical staff, or reported by the patient's parents/guardians spontaneously or in response to a direct question, that occur during the study period or a need for a change in therapy, will be evaluated by the investigator and noted in the adverse experience section of the patient's CRF. Events after the study period also thought to be due to a study intervention will be included.

A serious adverse event (SAE) is generally defined as any event that is fatal, life-threatening, permanently disabling, incapacitating or results in hospitalisation, prolongs a hospital stay or is associated with congenital abnormality, carcinoma or overdose.

Note: an event which is an expected and measured outcome of the trial can be treated as an adverse event rather than a serious adverse event (e.g. delayed discharge due to an infected IV site is an adverse event not an SAE).

Serious adverse events

For this trial, serious adverse events are the following:

- death during the study period
- aspiration pneumonitis associated with NG tube misplacement
- intrapulmonary infusion of fluid
- electrolyte disturbance causing seizure
- Any other event not mentioned above that is life threatening event or jeopardises the patient or requires medical or surgical intervention

Reporting SAEs

SAEs need to be reported within 24 hrs by telephone to the local site investigator. The local investigator must report the SAE to their local ethics committee within 48 hours (or in accordance with local ethics committee regulations). The local investigator must also report SAEs to the principal investigators who will report the event to the Data Monitoring Committee chairman. The principal investigator will also report the SAE to all Ethics Committees and other regulatory bodies involved in the trial as per regional regulatory requirements.

SAEs will also be reported to the consultant of the child's treating team. The medical consultant will initiate appropriate management and inform the family if the family is not already aware of the event. This reporting is the responsibility of the site investigator.

Limitations

This trial has a number of potential limitations. The interventions could not be blinded and clinician or researcher bias may influence clinical decision making. However, with the documented rates of use of each intervention approaching 50% - documented prior to the trial²³ - this is unlikely to significantly impact on the outcome. Further, the trial is attempting to assess the use of the interventions in the real world clinical environment where these biases are in play, so the ability to translate the trial results to actual clinical situations may actually be improved. The environment where this study is being performed has low use of ancillary medications (e.g. bronchodilators and steroids) in bronchiolitis patients^[23]. Although subgroup analysis would be desirable, the sample size to achieve this would not be possible within our study setting. The trial excludes children under 8 weeks of age and any results will not be generalisable to this population. No scoring system is used in this trial to determine severity, this remaining a clinical decision representing the real clinical environment, but may inhibit reproduction of the results.

Discussion

The study commenced recruitment in mid 2009. Currently over 190 patients have been randomised. Patient

recruitment is expected to be completed by December 2011.

Additional material

Additional file 1 Inclusion and exclusion criteria. This file is a list of the inclusion and exclusion criteria used for the study

Additional file 2 Guidelines for changing interventions. This file is the guidelines, supplied for the managing clinicians, on when patients should be changed from Nasogastric to Intravenous intervention, and from intravenous to Nasogastric intervention.

Abbreviations

IV: intravenous; NGT: nasogastric tube; IVR: intravenous rehydration; NGR: nasogastric rehydration; CPAP: continuous positive airway pressure; sd: standard deviation; SAE: serious adverse event; PREDICT: Paediatric Research in Emergency Departments International Collaborative

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

EO and FEB were responsible for identifying the research question, and contributing to drafting of the study protocol. SD, MS, AD, JA, MB, DK, TT and JN have all contributed to the development of the protocol and study design, as members of the research team. EO was responsible for the drafting of this paper, although all authors provided comments on the drafts and have read and approved the final version. EO, for the PREDICT research network, takes responsibility for the manuscript as a whole.

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Paper 2-2

Ed Oakley, Meredith Borland, Jocelyn Neutze, Jason Acworth, David Krieser, Stuart Dalziel, Andrew Davidson, Susan Donath, Kim Jachno, Mike South, Theane Theophilos, Franz E Babl, for the Paediatric Research in Emergency Departments International Collaborative (PREDICT).

Nasogastric hydration versus intravenous hydration for infants with bronchiolitis: a randomised trial.

Lancet Respiratory Medicine 2013;1(2), 113–120

The final approved manuscript submitted for publication is provided below

Title Page

A randomised trial comparing nasogastric with intravenous hydration in infants with bronchiolitis

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Running Title: Comparing Hydration Methods in Bronchiolitis

Keywords: Bronchiolitis, intravenous, nasogastric, emergency department, child

Background:

Bronchiolitis is the most common lower respiratory tract infection in infants and the leading cause of hospitalisation. Hydration is a mainstay of treatment, with insufficient evidence to guide clinical practice. This study aims to determine if intravenous hydration or nasogastric hydration is superior in treating infant with hydration

Methods:

We conducted a randomised trial comparing nasogastric (NGH) and intravenous (IVH) routes of hydration in 759 infants (aged 2 to 12 months) admitted to hospital with a clinical diagnosis of bronchiolitis. Patients were randomised using opaque sealed envelopes. Three randomly assigned block sizes were used to conceal allocation. Randomisation was stratified by hospital site and age group (2 months to <6 months, 6 months to <12 months). The study was performed in seven hospitals over three bronchiolitis seasons. The primary outcome was length of hospital stay (LOS). Secondary outcomes included Intensive Care Unit (ICU) admission, adverse events and ease of insertion.

Findings:

Baseline characteristics were similar in the two groups. Mean LOS in the NGH group was 86.6 (standard deviation (SD) 58.9) hours compared with 82.2 (SD 58.8) hours in the IVH group with an absolute difference in LOS of 4.5 hours (95% Confidence Intervals -3.9, 12.9). There was no difference in the rate of ICU admission, need for ventilatory support or adverse events. Seven NGH infants required change to IVH at time of randomisation and 56 IVH infants required change to NGH due to inability to successfully insert the study-assigned method. In the NGH group, 275 (85.1%) and in the IVH group 165 (56.1%) required only a single attempt for successful insertion.

Interpretation:

Both NGH and IVH are appropriate means to hydrate infants with bronchiolitis with no significant differences in LOS or adverse events. NG insertion appears to take fewer attempts, and has a higher success rate of insertion. Clinicians and families can make an informed decision on which hydration method to use for individual infants using this information.

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INTRODUCTION

Bronchiolitis is the leading cause of hospitalisation during the first year of life and is a major cause of morbidity and mortality.¹⁻⁵ In the United States of America bronchiolitis accounts for 21% of all hospital admissions for infants under 1 year of age, with an estimated annual cost of \$390 to \$700 million.⁶ The efficacy of bronchiolitis treatments is limited. International guidelines, including those of the American Academy of Pediatrics, recommend supportive care of breathing and maintenance of hydration only.^{1,2,7-11} Maintaining hydration is therefore an important component of the care of infants with bronchiolitis, with fluid replacement therapy being required in approximately 30% of infants admitted.¹²

Despite the frequency of its use, the evidence to determine the optimum route of hydration therapy for infants admitted with bronchiolitis is sparse. Internationally both nasogastric hydration (NGH) and intravenous hydration (IVH) are used. A survey of Australian and New Zealand paediatric emergency physicians, reported 48% using NGH and 52% using IVH in their initial management of infants admitted with bronchiolitis requiring fluid replacement.¹³ The use of NGH has been reported in small case series showing that it is well tolerated without incident.¹⁴ NGH is potentially advantageous due to the supply of additional nutrition and comfort associated with gastric filling. However there is a potential increased risk of aspiration and partial obstruction of the airway in an infant who already has airway compromise.¹⁵⁻¹⁹ While commonly used in North America,¹ IVH is associated with the potential for greater loss of nutritional status and iatrogenic hyponatremia, especially as these infants are already at increased risk for hyponatremia due to inappropriate secretion of antidiuretic hormone.^{20,21}

No trial has compared methods of hydration in infants admitted with bronchiolitis. Separate reviews have concluded that there is no good quality evidence that hydration by the nasogastric (NG) route is more or less effective or safe than via the intravenous (IV) route, and that these methods need to be compared in randomised studies.^{22 11 7} Two of these reviews^{7,11} recommended focussing on continuous outcome measures of interest to the clinician, such as length of hospital stay. This randomised trial was therefore designed to compare the effectiveness and complications of using NGH and IVH in the management of previously well infants admitted with bronchiolitis who require fluid replacement. The primary measure of effectiveness in this trial was length of hospital stay (LOS).

METHODS

Patients

Infants were enrolled into this open, randomised trial comparing NGH and IVH at seven hospitals in Australia and New Zealand, during the bronchiolitis seasons (from the first week of April to the last week of October each year) between 2009 and 2011. All hospital emergency departments who participated are members of the Paediatric Research in Emergency Departments International Collaborative (PREDICT) research network. Written informed consent was obtained from the parents or guardians of all infants, and the study was approved by the institutional ethics committee at each participating site. The trial protocol (described in detail previously²³) was developed by the study investigators. Data were collected by research nurses and the study was overseen by an independent data monitoring committee.

Infants admitted with a clinical diagnosis of bronchiolitis aged between 8 weeks (corrected for prematurity) and 12 months (chronological age) were eligible for enrolment. Bronchiolitis was defined as symptoms and signs of respiratory distress (tachypnea, recessions, nasal flaring, or cyanosis) associated with symptoms of a viral respiratory tract infection.^{1,11} Infants were ineligible for enrolment if they had: chronic respiratory, cardiac or neurological illnesses; had saturations below 90% despite up to 3 litres/minute supplemental oxygen; required immediate ventilatory support; required IV fluid resuscitation for shock; presented to hospital with an NG or IV *in situ*; or required an IV or NG for another reason. Infants under 8 weeks of age were excluded from the study due to concerns by some that NG placement may impinge on the airway of smaller infants. Infants were randomised into the study only once.

Randomisation and intervention

Infants enrolled into the study were not randomised to treatment groups until the treating clinicians deemed non-oral fluids to be necessary. Therefore randomisation could occur at admission or at any time during hospitalisation. Randomisation was stratified by hospital site and age group (2 months to <6 months, 6 months to <12 months). To ensure concealment of allocation three randomly allocated block sizes and opaque sealed envelopes were used.

Infants assigned NGH received NG fluids of continuous oral rehydration solution for the first 2 hours then their usual feed by bolus every subsequent 1-2 hours, with the total volume of fluid being 80% of daily maintenance. Infants assigned IVH received IV fluids of continuous 0.45% sodium chloride with 2.5, 4 or 5% dextrose at 80% of daily maintenance. The initial route, rate and type of fluid administration at the time of randomisation were determined by the study protocol. Subsequent management decisions including changes to the route, rate and type of fluid administration were at the discretion of the treating clinician.

Assessments

Research nurses collected data on medical interventions (including oxygen and fluid administration), medication received, complications experienced (including predefined complications of the study interventions), and physiological observations (oxygen saturation, heart rate, respiratory rate and effort, and hydration status including weight), need for intensive care unit (ICU) admission and level of respiratory support. Information on changing from one method of fluid administration to another, and on ease and success of insertion of the initial intervention at the time of randomisation was collected. Parents and guardians of infants were followed up with a telephone interview at 5 to 7 days post discharge using a standard questionnaire to determine the incidence of further complications, or need for further medical care.

Outcome measures

The primary outcome measure, length of hospitalisation, was determined from the computerised hospital records. Since length of hospitalisation may be affected by many administrative and social factors unrelated to the clinical condition of the infant, the time that the subject was ready for discharge was also recorded prospectively using objective criteria. An infant was considered ready for discharge if he/she had not received supplemental oxygen for 12 hours, had stable respiratory status for 4 hours (including slight or nil chest-wall recession) and was feeding adequately.

Secondary outcome measures included: 1) the incidence and type of complications of hydration therapy, including need for ICU admission, ventilatory support, adverse events including desaturation, bradycardia, apnoea and pulmonary aspiration, local complications of the insertion methods, ease of

insertion, need for IV/NG replacement, and 2) parental satisfaction measured at the end of hospital stay on a five point Likert scale. All safety reporting analysis was by intention to treat. A separate economic analysis will be subsequently undertaken.

Statistical analysis

Differences between the two study groups were assessed using t tests and 95% Confidence Intervals (CI) of difference of means for continuous outcome variables, and chi square and 95% CI of difference of percentages for categorical outcome variables. In order to reduce skewness in the distribution of the primary outcome variable (LOS), LOS was capped at 2 weeks for infants with LOS greater than 2 weeks. Medical records for these infants were reviewed to determine if the extended LOS was related to the study intervention. LOS for infants who died before 2 weeks was also set to 2 weeks. The capped LOS variable was used for the main analysis. Supplementary analyses using bootstrapping on the uncapped LOS, using log transformed uncapped LOS, and using survival analysis of uncapped LOS were also performed. Analysis of primary and secondary outcome measures was by intention to treat. No interim analysis of the data was planned or undertaken. Since this is a RCT and the primary outcome measure is measured on a continuous scale, t-tests were used to compare the 2 groups. Where necessary due to skewed data, the data was log-transformed. All other continuous data, such as duration of therapy were reported using t-tests. Data on parental satisfaction and complications were treated as categorical and a Chi-squared test was used. Exact methods were used for all means and standard deviations (SD). For all analyses SDo and KJ used Stata version 11.1 (StataCorp, Texas, USA).

Sample size: We aimed to recruit 750 infants (375 per arm) in order to have 80% power to detect a difference of at least 0.2 SD of LOS between the 2 treatment groups using a two group t-test with a 0.05 two-sided significance level. Data on estimated SD of LOS in bronchiolitis were available from 2 sources: (i) a retrospective review of 100 bronchiolitis cases (estimated SD 50 hours) and (ii) a pilot of the study protocol in 50 patients (estimated SD 70 hours). We therefore expected to have sufficient power to detect a minimum difference in mean LOS of between 10 and 14 hours. We considered that a difference in LOS less than this was clinically insignificant.

The trial was registered with the Australian and New Zealand Clinical Trials Registry, registration number ACTRN12605000033640.

Role of the funding source

Funding sources had no role in study design, data collection, data analysis and interpretation, and manuscript preparation and submission. Sdo, KJ, EO and FB had access to the raw data. The corresponding author had full access to all of the data and the final responsibility to submit for publication

RESULTS

During the study period 3899 infants aged 2 months to 12 months were admitted to the study hospitals with a diagnosis of bronchiolitis (Figure 1). Of the 3408 infants assessed for enrolment into the study, 964 infants fulfilled exclusion criteria and in 699 instances the guardians did not consent to participation. The remaining 1745 infants were enrolled, of whom 932 did not require non-oral fluids, and 54 deteriorated after enrolment and met exclusion criteria prior to randomisation. The remaining 759 (43.5%) were randomised to an intervention. Nine infants were randomised between the confirmation of 750 correct randomisations and the communication to cease recruiting. A review of the hospital records of the 491 missed infants concluded that 289 were potentially eligible for the study and of these, 121 (41.9%) required non-oral fluids during their hospital stay. The age and gender distribution of the infants who were missed and potentially eligible for the study, and whose guardians refused to participate did not differ from those randomised into the study.

Of the 759 infants randomised, 381 were assigned to the NGH group and 378 to the IVH group. Primary outcome data was available for all randomised infants. At the time of randomisation 24 infants in the NGH group and 77 in the IVH group did not receive the allocated intervention. No non-oral method was attempted for 17 of the 24 NGH infants and 21 of the 77 IVH infants as their oral intake spontaneously improved. The remaining seven NGH infants required change to IVH at time of randomisation and the remaining 56 IVH infants required change to NGH due to staff being unable to successfully insert the study assigned method.

Baseline demographic and clinical characteristics in the NGH and IVH groups are shown in Table 1.

Abnormal vital signs at triage, medical history, family environments, medication use in the week prior

to the ED visit, and history for this episode of bronchiolitis were similar in both groups. Of the 467 /759 (61.5%) infants who had viral testing performed there was a similar rate of Respiratory Syncytial Virus (RSV) infection (61.1% in the NGH vs. 55.8% in IVH). The time from enrolment of infants to randomisation did not differ between the treatment groups, with a median of 2.9 hours for NGH and 3.1 hours for IVH groups ($p=0.64$).

Primary Outcome Measure

There was no evidence of a clinically significant difference in mean LOS between the treatment groups. Mean LOS in the NGH group was 86.6 (SD 58.9) hours compared with 82.2 (SD 58.8) hours in the IVH group with an absolute difference in LOS of 4.5 hours (95% CI -3.9, 12.9) (Table 2). A comparison of LOS is presented visually in a Kaplan Meier survival analysis of time to discharge shown in Figure 2. Similar results were obtained using the alternative methods of analysis described in Methods, and using the time ready for discharge LOS with a time of 84.1 hours for NGH and 80.2 hours for IVH, a difference of 3.9 hours (95% CI -4.3, 12.2).

Six infants had LOS of more than 14 days, 4 in the NGH and 2 in the IVH group (Table 3). In none of the infants with stays beyond 2 weeks was the cause of the prolonged hospitalisation thought to be study intervention related. A 6 month old infant (randomized to the IVH group) died within 24 hours of admission after developing staphylococcal septic shock and empyema. The death was unrelated to study intervention.

As 101 infants did not receive the randomised treatment, *post hoc* analysis by treatment received was undertaken. Mean LOS in the NGH group was 88.1 hours compared with 83.2 hours in the IVH group with an absolute difference in LOS of 4.9 hours (95% CI -4.0, 13.8); $p=0.28$.

Secondary Outcome Measures

Intensive care admissions

Overall, 6.6 % of infants required ICU admission (Table 2). There was no difference between the groups in terms of ICU admission rate ($p=0.53$), need for ventilation ($p=0.99$) or continuous positive airway pressure (CPAP) support ($p=0.83$).

Adverse events and duration of treatment

Few infants in either group developed oxygen desaturations, bradycardia or apnea with no difference between groups in these outcomes. No patient suffered pulmonary aspiration, and the duration of

oxygen therapy did not differ between groups. The duration of non-oral hydration was the same for the two groups (Table 2).

Success at insertion

In the NGH group 323 (84.8%) and the IVH group 294 (77.8%) had the number of attempts at insertion of the allocated treatment recorded. First attempt success was higher in the NGH group, where 275 (85.1%) had 1 attempt at insertion, 30 (9.3%) had 2 attempts, 11 (3.4%) had 3 attempts and 7 (2.2%) had 4 to a maximum of 8 attempts at insertion, while in the IVH group 165 (56.1%) had 1 attempt at insertion, 69 (23.5%) had 2 attempts, 41 (13.9%) had 3 attempts and 19 (6.4%) had 4 to a maximum of 8 attempts at insertion, $p<0.001$ (Figure 3).

In infants who had the allocated treatment successfully inserted at the time of allocation, for the NGH group the number of attempts at insertion was known in 321 (84.3%), with 274 (85.3%) inserted at first attempt. For the IVH group the number of attempts at insertion was known in 261 (69.1%), and 163 (62.4%) were inserted at first attempt ($p<0.001$). Details of the number of attempts needed for successful insertions of IV and NG is shown in Figure 3.

Problems with hydration methods

The most common complications associated with the method of hydration were, in the NGH group "NG pulled out" ($n=131$), "NG reinserted" ($n=54$) and "NG not working" ($n=7$); and in the IVH group, "IV fluid extravasation" ($n=80$) and "IV requiring reinsertion" ($n=45$).

Change of therapy to the alternative, was less common in the NGH group 50 (13.1%) than the IVH group 95 (25.1%); absolute difference 12.0% (95%CI 6.5% to 17.5%), $p<0.001$. The reasons for changing from NG to IV were "admission to ICU" ($n=19$), "required an IV bolus" ($n=13$), "IV drugs or blood tests required" ($n=5$), "increased work of breathing" ($n=5$), "cannot maintain oxygen saturation" ($n=4$), "abdominal distension or increased aspirate" ($n=2$), "parental request" ($n=1$) and "other" ($n=3$). The reasons for changing from IV to NG were "unable to place IV" ($n=56$), "IV fluid extravasation" ($n=11$), "hungry, crying and needing feeding" ($n=9$), "parental or medical staff request" ($n=13$), "gastric decompression required" ($n=3$) and "other" ($n=4$).

Other hospital interventions and findings

In the NGH group 73/380 (19.2%) infants received salbutamol at any time point compared with 95/378 (25.1%) in the IVH group. In the NGH group 9/380 (2.4%) infants received nebulised adrenaline at any time point compared with 13/378 (3.4%) in the IVH group. In the NGH group 23/380 (6.1%) infants received IV or oral steroids at any time point compared with 23/378 (6.1%) in the IVH group. In the NGH group 13/381 (3.4%) had pneumonia listed as an additional discharge diagnosis, compared with 22/378 (5.8%) in the IVH group.

Parent satisfaction

Overall parental satisfaction at the end of stay did not differ between groups: IVH (median 5 (IQR 4-5)) versus NGH (median 5 (IQR 4-5)). No subgroup analysis for satisfaction was undertaken.

Follow up after discharge

Overall 678 (89.3%) infants could be contacted in follow up. Similar proportions in both groups had unscheduled medical visits after discharge or were re-hospitalised (Table 4). Few parents reported adverse events possibly related to the interventions, mainly bruising in infants with IV insertion and a sore nose with NG insertion.

DISCUSSION

When comparing intravenous (IVH) to nasogastric (NGH) hydration in infants hospitalised with bronchiolitis, this study demonstrated no clinically or statistically significant difference in length of hospital stay. However, a higher likelihood of failure to initiate the assigned treatment and more attempts to initiate treatment in the IVH group were demonstrated. With the SD of the LOS in our study population of 59 hours we had power to determine a difference of 12 hours or more in LOS. No such difference was found.

The previous literature on hydration methods in bronchiolitis is sparse. Sammartino¹⁴ published a case series of 37 infants with bronchiolitis who were successfully hydrated via the NG route. Walker *et al*²⁴ published experience from Aberdeen where a bronchiolitis pathway was implemented with NGH as the suggested intervention for infants admitted and requiring supplemental non-oral fluids.

These clinicians reported that NGH was safe and effective. Reviews of hydration methods in bronchiolitis management have concluded that there is no strong evidence for one method over the other.^{11,22} Both NGH and IVH in bronchiolitis have been recommended by expert and consensus opinion.^{1,25}

In children with dehydration due to gastroenteritis, NG rehydration is the treatment of choice as it provides faster recovery, shorter hospital stay.^{26,27} Cost-minimisation analysis of NGH versus IVH for rehydration of gastroenteritis in children has shown NGH to be more cost effective.²⁸ However, concerns have been raised regarding the use of nasogastric tubes in infants with bronchiolitis as there may be an increased risk of aspiration.¹⁶ There have also been reported concerns that partial obstruction of the upper airway may compromise respiratory function,^{15,17-19} with some studies showing an increase of up to 50% in the work of breathing associated with placement of an NG.¹⁹ Our results show no evidence of worsening illness, need for ICU admission, duration of oxygen treatment, or risk of aspiration or deterioration with the use of NGH. While this study was not designed or powered to assess the safety of NG insertion this study adds to another large series showing the safety of this procedure for children in the emergency setting.²⁹ The lack of a difference in complications further suggests that as in the gastroenteritis, it is possible that NGH may be a more cost effective treatment than IVH for bronchiolitis.

Infants could be randomised into the study once. We considered including multiple presentations however decided that our data would be easier to interpret if only first presentations in the study period were included. Including only up to 1 year of age meant that we were not excluding a large number of re-visits. We had some concerns that experience on the initial visit may change preference for future visits and effect enrolment or satisfaction.

The two groups in our study had similar ages and gender, and similar clinical characteristics that measure severity of illness. Despite this, our study showed that subjects randomized to IVH were less likely to receive the allocated intervention (requiring change to the alternative treatment), with inability to initially site the allocated intervention in 56 (25.6%) compared with 17 (5.5%) in the NGH group. Also the number of attempts taken to site the IV was greater than those taken to place the NG, with NG 52% more likely (85.1% vs. 56.1%) to be inserted at the first attempt than IV. This represents a clear advantage of NGH clinically and administratively.

As a multicentre study that included tertiary children's hospitals as well as mixed adult and children's hospitals, and enrolled infants over three bronchiolitis seasons, the study has covered a broad population strengthening the external validity of the results. The chosen outcome measure (LOS) has been suggested as a desirable metric for analysis of interventions in bronchiolitis.⁷ It is an accurately recorded outcome that is of significant interest to health care administrators. Length of hospital stay is also a recognised surrogate measure of significant complications and worsening of disease. We also measured the readiness for discharge (using defined criteria) to ensure social and practical issues did not effect the discharge times. This measure is more subjective and thus harder to record; however there was concordance between the two outcome measures, strengthening the validity of our data. The study had limitations. The interventions were not blinded, as this was not pragmatic. All the institutions included in the study have had significant experience in using both NGH and IVH as interventions in bronchiolitis, so lack of understanding or experience with either was not an issue. The primary outcome measure was such that individual clinician preferences for one intervention over another were unlikely to have any effect. It is possible however that individual preference for NGH lead to more infants in the IVH group not receiving that allocated intervention. The unblinded nature of the primary outcome may have been subject to bias as discharge time varies according to non-clinical influences such as time of consultant ward round. However the pre-specified time ready for discharge did not differ between groups, suggesting that non-clinical influences had little effect on the conclusions of the study. To assess parental satisfaction we used a standard Likert scale that is a commonly used tool but not validated for this use. We have not assessed small subgroups of the study population regarding satisfaction and have only reported an overall satisfaction assessment. There may be subgroups with differing satisfaction. The study was not sufficiently powered to detect rare but clinically significant events that may be associated with either treatment. Patients younger than 8 weeks of age were excluded from the study. This was a practical decision made at the beginning of the study design, due to concerns by some that NG placement may impinge on the airway of smaller infants. This limits the extrapolation of the results to infants in this age category. In retrospect we suspect that previously well infants down to 4 weeks could safely have been included, but that the application of the results in these infants with no pre-existing illnesses would require close clinical assessment and monitoring.

Our study demonstrated a 6% ICU admission rate, 3% having CPAP and 0.2% requiring invasive ventilation with no difference between groups. This data is similar to that presented for previously well children with RSV positive bronchiolitis in a systematic review of interventions for bronchiolitis,⁷ and a review of bronchiolitis outcomes in Canada.³⁰ Both report that 10% of children will need admission to ICU with half of those requiring ventilatory support. This suggests our population of infants is similar to those in other developed countries, and the results would be transferrable to those settings. In resource poor settings where IV treatment may be more difficult, more complex, and cause more complications, the balance may shift towards NGH.

The number of adverse events associated with the interventions was small, with both methods of hydration having a number of complications. Parental satisfaction with the treatment method was high, and did not differ between groups despite more failures and more attempts at insertion in the IVH group.

Both NGH and IVH are appropriate means to hydrate infants with bronchiolitis with no significant differences in LOS or adverse events. NG insertion appears to take fewer attempts, and has a higher success rate of insertion.

Conflicts of Interest

The authors declare they have no conflicts of interest.

Author Contribution:

All authors contributed to the design and implementation of the study, or analysis and interpretation of the study results. EO, FB, MB, JA, JN, DK, MS, AD contributed to all stages of the study. SDo contributed to the implementation of the study. EO was the principal investigator. TT was the study coordinator. SDo, and KJ performed the statistical analysis. KJ controlled the database. EO, FB, MB, SDo, DK, JA contributed to interpretation of the results. All authors contributed to the manuscript preparation and review, and approved the final version. The report was written by EO. All authors contributed to the writing of the article.

Knowledge in Context

Systematic Review

- A systematic review of Medline, Embase, and the Cochrane Library was undertaken using search terms bronchiolitis, pediatric, hospital, nasogastric, and respiratory syncytial virus individually and in combination.
- All references returned were reviewed from title or abstract for relevance. Evidence was selected if it related to epidemiology, outcome, or treatment of viral bronchiolitis.
- There were recent review articles, evidence based analyses and RCTs of treatment.
- Only small cohort studies of methods of hydration were found

Interpretation

- To our knowledge this trial is the first randomised evidence for methods of hydration and addresses the endpoints requested in recent review articles
- Non-oral hydration is required in about one third of patients admitted with bronchiolitis
- Nasogastric and intravenous routes are both acceptable routes for hydration in patients with bronchiolitis. The choice of the intravenous route is likely to be associated with more failures and more attempts to achieve hydration
- This trial supports an increased use of the nasogastric route of hydration in previously well infants over 2 months of age with bronchiolitis.

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Table 1

Demographics and Baseline Clinical Characteristics

Characteristic	Nasogastric hydration (n=381)	Intravenous hydration (n=378)
Gender (% male)	228 (59.8%)	227 (60.1%)
Age group		
Age (days; mean, (SD))	177.6 (79.8)	186.3 (84.6)
2-6 months	201 (52.8%)	196 (51.9%)
6-12 months	180 (47.2%)	182 (48.1%)
Vital signs at presentation		
RR greater than normal *	201/379 (53.0%)	208/377 (55.2%)
HR greater than normal *	146/380 (38.4%)	138/378 (36.5%)
O2 saturation < 90% +	60/374 (16.0%)	60/367 (16.3%)
Retractions/recessions (n=755)		
None	10 (2.7%)	3 (0.8%)
Mild	81 (21.5%)	95 (25.1%)
Moderate	242 (64.2%)	251 (66.4%)
Severe	44 (11.7%)	29 (7.7%)
Previous medical history		
History of previous wheeze	52/379 (13.7%)	50/375 (13.3%)
History of asthma	5/378 (1.3%)	2/275 (0.5%)
History of eczema	61/379 (16.1%)	52/375 (13.9%)
History of previous bronchiolitis	108/379 (28.5%)	101/375 (26.9%)

Other medical disorder	55/380 (14.5%)	48/378 (12.7%)
Premature (less than 36 weeks)	39/381 (10.2%)	41/378 (10.8%)

Family environment

Family history of asthma	222/364 (61.0%)	207/366 (56.6%)
Smokers in home	168/369 (45.5%)	171/365 (46.8%)
Pet in home	135/362 (37.3%)	125/359 (34.8%)

Medications used in week prior to ED visit

Bronchodilators	41/330 (11.1%)	43/330 (11.5%)
Inhaled steroids	6/365 (1.6%)	2/371 (0.5%)
Oral steroids	25/346 (6.7%)	27/346 (7.2%)
Antibiotics	54/317 (14.6%)	61/312 (16.4%)

This illness

Time from enrolment to randomisation		
(hours; median, (IQR))	2.9 (1.55, 8.55)	3.1 (1.65, 8.4)
Time since onset of symptoms (days; mean,		
(SD))	3.8 (1.1)	3.8 (1.1)
RSV positive ‡	143/234 (61.1%)	130/233 (55.8%)

SD Standard deviation; IQR interquartile range

* Abnormal defined as >2 standard deviations from normal range, taken from

http://www.rch.org.au/clinicalguide/cpg.cfm?doc_id=7783

† Oxygen saturation in room air

‡ RSV status determined in 467 cases

Table 2

Results: Length of Stay, Intensive Care Unit (ICU) Admission, and Adverse Events

Characteristic	Nasogastric hydration (n=381)	Intravenous hydration (n=378)	Difference (95% CI)*
Length of stay (hours, mean, (SD))	86.6 (58.9)	82.2 (58.8)	4.5 (-3.9, 12.9)
ICU admission	21 (5.5%)	25 (6.6%)	-1.1% (-4.5%, 2.3%)
CPAP	12 (3.2%)	13 (3.4%)	-0.3% (-2.8%, 2.3%)
Intubated and ventilated	5 (1.3%)	5 (1.3%)	0.01% (-1.6%, 1.6%)
Oxygen saturation <90% †	19 (5.0%)	14 (3.7%)	1.3% (-1.6%, 4.2%)
Duration of non-oral hydration (hours, mean (SD))	43.7 (48.6)	41.7 (44.8)	2.1 (-4.6 – 8.8)
Duration of oxygen therapy (hours, mean (SD))	45.8 (52.1)	43.2 (51.9)	2.2 (-5.1, 9.7)
Bradycardia	6 (1.6%)	4 (1.1%)	0.5% (-1.1%, 2.1%)
Apnoea	1 (0.3%)	1 (0.3%)	0.0% (-0.7%, 0.7%)
Epistaxis	0 (0.0%)	1 (0.3%)	-0.3% (-0.8%, 0.3%)
Aspiration	0 (0.0%)	0 (0.0%)	-

ICU intensive care unit

CPAP continuous positive airway pressure

SD standard deviation

*All differences non significant

†Oxygen saturation in room air

Table 3

Infants with Prolonged Length of Stay (LOS) (>14 days)

Age	LOS	Study Group	Outcome	Comments
11 m	16d	IVH	Discharged	Persistent low oral intake; no ICU.
3m	18d	IVH	Discharged	Disease progression; ICU for 4d – intubated.
7m	14d	NGH	Discharged	Para influenza positive, developed empyema/pneumonia. ICU for 2d - intubated.
2m	17d	NGH	Discharged	Respiratory syncytial virus positive, disease progression, ICU for 12d- intubated
3m	20d	NGH	Discharged	Human metapneumovirus positive, disease progression, ICU for 2d – CPAP
6m	280d	NGH	Discharged	Rhinovirus positive, ex-premature baby with undiagnosed subglottic stenosis. Complex course requiring tracheostomy and tracheal reconstruction with ICU admissions.

d days

m months

NGH nasogastric hydration

IVH intravenous hydration

ICU intensive care unit

CPAP continuous positive airway pressure

Table 4

Follow up data after Discharge from Hospital

Characteristic	Total	Nasogastric hydration (n=381)	Intravenous hydration (n=378)
Successful follow up	678	336 (88.2%)	342 (90.5%)
Unscheduled medical visit	81/678	40/336 (11.9%)	41/342 (12.0%)
Hospitalized for any reason	18/678	8/336 (2.4%)	10/342 (2.9%)
Hospitalized for bronchiolitis	11	4	7
Adverse event reported	79/678	32/336 (9.5%)	47/342 (13.7%)
IV site bruising	36	3	33
Sore nose	10	9	1
IV site soreness	9	0	9
Epistaxis	5	4	1
Any sign nasal trauma	3	3	0
IV site infection	0	0	0
Other	22	11	11

IV Intravenous

Figure 1: Eligibility, Randomisations and Follow up

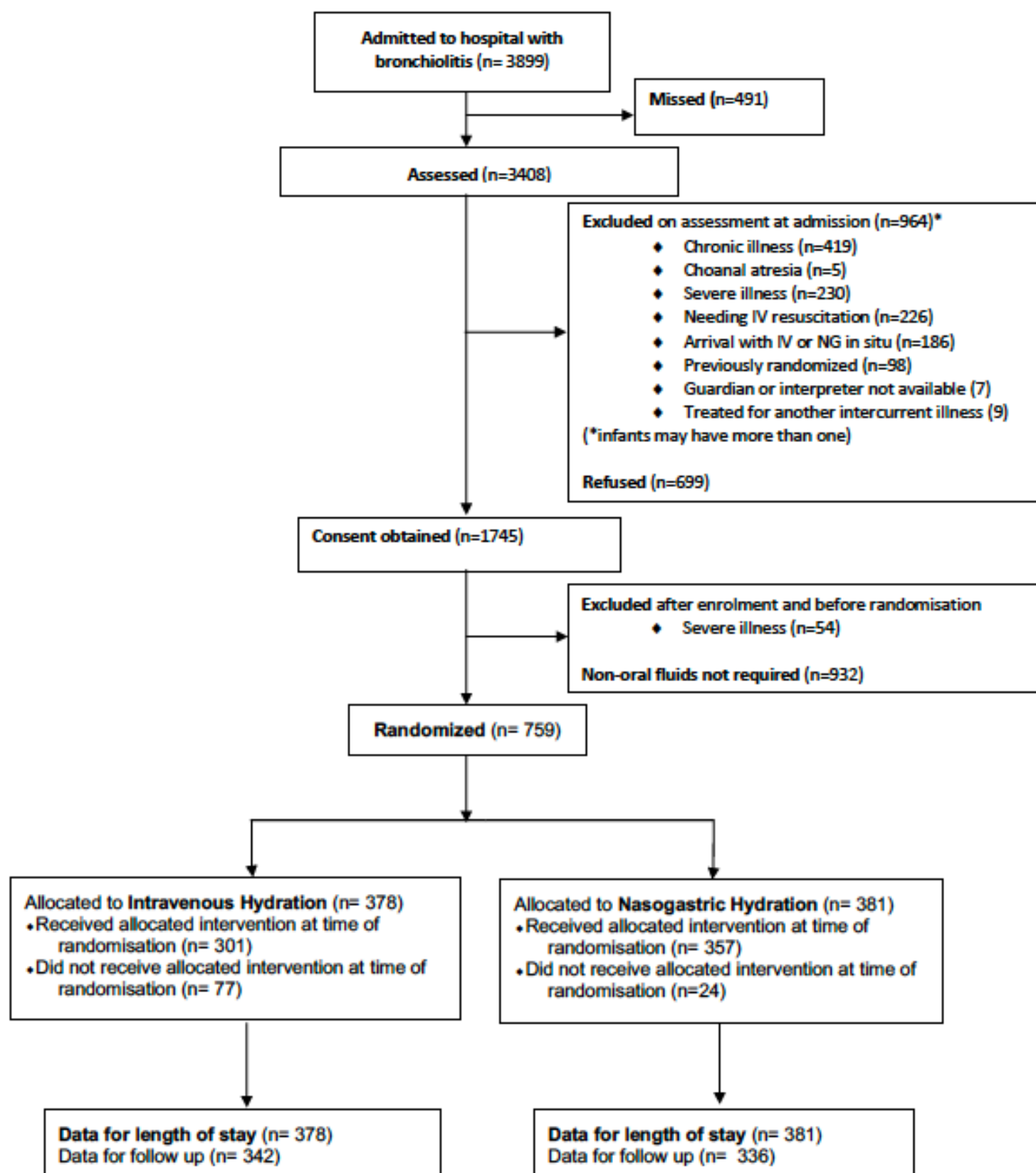
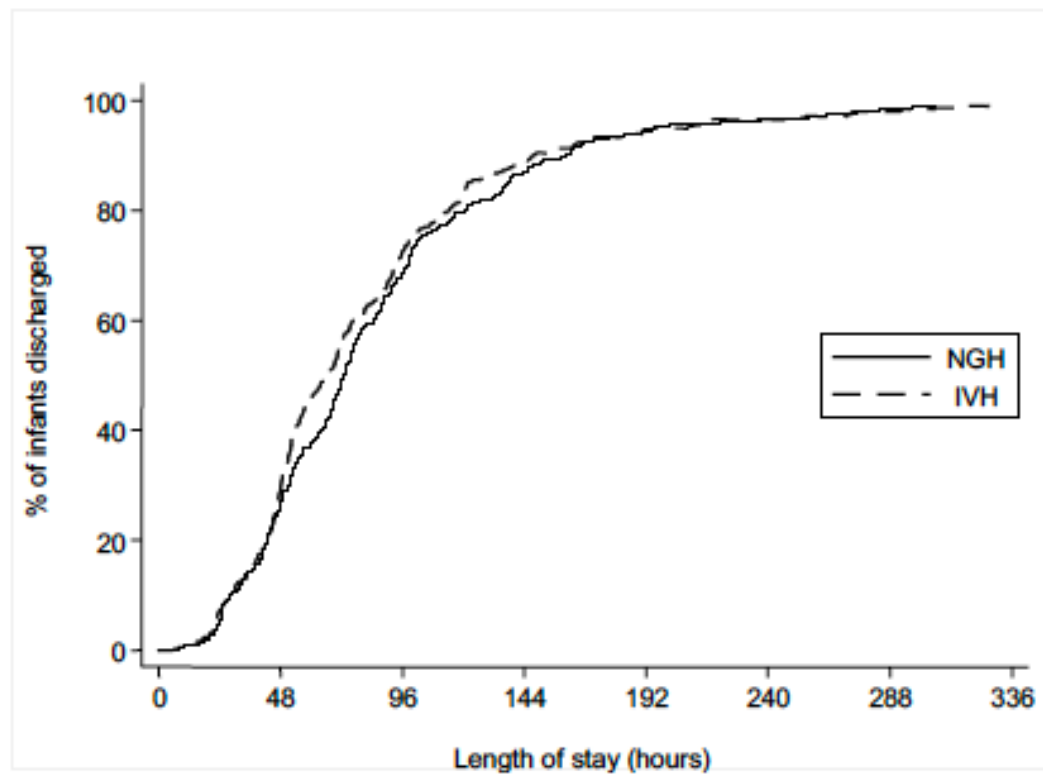


Figure 2: Kaplan Meier Analysis of Length of Stay

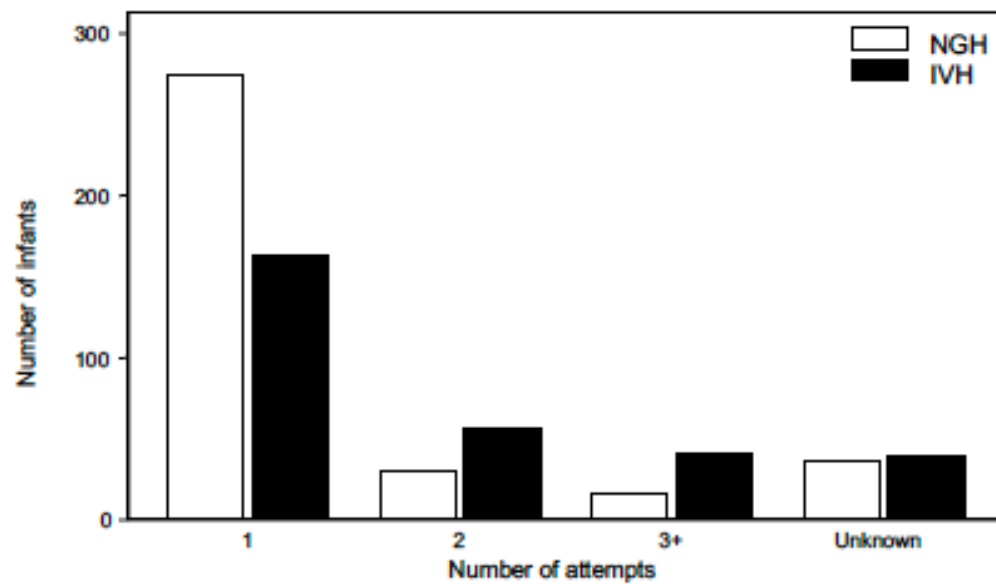


NGH nasogastric hydration group (n=381)

IVH intravenous hydration group (n=378)

(Graph truncated at 336 hours = 14 days)

Figure 3: Number of Attempts Required to Successfully Insert Nasogastric (NG) Tube or Intravenous (IV) Access



NGH nasogastric hydration

IVH intravenous hydration

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Paper 2-3

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TITLE PAGE

An economic evaluation of nasogastric versus intravenous hydration in infants with bronchiolitis

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ABSTRACT

Background:

Bronchiolitis is the most common lower respiratory tract infection in infants and the leading cause of hospitalisation. We aimed to assess whether intravenous hydration (IVH) was more cost-effective than nasogastric hydration (NGH), as a planned secondary economic analysis of a randomised trial involving 759 infants (aged 2 to 12 months) admitted to hospital with a clinical diagnosis of bronchiolitis and requiring non-oral hydration. No Australian cost data exist to aid clinicians in decision making around interventions in bronchiolitis.

Methods:

Cost data collections included hospital and intervention-specific costs.) The economic analysis was reduced to a cost-minimization study, focusing on intervention-specific costs of IVH verses NGH, as LoS was equal between groups. All analyses are reported as intention to treat.

Results:

Intervention costs were greater for IVH than NGH (\$113 vs \$74; cost difference of \$39 per child). The intervention-specific cost advantage to NGH was robust to inter-site variation in unit prices and treatment activity.

Conclusion:

Intervention-specific costs account for <1% of total costs of bronchiolitis admissions, with NGH having a small cost saving across all sites.

Funding:

We acknowledge grant support from the National Health and Medical Research Council, Canberra, Australia, the Samuel Nissen Charitable Foundation managed by Perpetual, Melbourne Australia, the Murdoch Children's Research Institute, Melbourne, Australia, and the Victorian Government's Operational Infrastructure Support Program.

Registered with the Australian and New Zealand Clinical Trials Registry, ACTRN12605000033640.

INTRODUCTION

Bronchiolitis is the leading cause of hospitalisation during the first year of life and is a major cause of morbidity and mortality.¹⁻⁶ In the United States of America bronchiolitis accounts for 21% of all hospital admissions for infants, with an estimated annual cost of \$390 to \$700 million.⁷ As the efficacy of bronchiolitis treatments is limited, international guidelines, including those of the American Academy of Pediatrics, recommend only supportive care of breathing and maintenance of hydration.^{1,2,6,8-12} Maintaining hydration is therefore an important component of the care of infants with bronchiolitis, with fluid replacement therapy being required in approximately 30% of infants admitted.¹³ Evidence to determine the optimum route of hydration therapy for infants has been limited, while evidence to inform the cost-effectiveness of alternative therapy options is scarce.

A recent study comparing intravenous hydration (IVH) with nasogastric hydration (NGH) in the treatment of inpatients with bronchiolitis has been performed by our team.¹⁴ Mean LOS in the NGH group was 86.6 (SD 58.9) hours compared with 82.2 (SD 58.8) hours in the IVH group with an absolute difference in LOS of 4.5 hours (95% CI -3.9, 12.9). NGH insertion was successful at the first attempt in 85.3% compared with IV insertion success in 62.4% ($p<0.001$). Switching treatments was less common in the NGH group (13.1%) compared with the IVH group (25.1%); absolute difference 12.0% (95%CI 6.5% to 17.5%) $p<0.001$. Overall there was a difference in the length of fluid treatment between arms with an average length of fluid treatment of 41.05 hours (SD 38.91) for IVH and 48.28 (SD 48.84) for NGH groups; absolute difference of 7.23 hours (95%CI 5.21, 9.25). There was no difference in the ICU admission rate (NGH 5.5% and IVH 6.6%) $p=0.53$. There was no difference in adverse events between the groups, including: the incidence and type of complications of hydration therapy; ventilatory support; adverse events including desaturation, bradycardia, apnoea and pulmonary aspiration; local complications of the insertion methods; need for intravenous cannula or nasogastric tube replacement.¹⁴

This paper reports the economic evaluation of this recent study, and is undertaken to determine whether intravenous fluid replacement is more cost-effective at treating children admitted to hospital with a clinical diagnosis of bronchiolitis than nasogastric fluid replacement, determined by the 'cost per child discharged' ratio.

METHODS

Patients

1 The study was a three-year, open, randomized trial comparing NGH and IVH in children between two months
2 and 12 months of age, admitted to hospital with bronchiolitis and requiring non-oral fluid hydration. Inclusion
3 and exclusion criteria are described elsewhere.^{14,15} Recruitment was at 7 hospitals in Australia and New
4 Zealand during the bronchiolitis season (April-October) between 2009 and 2011. The study received approval
5 from the research ethics committee at all participating sites. The trial protocol (described in detail previously)¹⁵
6 was developed by the study investigators. Data were collected by research nurses and the study was overseen
7 by an independent data monitoring committee. Funding agencies had no role in study design, data analysis or
8 manuscript preparation. The trial was registered with the Australian and New Zealand Clinical Trials Registry,
9 registration number ACTRN12605000033640.

10 **Economic evaluation**

11 The economic evaluation was designed to inform which of the treatment methods to use based on cost, rather
12 than whether the treatment should be provided or not which may be influenced by many actors including
13 treatment availability and family preference. As the intervention impacts primarily on the health sector, a
14 health sector perspective was adopted focussing on the hospital as primary service provider (and government
15 as '3rd party funder').

16 The primary study design was to be a cost-effectiveness analysis (CEA), where the outcomes were to
17 be expressed in terms of 'cost per infant discharged' capturing both treatment-specific costs and associated
18 LoS. Length of stay is of particular interest to health-care administrators, not only for its cost/revenue
19 implications, but because it captures significant complications, case complexity and worsening of disease. In
20 this case, as there was no statistical difference between the intervention and comparator in terms of the
21 primary outcome (LOS), nor in the key secondary outcomes (Adverse Events and the rate of ICU admissions) a
22 cost-minimisation analysis (CMA) was performed. This is the method of choice where equivalence in outcomes
23 has been demonstrated and/or where researchers are prepared to accept there are no significant differences
24 in outcome. CMA is used to assess cost differences between arms of the trial, focusing on understanding
25 associated cost drivers.

26 **Outcomes**

27 The primary outcome measured for this economic analysis is therefore the cost of each intervention arm and
28 associated treatments.
29
30

Costs

All relevant resource costs to the hospital (the direct health care costs) associated with the NGH and IVH arms of the trial were identified through 'pathway analysis' and 'patient flowcharts'. Costs to the family or carers (the indirect health care costs e.g. child minding; travel expenses; time costs) were not included in this evaluation. All analyses are reported as 'intention to treat', with subsequent costs assigned to the allocated intervention group. All costs are reported in Australian dollars with New Zealand costs converted at the exchange rate of \$0.95.

Under the pathway costing approach all treatment activities are clearly specified (e.g. activity; staff involved; number of times activity occurs). All costs and events associated with the administering of each intervention and those that are a consequence of an adverse event were included. Prior to the start of the study a list of the likely resource cost categories (equipment, products, clinical staff time, etc.) was compiled (Table 1). An event series of activities involved with each intervention was then agreed between all investigators and sites (Table 2). Cost data including unit prices for all products, services and activities was collected from study hospitals using a costing template. The data was audited for any potential errors or significant variation across the 7 hospital sites. Staffing numbers and seniority were obtained from each hospital. An average procedure time was calculated from 20 procedures (10 of each intervention) at 5 different sites. An average cost per intervention (including equipment and staff time costs) was developed from this data.

The procedure (Nasogastric tube insertion or Intravenous insertion) were costed using the average cost per intervention. For the initial randomised intervention, a cost was allocated to each attempt at insertion. For patients crossing over to the alternate intervention the number of attempts at insertion were not recorded, so this is costed on all occasions as a single insertion attempt. Tests and unexpected interventions were costed individually with actual costs.

RESULTS

During the study period 759 infants were randomised to an intervention, 378 to the intervention (IVH) and 381 to the comparator (NGH). (Figure 1)

Cost of the treatment pathways

The costs of providing the assigned intervention were determined as a 'cost per child treated' to standardize total costs over the number of children per arm. The average cost per child treated was calculated using the average cost per procedure (confirmed in assessment of 20 procedures) with key elements set out in Table 2, and including equipment, staff grade, procedure time and the number of attempts at the procedures at randomisation. Group averages for the number of attempts, and number switching to the alternate intervention were used to calculate group intervention costs which were then divided by the number of infants in the group.

Using the 'cost per child assigned to treatment' result, there was a cost difference of \$39.01 in favour of NGH (Table 3). Subgroup analysis was conducted using the outcomes of each treatment arm stratified by age (2 months to <6 months and 6 months to <12 months) and by hospital site. The cost difference was lower in the 6-12 month age group (\$31.98 compared with \$45.60). The cost difference varied between sites, ranging from \$31.51 to \$67.08, with costs lower for NGH at all sites.

The largest drivers of cost were switching from one treatment arm to the other (25.1 IVH vs 13.1 NGH $p<0.001$) and the failure of insertion of the intervention on the first attempt (62.3% IVH vs 85.3% NGH $p<0.001$).

DISCUSSION

Bronchiolitis is a significant cause of hospital admissions in infants and a large cost burden on the health system.³⁻⁵ The largest driver of the cost of bronchiolitis admission is the hospital-related and bed day costs, which are tenfold greater than the intervention-related costs. The lack of difference in LoS between groups therefore made it unlikely that any substantial cost savings would be associated with either intervention. As switching between treatments was a large driver of cost it is of little surprise that hospitals with the greatest intervention-related costs had a higher proportion randomised to IVH who changed to NGH. The other largest drivers of intervention cost was the number of attempts at insertion of the randomised treatment and the rate of switching from the randomised to the alternative intervention. Both of these were higher in the IVH group. Hospitals with higher unit prices naturally experienced higher costs across both arms, but this did not necessarily impact the size of the cost differences between arms.

One of the strengths of this analysis is that the measurement of both the costs and activities is sourced directly from the treating hospitals and from a large sample of patients across a number of different hospitals. Actual treatment-related cost differences were relatively small, but were consistently in favour of

1 NGH across all sites and by age sub-group. A health service at the upper end of the range in this cost difference
2 with a large number of patients admitted with bronchiolitis needing fluid replacement could be driven toward
3 NGH.

4 This is the first analysis published of the costs of one of the key interventions in care of infants with
5 bronchiolitis, and reinforces the recommendations in new clinical guidelines that NGH is an acceptable
6 alternative to IVH, and may have some benefits in allaying hunger and associated agitation.⁶

9 LIMITATIONS

10 Whilst the number of attempts at inserting the intervention was captured for the assigned intervention, if a
11 patient switched intervention, the number of attempts at inserting the second or subsequent intervention was
12 not captured. This denotes that any costs associated with multiple attempts at inserting the switched
13 intervention were not captured or allocated to the randomised treatment. Length of treatment (fluid duration)
14 for the assigned treatment was not captured for 76/378 (20.1%) IVH patients compared to 30/381 (7.9%) of
15 NGH patients. As a greater proportion of patients randomised to the IVH group switched treatment, and a
16 larger proportion had multiple insertion attempts it is likely the cost difference between the two treatment
17 arms has been underestimated.

18 Costs of the intervention were not directly captured for each patient. They were estimated based on a
19 set protocol of delivering the interventions. The personnel time required to insert each intervention was
20 estimated based on the average time taken to successfully insert the intervention (based on data from 20
21 insertion attempts). This means the personnel costs assigned to patients who had the assigned intervention
22 inserted on first attempt were identical to those that required multiple attempts. This would have
23 underestimated the cost of IVH where more insertions attempts were undertaken.

24 The set protocol for NGH in the trial included the use of gastrolyte for the first two hours of hydration.
25 This is not standard practice at most institutions and likely represents an unnecessary intervention and cost.

26 These limitations represent an overall uncertainty around the estimated treatment-related cost
27 difference and suggest that it may be an underestimate. However the base cost and treatment activities
28 relating to IVH were higher than NGH and IVH was more costly across all sites.

30 CONCLUSION

1 Costs associated with the intervention make up a small proportion (<10%) of the overall costs of hospital
2 admissions with bronchiolitis, which is dominated by LoS. NGH appears to have a small cost saving, taking
3 fewer attempts, less switching to alternative treatment arm, and having a higher success rate of insertion. This
4 study provides a valuable insight into the costs and activities associated with the methods of fluid replacement
5 therapy used in infants with bronchiolitis, and given the large number of admissions may present significant
6 health system savings.

7

8

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Conflicts of Interest

The authors declare they have no conflicts of interest.

Author Contribution:

All authors contributed to the design and implementation of the study, or analysis and interpretation of the study results. EO, FB, MB, JA, JN, DK, MS, AD contributed to all stages of the study. SDa contributed to the implementation of the study. EO was the principal investigator. SDo, and KJ performed the statistical analysis. KJ controlled the database. RC and BM ensured appropriate data collection for and performed analysis of the economic evaluation. EO, FB, MB, SDa, DK, JA, BM, RC contributed to interpretation of the results. All authors contributed to the manuscript preparation and review, and approved the final version. The report was written by EO.

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4 **Table 1: Preliminary identification of cost categories**

Study arm	Cost categories
IVH	• Time taken to insert IV/ (mins) • Number and type of people assisting (e.g. nurse, doctor) • Disposables used (e.g. dressing packs, cannulas, tubing, Tegaderm™, Micropore™ tape etc.) • Other equipment or products used (e.g. fluid bag, IV line, Infusion pump, local anaesthetic cream etc.) • Additional tests (e.g. laboratory tests for electrolytes) • Any complications
NGH	• Time taken to insert NGT (mins) • Number and type of people assisting (e.g. nurse, doctor) • Disposables used (e.g. tubing, Tegaderm™, Micropore™ tape, pH strips, syringes etc.) • Other equipment or products used, (e.g. gastrolyte solution, formula, pump, anaesthetic spray) • Additional procedures or tests (e.g. chest X-ray to confirm NGT placement) • Any complications

5

6

1 Table 2: Pathway analysis – specification of activities involved in fluid replacement

Intravenous Hydration (IVH)
- Local anaesthetic cream applied to IV site and covered with Tegaderm™ patch for 30 minutes. - The skin then cleaned with chlorhexidine wash and cannula placed. 10cm extension tube attached to cannula and saline used to flush IV tubing. Cannula then taped and bandaged to a backboard. - The extension tubing is then attached to 1000mL fluid bag containing 0.45% saline with dextrose (2.5%, 4%, or 5%) via an IV line, burette and I-MED pump. Fluids given continuously at 80% of daily maintenance - Laboratory tests, measuring electrolytes, urea and creatinine levels are costed to individuals as performed in the study - Bandage is changed daily - Tubing is replaced every 3 days requiring new tubing and disposables.
Nasogastric Hydration (NGH)
- Local anaesthetic spray applied to nostril 2 minutes prior to NGT insertion. - Tubing, size 6 French <6 months of age and 8 French 6-12 months of age, is measured against child from nares to epigastrium to determine depth of insertion. Tubing then inserted to correct depth. - Tube placement confirmed by aspiration of stomach contents using 5mL syringe to draw sample of stomach contents which are applied to pH strip. If pH less than 4, tubing secured to face using Micropore™ tape and Tegaderm™. If pH greater than or equal to 4, aspiration is repeated after 30 minutes. If unable to confirm placement, abdominal/chest X-ray performed to confirm position of tube prior to use. If any doubt of placement, tubing removed and replaced, and procedure repeated. X-ray and replacement tubes costed to individuals as performed in the study. - Oral rehydration powder, prepared using single sachet added to 200mL boiled water; given continuously for 2 hours. - Infants then given normal feed of either formula or expressed breast milk (EBM), continuously or 2 hourly bolus with the total volume of fluid being 80% of daily maintenance. - Tubing replaced every 3 days requiring new tubing and disposables as above.

Table 3: Cost results presented as 'cost per child treated' for each arm and by age group

	N		Estimated cost of treatment*		Cost
	NGH	IVH	NGH	IVH	Difference
Total population	381	378	\$74.30	\$113.31	\$39.01
By Age					
<6 months	201	196	\$75.75	\$121.34	\$45.60
6-12 months	180	182	\$72.68	\$104.66	\$31.98

Notes

*Costs associated with a patient switching from one intervention to the other and all subsequent treatment costs were assigned to the original randomised treatment group to give the real cost of each treatment arm.

Prices are reported in 'real prices' for the reference year of the clinical trial (2009). All cost estimates are 'intention-to-treat'.

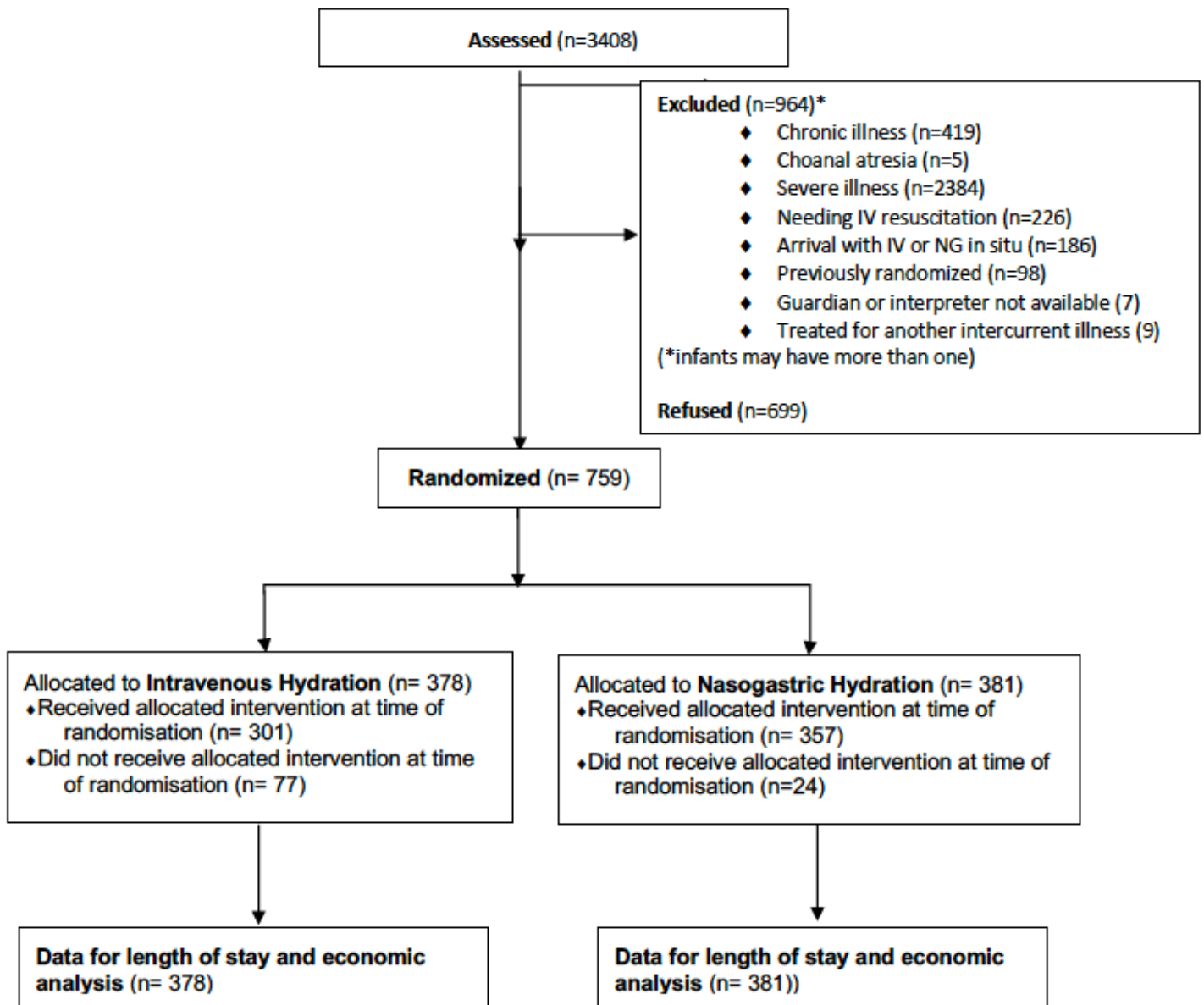
Table 4: Variation in 'cost per child treated' across the participating hospital sites

	N		Estimated cost of treatment		Cost difference
	NGH	IVH	NGH	IVH	
Total population	381	378	\$74.30	\$113.31	\$39.01
By site					
Hospital 1	109	107	\$76.11	\$116.16	\$40.05
Hospital 2	25	25	\$82.02	\$125.24	\$43.22
Hospital 3	36	37	\$59.53	\$119.43	\$59.90
Hospital 4	20	18	\$64.17	\$104.27	\$40.10
Hospital 5	103	102	\$76.28	\$107.78	\$31.51
Hospital 6	24	25	\$58.89	\$103.87	\$44.98
Hospital 7	64	64	\$48.31	\$115.39	\$67.08

Notes

All cost estimates are 'intention-to-treat'. Prices are reported in 'real prices' for the reference year of the clinical trial (2009) and converted to \$Australian for the New Zealand sites.

Figure 1: Eligibility and Randomisation



CHAPTER 3

Exploring Hydration Methods Used for Infants Under 2 Months of Age with Bronchiolitis

Problem

Hydration methods for infants with bronchiolitis have been explored in **Chapter 2** of this thesis, and found that nasogastric and intravenous hydration are both safe and efficacious, with some reasons for a preference for nasogastric hydration. However these studies excluded children under two months of age, an age group associated with more severe disease and possibly more complications.[6, 60-62] Further there are concerns that these young infants would be at higher risk from airway obstruction with nasogastric tube placement[20], and more at risk of aspiration if nasogastric feeding is used.[18]

The only available evidence for use of nasogastric versus intravenous hydration in this age group comes from a pilot study of 51 children under six months of age randomised to nasogastric or intravenous hydration, with a mean age of two months in each group, suggesting nasogastric hydration may be appropriate.[63] This pilot study is clearly not adequate to base clinical decision making upon, particularly for children under two months of age, and further evidence is needed.

Questions

Can nasogastric hydration be safely used in children under 2 months of age with bronchiolitis?

Answers

Can nasogastric hydration be safely used in children under 2 months of age with bronchiolitis?

Paper 3-1:

Ed Oakley, Sonny Bata, Sharmila Rengasamy, David Krieser, John Cheek, Kim Jachno, Franz E. Babl

Nasogastric Hydration in Infants with Bronchiolitis Less Than 2 Months of Age.

The Journal of Pediatrics. 2016;**178**, 241–245.e1

To add to the existing evidence aimed at answering this question, to do so relatively quickly and without the expense of a randomised trial, a retrospective review of three years of bronchiolitis admissions (2011 - 2013) at three hospitals in Victoria was undertaken. The aim of this study was to determine the adverse events profile of nasogastric hydration in infants with bronchiolitis less than 2 months of age, compared with intravenous hydration, and with published data on nasogastric hydration in infants two months of age and older presented in **Chapter 2 (Paper 2-2)**. Infants were eligible if they were under two months of age, were admitted with bronchiolitis, had nasogastric or intravenous hydration commenced in the emergency departments and did not require respiratory support with either invasive or non-invasive ventilation at the time of admission.

The primary outcome was the rate of adverse events – defined as desaturation, bradycardia, apnoea, and pulmonary aspiration. Secondary outcomes included length of hospital stay, duration of non-oral hydration, and intensive care unit admission. For those infants receiving nasogastric hydration, adverse event rates and profile were compared with the adverse events described in **Chapter 2; Paper 2-2**.

Over the three years of the study 491 infants less than two months of age were admitted to the three hospitals. Of these 232 required non-oral hydration, with 22 infants excluded due to receiving ventilatory support. Thus, the study population was 211 infants, with 146 (69%) receiving nasogastric and 65 (31%) receiving intravenous hydration. Infants receiving intravenous hydration were younger than those receiving nasogastric hydration (4.8 versus 5.4 weeks of age), were more likely to have oxygen saturations below 90% on presentation (15.6% versus 8.2%), and received more intravenous antibiotics (44.6% versus 14.5%).

The frequency of adverse events is shown in **Table 3-1**, with adverse events seen in 27.4% of those receiving nasogastric hydration compared with 23.1% receiving intravenous hydration, an absolute difference of 4.3% (95% CI -8.2 to 16.9; $P = 0.51$).

Infants receiving intravenous therapy were more likely to be admitted to the intensive care unit (38.5% versus 19.9%), more likely to receive any ventilation (27.7% versus 15.1%) and more likely to have treatment changed to the alternative than infants receiving initial nasogastric hydration (47.7% versus 12.3%) .

Adverse events in this study's nasogastric hydration group are compared with those published for infants 2 to 12 months of age receiving nasogastric hydration for bronchiolitis in **Table 3-2**. The younger infants had more intensive care unit admissions, a higher ventilation rate, and higher rate of apnoea and desaturation.

Table 3-1 Adverse events, ICU admission and duration of fluid therapy

Descriptions	Nasogastric hydration (n = 146)	Intravenous hydration (n = 65)	Difference (95% CI)	P value
Any adverse events*	40/146 (27.4%)	15/65 (23.1%)	4.3% (-8.2, 16.9)	.51
Apnea	8/146 (5.5%)	4/65 (6.2%)	-0.7% (-7.6, 6.2)	.85
Desaturation	32/146 (21.9%)	14/65 (21.5%)	0.4% (-11.7, 12.4)	.95
Aspiration	0/146 (0%)	0/65 (0%)		
Bradycardia	4/146 (2.7%)	1/65 (1.5%)	1.2% (-2.8, 5.2)	.60
Change of hydration method	18/146 (12.3%)	31/65 (47.7%)	-35.4% (-48.6, -22.1)	<.001
LOS, h	78.3	93.0	-14.7 (-27.9, 1.2)	.07
ICU admission	29/146 (19.9%)	25/65 (38.5%)	-18.6% (-32.1, -5.1)	.004
ICU LOS, h	88.2	73	15.2 (-15.1, 61.2)	.37
Any ventilation	22/146 (15.1%)	18/65 (27.7%)	-12.6 (-25, -0.3)	.03
Noninvasive ventilation	21/146 (14.4%)	18/65 (27.7%)	-13.3% (-25.6, -1)	.02
CPAP (noninvasive)	11/146 (7.5%)	12/65 (18.5%)	-10.9% (-21.3, -0.6)	.02
CPAP duration, h	44.6	30.6	14 (-12.2, 77.4)	.39
HFNP (noninvasive)	17/146 (11.6%)	13/65 (20%)	-8.4% (-19.4, 2.7)	.11
HFNP duration, h	23.1	23.7	-0.6 (-14.3, 33.1)	.95
Invasive ventilation	2/146 (1.4%)	1/65 (1.5%)	-0.1% (-3.7, 3.4)	.92
Fluid therapy duration, h	35.1	30.3	4.8 (-4.3, 16.9)	.33

CPAP, continuous positive airway pressure; HFNP, high flow nasal prong, LOS length of stay, ICU intensive care unit . Data are n/N assessed (%), or mean. *Patients may have more than 1 adverse event.

Table 3-2: Comparison of nasogastric hydration under 2 months old vs over 2-12 months old: ICU admission and adverse events. [30]

Descriptions	< 2 months old	2-12 months old	Difference (95% CI)	P value
Apnea	8/146 (5.5%)	1/381 (0.3%)	5.2%(1.5, 8.9)	<.001
Desaturation	32/146 (21.9%)	19/381 (5.0%)	16.9 (9.9, 24.0)	<.001
Aspiration	0/146 (0%)	0/381 (0%)		
Bradycardia	4/146 (2.7%)	6/381 (1.6%)	1.2% (-1.8, 4.1)	.38
LOS, h	86.7*	86.6	0.1 (-10.8, 11.0)	.99
ICU admission	29/146 (19.9%)	21/381 (8.5%)	14.4% (7.4, 21.2)	<.001
ICU LOS, h	121.3	58.6	62.7 (-10.5, 135.9)	.09
Any ventilation	22/146 (15.1%)	12/381 (3.2%)	11.9% (5.9, 18.0)	<.001
Noninvasive ventilation	21/146 (14.4%)	12/381 (3.2%)	11.2% (5.3, 17.2)	<.001
Invasive ventilation	2/146 (1.4%)	5/381 (1.3%)	0.1% (-2.2, 2.3)	.96

Data are n/N assessed (%), or mean (SD).

ICU intensive care unit , LOS Length of Stay

Limitations

This study was a retrospective review of the charts and as such is limited by accuracy of documentation. It is possible documentation of adverse events is incomplete , leading to underreporting, and it is possible that this favours one intervention more than the other. The study did not randomly or otherwise allocate treatment to the infants and therefore the information does not allow for an interpretation or understanding of decision making associated with the assignment of the treatments. The study reported on clinical incidents as a group and was not able to determine differences in rare clinical events that might be life threatening and cannot make a conclusion about safety.

Implications

This retrospective study adds supportive data to the existing evidence that nasogastric hydration can be used safely in younger infants with bronchiolitis.[63] However as a retrospective study the reasons for the differences in the rates of ventilation, intensive care unit admission and change of therapy between the nasogastric and intravenous hydration groups are not able to be determined. It is possible sicker infants were treated with intravenous therapy. It is also possible that change from nasogastric to intravenous therapy was due to a deterioration due to the presence of a nasogastric tube, confirming the previously documented fears regarding its use. [18, 20] Adverse events while more common in this population than in previous reports in infants older than two months of age,[30] were not different between groups. This does not support concerns previously raised concerning the use of nasogastric tubes in very young children with bronchiolitis. [18, 20]

The greater frequency of change from intravenous to nasogastric therapy may not represent a problem with the therapy but an improvement in the infant's condition and a desire to feed the infant before oral intake is adequate. This lack of standardisation of the infants receiving treatments and the inability to attribute cause due to lack of documentation about reasons for change in treatment are a limitation of retrospective studies and restrict the ability to confirm the safety of either treatment strategy.

What can be said is that in this young population with the potential for more severe disease and adverse events, nasogastric hydration is frequently used and that both total adverse events and length of hospital stay do not appear to be different whether nasogastric or intravenous routes are used as the initial non-oral hydration option.

PDFs of Papers Chapter 3

Paper 3-1

Ed Oakley, Sonny Bata, Sharmila Rengasamy, David Krieser, John Cheek, Kim Jachno, Franz E. Babl

Nasogastric Hydration in Infants with Bronchiolitis Less Than 2 Months of Age.

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None of the authors have declared a conflict of interest.

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Abbreviations:

NGH – nasogastric hydration

IVH – intravenous hydration

ICU – intensive care unit

PICU – pediatric intensive care unit

NICU – neonatal intensive care unit

RCT – randomized controlled trial

PREDICT - Paediatric Research in Emergency Departments International
Collaborative

ED – emergency department

LOS – length of stay

PCR – polymerase chain reaction

RSV – respiratory syncytial virus

CPAP – continuous positive airway pressure

HFNP – high flow nasal prong

ABSTRACT

Objectives: To determine whether nasogastric hydration (NGH) can be used in infants less than 2 months of age with bronchiolitis, and characterize the adverse events profile of these infants compared with infants given intravenous hydration (IVH).

Study Design: A retrospective cohort study of children with bronchiolitis under 2 months of age admitted for hydration at 3 centers over three bronchiolitis seasons was done. We determined type of hydration (NGH vs IVH) and adverse events, intensive-care unit (ICU) admission, and respiratory support.

Results: Of 491 infants under admitted with bronchiolitis, 211 (43%) received non-oral hydration: 146 (69%) via NGH, 65 (31%) via IVH. Adverse events occurred in 27.4% (NGH) and 23.1% (IVH), difference of 4.3%; 95%CI (-8.2 to 16.9), $p=0.51$. The majority of adverse events were desaturations (21.9% NGH vs 21.5% IVH, difference 0.4%; (-11.7 to 12.4), $p=0.95$). There were no pulmonary aspirations in either group. Apneas and bradycardias were similar in each group. IVH use was positively associated with ICU admission (38.5% IVH vs 19.9% NGH; difference 18.6%, (5.1 to 32.1), $p=0.004$); and need for ventilation support (27.7% IVH vs 15.1% NGH; difference 12.6 (0.3 to 23), $p=0.03$). Fewer infants changed from NGH to IVH than from IVH to NGH (12.3% vs 47.7%; difference -35.4% (-49 to -22), $p<0.001$).

Conclusions: NGH can be used in the majority of young infants admitted with bronchiolitis. NGH and IVH had similar rates of complications.

Contributors' Statements:

Ed Oakley: Dr. Oakley conceptualized and designed the study, critically reviewed and revised the manuscript, and approved the final manuscript as submitted.

Sonny Bata: Dr. Bata designed the data collection instruments, drafted the initial manuscript and revised the manuscript, coordinated data collection in 3 centers, and approved the final manuscript as submitted.

Sharmila Rengasamy: Dr. Rengasamy designed the data collection instruments, and coordinated data collection in 3 centers, reviewed the manuscript, and approved the final manuscript as submitted.

David Krieser: Dr Krieser coordinated and supervised data collection at one of the three sites, critically reviewed the manuscript, and approved the final manuscript as submitted.

John Cheek: Dr Cheek coordinated and supervised data collection at one of the three sites, critically reviewed the manuscript, and approved the final manuscript as submitted.

Kim Jachno: Ms. Jachno carried out the statistical analyses including designing study methods, reviewed and revised the manuscript, and approved the final manuscript as submitted.

Franz Babl: Dr. Babl conceptualized and designed the study, critically reviewed the manuscript and revised the manuscript, and approved the final manuscript as submitted.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

INTRODUCTION

Bronchiolitis is a leading cause of hospital admission of young infants in developed countries. In the United States, approximately 100,000 infants under 12 months old are admitted to hospitals due to bronchiolitis incurring an estimated cost of \$1.73 billion.^{1,2}

There is a very limited role for pharmacologic treatment in bronchiolitis;^{1,3} hence, management of these infants is mainly focused on respiratory support and fluid replacement therapy. Fluid replacement therapy is required in around 30% of children admitted with bronchiolitis.⁴ A recent multicenter randomized controlled trial (RCT) in infants with bronchiolitis aged 2 months to 12 months conducted by Oakley et al⁵ has shown that intravenous hydration (IVH) and nasogastric hydration (NGH) are equally efficacious and safe methods to hydrate infants with bronchiolitis. NGH was associated with a higher success rate of insertion, and in most centers in Australia and New Zealand, NGH is now standard of care in bronchiolitis. A pilot study by Kugelman et al⁶ has also shown that NGH was feasible and had comparable outcome with IVH in under 6 month old infants with moderate bronchiolitis. There were no aspiration events or worsening of respiratory status.

Patients younger than 8 weeks old were excluded from the study by Oakley et al⁵ due to concerns about a more severe course of the disease and a higher rate of adverse events. Risk factors for more severe disease are age less 1 month, or postconceptional age of <48 weeks for preterm infants.^{1,3,7-9} Concerns that nasogastric (NG) tube placement in young infants might impinge on their airway,¹⁰ as they are obligate nasal breathers; and that there is an increased risk of aspiration¹¹ in infants with RSV bronchiolitis have been raised. While concerns regarding an increased risk of desaturation, aspiration, apnea, and ICU admissions with NGH have been put to rest in older infants with bronchiolitis, it is unclear if NGH is safe in infants less than 2 months of age. Yet, NGH is now frequently used in infants less than 2 months of age.

The aim of this study was to assess if NGH can be used in infants with bronchiolitis less than 2 months of age. This was done by determining the adverse events profile of these infants treated with NGH and IVH, and comparing this with published data on NGH in infants 2 months of age and older.⁵

METHODOLOGY

Study design and patients

This was a retrospective cohort study of infants younger than 2 months of age with bronchiolitis at three pediatric centers in the state of Victoria, Australia. The 3 hospitals, Royal Children's Hospital, Monash Medical Center, and Sunshine Hospital, are part of the Paediatric Research in Emergency Departments International Collaborative (PREDICT)¹² and were study sites of the original RCT comparing NGH and IVH in older infants.^{5,13} The study included patients admitted during three

bronchiolitis seasons in the Southern Hemisphere (April 1st to October 31st 2011 to 2013).

Eligible patients included infants younger than 2 months old who presented to the Emergency Department (ED) with bronchiolitis, and received hydration via NG or intravenous (IV) route. Infants who at admission only received oral hydration, or who required invasive or non-invasive ventilation on initial presentation were excluded.

The study was approved by the human research ethics committees at the three participating sites.

Study procedure

The electronic databases were searched for all infants under 2 months old admitted to hospital from the ED. Search terms include “bronchiolitis” or “lower respiratory tract infection.” The medical records were then reviewed and patients with a discharge diagnosis assigned by the admitting medical team of bronchiolitis were included. The three study hospitals used the same statewide clinical practice guidelines on bronchiolitis.¹² Baseline demographic data including age, sex, age of gestation and weight were collected. Infants who needed non-oral hydration either received NGH or IVH as outlined in the statewide clinical practice guideline.¹⁴ Initial clinical observations of oxygen saturation (SpO₂) in room air, supplemental oxygen requirement, respiratory rate, increased respiratory effort (defined as presence of retractions, nasal flaring or accessory muscle use), heart rate, temperature, and systolic blood pressure were extracted. Clinical parameters such as prematurity (defined as <37 weeks of gestation), previous medical history (including bronchiolitis

or wheezing, chronic respiratory, neurologic or congenital cardiac conditions), and medications received in hospital were recorded. Other data extracted included admission to the intensive care unit (ICU), level of respiratory support, and initial route, volume, and type of fluid administered. Patients requiring intensive care were either admitted to a pediatric intensive care unit (PICU) or a neonatal intensive care unit (NICU). Adverse events recorded were episodes of apnea (no respiratory effort for greater than 20 seconds, or shorter periods of time if accompanied by cyanosis or bradycardia); bradycardia (heart rate <100 beats per minute); oxygen desaturation (defined as episodes where the SpO₂ was recorded at <90%); and pulmonary aspiration. Any change in the hydration method was documented, as well as reasons for this.

The extracted demographic and clinical data were entered into a standardized, piloted data collection form used at all three sites modelled on the study documents used in the RCT in older infants.^{5,13} Three medically trained abstractors assisted in collecting data. These abstractors were trained in extracting data from electronic charts, and on the definitions of the data points for the study. The abstractors were not blinded to the study hypothesis¹⁵.

The primary outcome of the study was the rate of adverse events (desaturation, bradycardia, apnea, and pulmonary aspiration). Secondary outcome measures were hospital length of stay (LOS), duration of non-oral hydration, ICU admission and duration of ICU admission. Key outcomes of infants under 2 months hydrated via NGH were compared with previously published RCT data on infants 2 months to 12

months of age from the same study sites in the state of Victoria, Australia.⁵ LOS was capped at 14 days to be comparable to the data from this study.

Statistical analysis

Results for the three sites were pooled. Data were presented descriptively using mean and standard deviations or as counts and proportions. Student's t-test was used to compare all continuous variables. Continuous outcome variables were assessed for possible violations of the normality assumption, and those that were skewed were log transformed for analysis. Logarithmic means and standard deviations were back transformed to allow presentation in the clinically meaningful measurement of hours. Differences in proportions and chi square analysis were used to assess differences in categorical outcome variables. A p value of less than 0.05 was taken to be significant.

RESULTS

A total of 491 infants under 2 months old with bronchiolitis were admitted to the participating hospitals. Two hundred and fifty-eight patients were excluded, as they only required oral hydration. Twenty-two infants were excluded for requiring invasive or non-invasive ventilation in the ED. Of the remaining 211 infants requiring non-oral hydration on admission, 146 (69%) were hydrated via an NG tube, and 65 (31%) received IV fluids. (Figure 1)

Table 1 shows baseline demographic and clinical characteristics. Infants in the IVH group were younger than the NGH group (4.8 weeks vs 5.4 weeks). Gender, weight,

vital signs on admission, and past medical history were similar in NGH and IVH groups. More infants were treated with antibiotics (44.6% vs 14.5%) in the IVH group compared to the NGH group. More infants who subsequently received IVH had documented oxygen desaturations below 90% (15.6% vs 8.2%) when first assessed in the ED. There was no significant difference in the respiratory syncytial virus (RSV) swab results between the 2 groups.

Adverse events are shown in Table 2. The frequency of any adverse event was 27.4% in the NGH group compared with 23.1% (IVH), absolute difference of 4.3% (95%CI - 8.2 to 16.9; $p=0.51$). The majority of adverse events were desaturations, recorded in 21.9% in the NGH group and 21.5% with IVH, an absolute difference of 0.4% (95% CI -11.7 to 12.4; $p=0.95$). No pulmonary aspirations were seen in either group. Apnea and bradycardia occurred infrequently and in similar proportions in each group.

Table 2 shows that more infants in the IVH group were admitted to ICU (38.5% IVH vs 19.9% NGH) difference 18.6% 95%CI 5.1-32.1; $p=0.004$, with mean ICU LOS similar between groups (88.2h NGH vs 73h IVH, difference 15.2 (95%CI -15.1,61.2), $p=0.37$). More patients in the IVH group received any form of ventilation (27.7% IVH vs 15.1% NGH; difference 12.6%; 95% CI 0.3 to 25; $p=0.03$). IVH infants received more non-invasive ventilation while invasive ventilation requirements did not differ between groups. Hospital LOS and duration of non-oral fluid therapy were comparable between groups.

Thirty-one out of 65 (47.7%) of the patients initially receiving IVH were later changed to NGH. This was 4 times the rate of change in hydration method of those

initially receiving NGH (18/146: 12.3%; difference 35.4% (95%CI (22.7 to 49.4), $p<0.001$). Reasons for changing IVH to NGH were often unrecorded (16), but included clinical improvement (9), IV extravasation (3), and other reasons (3). Infants in the NGH group who later required IVH were due to increased work of breathing (6), frequent vomiting (1), requiring fluid bolus (3), needing ventilatory support (7), or not recorded (1).

Table 3 lists the features of infants who developed bradycardia or required inotropic support. Five out of 6 of these children were initially hydrated through NG means. Most of them were ex-premature neonates, or had other medical conditions.

Table 4 (online) compares adverse events of nasogastric hydration therapy in young infants (under 2 months old) and older infants (2 to 12 months old) with bronchiolitis based on previously published RCT data.⁵ The younger infants with bronchiolitis resulted in more apnea (5.5% vs 0.3%, $p<0.001$) and desaturation (21.9% vs 5%, $p<0.001$). No cases of pulmonary aspiration were seen in either group, and there was no difference in the need for invasive ventilation.

DISCUSSION

The updated AAP guidelines on bronchiolitis state that if infants older than 1 month old are unable to take fluids orally, alternative routes of fluid administration are NGH or IVH¹ with NG feeding also allowing more physiologic nutrition, including provision of expressed breast milk or formula.⁶ Our data show that NGH can be used in infants younger than 2 months old and appears to be safe. This confirms now

widespread Australian and New Zealand use of NGH in younger infants since the publication of the RCT comparing NGH and IVH in older infants with bronchiolitis.⁵ This RCT showed no evidence of worsening illness, increased need for intensive care unit admission, increased duration of oxygen treatment, or risk of aspiration or deterioration with the use of NGH. The RCT had excluded infants under 8 weeks of age due to concerns about adverse events associated with NGH such as an increased risk of aspiration and desaturation due to nasal occlusion.¹⁰ Results from this retrospective study of infants under 2 months of age, we have demonstrated a low incidence of serious adverse events (e.g. apnea, desaturations, and bradycardia) in either IVH or NGH groups, with no significant difference between the 2 groups. There were no pulmonary aspirations recorded.

In the RCT comparing NGH and IVH for hydration in older children with bronchiolitis, NGH resulted in fewer attempts at insertion, and a lower rate of switching to the opposite treatment compared to IVH.⁵ In this current retrospective study, the number of attempts for NGT or IV cannulae insertion was not adequately recorded to be reportable. Although a portion of infants who were hydrated through the NG route required change to IVH, mostly for clinical deterioration, four times as many infants were changed from IVH to NGH.

The IVH group received more IV antibiotics, were admitted to ICU at a higher rate,³ and received more non-invasive ventilation, possibly indicating they were a sicker cohort.

When comparing NGH in infants younger than 2 months old with the 2 to 12 months old group, the younger infants had more ICU admissions, a higher ventilation rate, and higher rate of apnea and desaturation. This is consistent with the literature indicating a higher risk of more severe disease in infants with bronchiolitis younger than 12 weeks of age.^{1,3,7,9}

This study has several limitations. Most obviously this study did not assign patients to the two treatment groups. While the data suggest that the clinicians chose NGH for the less sick patients under 2 months requiring hydration, our data do not allow us to understand the decision making process used or whether sicker patients could also have been managed with NGH. Although we followed recommendations for high quality retrospective medical chart review studies¹⁵ not all suggested steps to mitigate bias were implemented in this study; our data extractors were trained in medical record review but were not blinded to the interventions, and thus bias in coding cannot be completely excluded. Kappa statistic for inter-rater reliability was not calculated for this study and double data entry was not undertaken so consistency of data extraction is not proven. The retrospective nature of the study could have impacted on the recording of adverse events, likely leading to underreporting, however it is unlikely this would impact patients in one group more than the other. Another limitation was poorly documented data; the number of attempts for NG and IV cannula insertion and the occurrence of local complications were not adequately documented, thus, we are unable to report this. Retrospectively collected data could also impact on the comparison with the prospectively collected data from the RCT for older infants.⁵ Our study was not powered to detect rare clinically significant events that might be associated with either intervention.

NGH can be used in a majority of young infants admitted with bronchiolitis. It had comparable clinical outcome with those given IVH and had similar rates of complications.

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Figure 1. Study profile

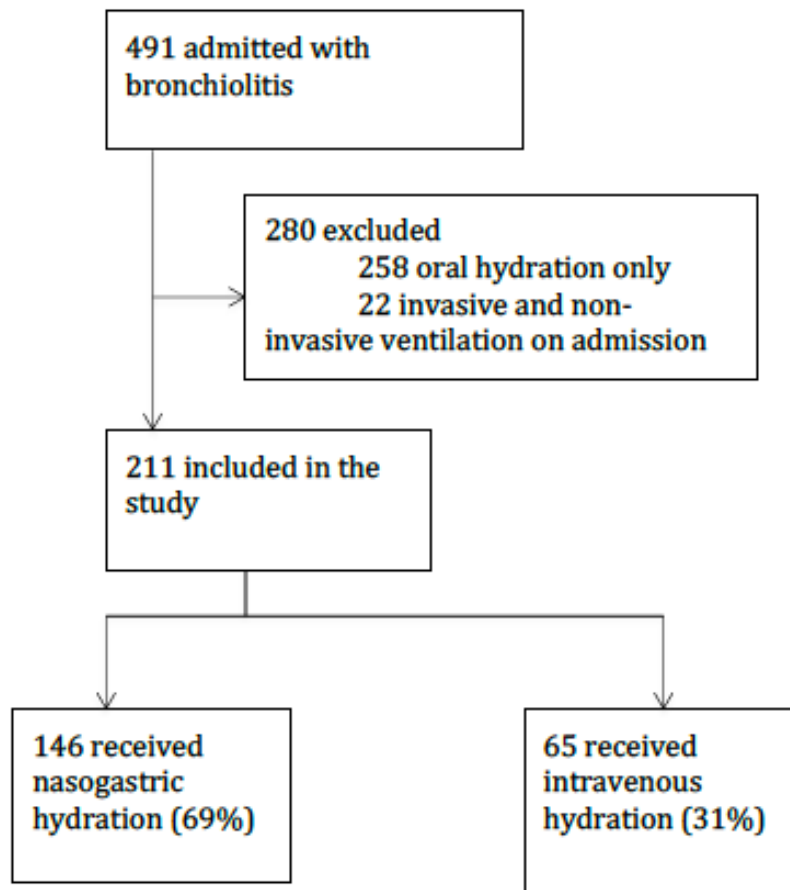


Table 1. Demographics and Baseline Clinical Characteristics

	Nasogastric Hydration (n=146)	Intravenous Hydration (n=65)	p-values
Age, weeks	5.4 (1.9)	4.8 (1.9)	0.025
Gender, male	83 (57%)	36 (55%)	0.84
Weight (grams)	4344.7 (789.0)	4266.6 (914.9)	0.53
Vital signs on Presentation: Heart rate (beats per minute)	165.4 (17.6)	164.8 (20.9)	0.85
Respiratory rate (breaths per minute)	54.1 (13.8)	54.1 (15.0)	1.00
Oxygen saturations <=90% *	12 (8.2%)	10 (15.6%)	0.047
Increased respiratory effort	126 (88.1%)	61 (93.8%)	0.2
Previous medical history	6 (4.1%)	2 (3.1%)	0.72
History of previous bronchiolitis	4 (2.7%)	2 (3.1%)	0.89
Premature (<37weeks)	15 (10.3%)	8 (12.3%)	0.66
Medications given in			0.49

Inhaled medications			
Oral or IV steroids	6 (4.1%)	1 (1.5%)	0.33
IV antibiotics	21 (14.5%)	29 (44.6%)	<0.001
Caffeine	4 (2.8%)	4 (6.2%)	0.23
Inotropes	2 (1.4%)	0 (0%)	0.34
NPA/Nasal swab performed	87/145 (60%)	46/64 (71.9%)	0.10
Respiratory syncytial virus positive	67/87 (77%)	40/46 (87.0%)	0.17

Data are n (%), n/N assessed (%), or mean (SD)

*Oxygen saturation in room air on arrival in the ED

IV intravenous

NPA nasopharyngeal aspirate

Table 2. Length of Stay, ICU admission, and adverse events.

Description	Nasogastric hydration (n=146)	Intravenous hydration (n=65)	Difference (95% CI)	P value
Any adverse events*	40/146 (27.4%)	15/65 (23.1%)	4.3% (-8.2, 16.9)	0.51
Apnea	8/146 (5.5%)	4/65 (6.2%)	-0.7% (-7.6, 6.2)	0.85
Desaturation	32/146 (21.9%)	14/65 (21.5%)	0.4% (-11.7, 12.4)	0.95
Aspiration	0/146 (0%)	0/65 (0%)		
Bradycardia	4/146 (2.7%)	1/65 (1.5%)	1.2% (-2.8, 5.2)	0.60
Change of hydration method (NG to IV; IV to NG)	18/146 (12.3%)	31/65 (47.7%)	-35.4% (-48.6, -22.1)	<0.001
LOS, hours	78.3	93.0	-14.7 (-27.9, 1.2)	0.07
ICU admission	29/146 (19.9%)	25/65 (38.5%)	-18.6% (-32.1, -5.1)	0.004
ICU LOS, hours	88.2	73	15.2 (-15.1, 61.2)	0.37
Any ventilation	22/146 (15.1%)	18/65 (27.7%)	-12.6 (-25, -0.3)	0.03
Non-invasive ventilation	21/146 (14.4%)	18/65 (27.7%)	-13.3% (-25.6, -1)	0.02

CPAP (Non-invasive)	11/146 (7.5%)	12/65 (18.5%)	-10.9% (-21.3, -0.6)	0.02
CPAP duration, hours	44.6	30.6	14 (-12.2, 77.4)	0.39
HFNP (Non-invasive)	17/146 (11.6%)	13/65 (20%)	-8.4% (-19.4, 2.7)	0.11
HFNP duration, hours	23.1	23.7	-0.6 (-14.3, 33.1)	0.95
Invasive ventilation	2/146 (1.4%)	1/65 (1.5%)	-0.1% (-3.7, 3.4)	0.92
Fluid therapy duration, hours	35.1	30.3	4.8 (-4.3, 16.9)	0.33

Data are n/N assessed (%), or mean

* Patients may have more than one adverse event.

NG nasogastric

IV intravenous

ICU intensive care unit

LOS length of stay

CPAP continuous positive airway pressure

HFNP high flow nasal prong

Table 3. Infants with bradycardia or needed inotropic support

	Age	LOS	Study group	Comments
Patient 1	1 month	8 days	NGH	Respiratory syncytial virus positive, bradycardic episodes, NICU for 8 days (CPAP 2 days)
Patient 2	10 days	11 days	NGH	Respiratory syncytial virus positive, disease progression; Hypotension requiring noradrenaline, PICU for 6 days (HFNP)
Patient 3	20 days	8 days	NGH	Respiratory syncytial virus positive, disease progression, previously premature twin, Caffeine load for brief apneas, NICU for 8 days (HFNP 2 days)
Patient 4	30 days	4 days	IVH	Respiratory syncytial virus positive, previously premature, apneic episodes, NICU for 4 days
Patient 5	18 days	35 days	NGH	Respiratory syncytial virus positive, CHARGE syndrome, required milrinone, heart failure, NICU for 17 days (CPAP 9 days)
Patient 6	51 days	4 days	NGH	Brief bradycardia

NGH nasogastric hydration

CPAP continuous positive airway pressure

HFNP high flow nasal prong

IVH intravenous hydration

CHAPTER 4

Bronchiolitis management in Australian and New Zealand Intensive Care Units

Problem

About 10% of bronchiolitis admissions require an intensive care unit admission, with bronchiolitis being one of the most common reasons for non-elective admission to the intensive care unit.[64, 65] The mainstay of treatment is supportive care including ensuring adequate oxygenation.[2, 4, 66, 67] Frequent use of high flow nasal cannulae and non-invasive ventilation strategies has been demonstrated in children under two months of age and presented in **Chapter 3, Paper 3-1**. Recent data had showed a high rate of ventilation support in intensive care admissions for bronchiolitis (>70%) with an increasing number receiving non-invasive ventilation.[6, 13] Non-invasive ventilation has been shown to be an effective strategy to prevent clinical deterioration, avoid the need for invasive ventilation, and shorten the length of intensive care unit stay, and has become the preferred initial ventilation strategy for bronchiolitis.[10, 52, 68-71]

There is emerging evidence that high flow nasal cannula therapy can not only reduce the need for invasive ventilation but shorten intensive care unit and hospital length of stay with no increase in complications.[14, 72-75] We proposed a study to assess intensive care unit admission rates for bronchiolitis and ventilation strategies used in these infants in seven Australian and New Zealand hospitals.

Question

What are the ventilation and oxygenation strategies used in Australian and New Zealand intensive care units for infants with bronchiolitis?

Answers

What are the ventilation and oxygenation strategies used in Australian and New Zealand intensive care units for infants with bronchiolitis?

Paper 4-1:

Oakley E; Chong V; Borland M; Neutze J; Phillips N; Krieser D; Dalziel S; Davidson A; Donath S; Jachno K; South M; Fry A; Babl FE.

Intensive care unit admissions and ventilation support in infants with bronchiolitis.

Emergency Medicine Australasia. 2017;**29**(4), 421-428

This multicentre study used two existing databases, and retrospective medical record review to obtain information on intensive care admissions and ventilation strategies used in children admitted to hospital with bronchiolitis. The objective of the study was to describe the number of infants between 2 months and 12 months of age with bronchiolitis receiving intensive care, the type of ventilation support used, and to determine factors associated with infants with bronchiolitis requiring intensive care unit admission.

The study used the database from the randomised controlled trial described in **Chapter 2; Paper 2-2** including all 3899 children presenting to the seven emergency departments involved in the study with bronchiolitis between April and November in the years 2011-2013 inclusive. These infants' medical records were all reviewed to obtain demographic information, co-morbidities, medications used, investigations performed (and results) and whether they were admitted to an intensive care unit. The intensive care unit databases at the seven hospitals were then queried to find all children admitted to intensive care during the same time periods. Information including length of intensive care unit stay, ventilation methods used and duration of ventilation was obtained. Patients transferred from non-study hospitals were excluded and the databases were combined.

Data were collected from 3589 infants, including 204 (5.7%) admitted to an intensive care unit, with 162 (79.4%) of these infants receiving some form of ventilatory support. As depicted in **Figure 4-1** most infants received non-invasive ventilation only, with 29 receiving invasive ventilation (17.9% [95% CI 12.3–24.7%] of those receiving any ventilation and 14.2% [95% CI 9.7–19.8%] of those admitted to intensive care). The proportion of infants admitted to the intensive care unit over the study period remained stable (ranging from 5.1% in 2009 to 6.7% in 2011 [$P = 0.21$]), as did the proportion of infants admitted to the intensive care unit requiring ventilatory support (**Table 4-1**). Ventilatory assistance over the three years demonstrated a stable invasive ventilation and total non-invasive ventilation rate, but a changing use of high flow nasal cannula, increasing

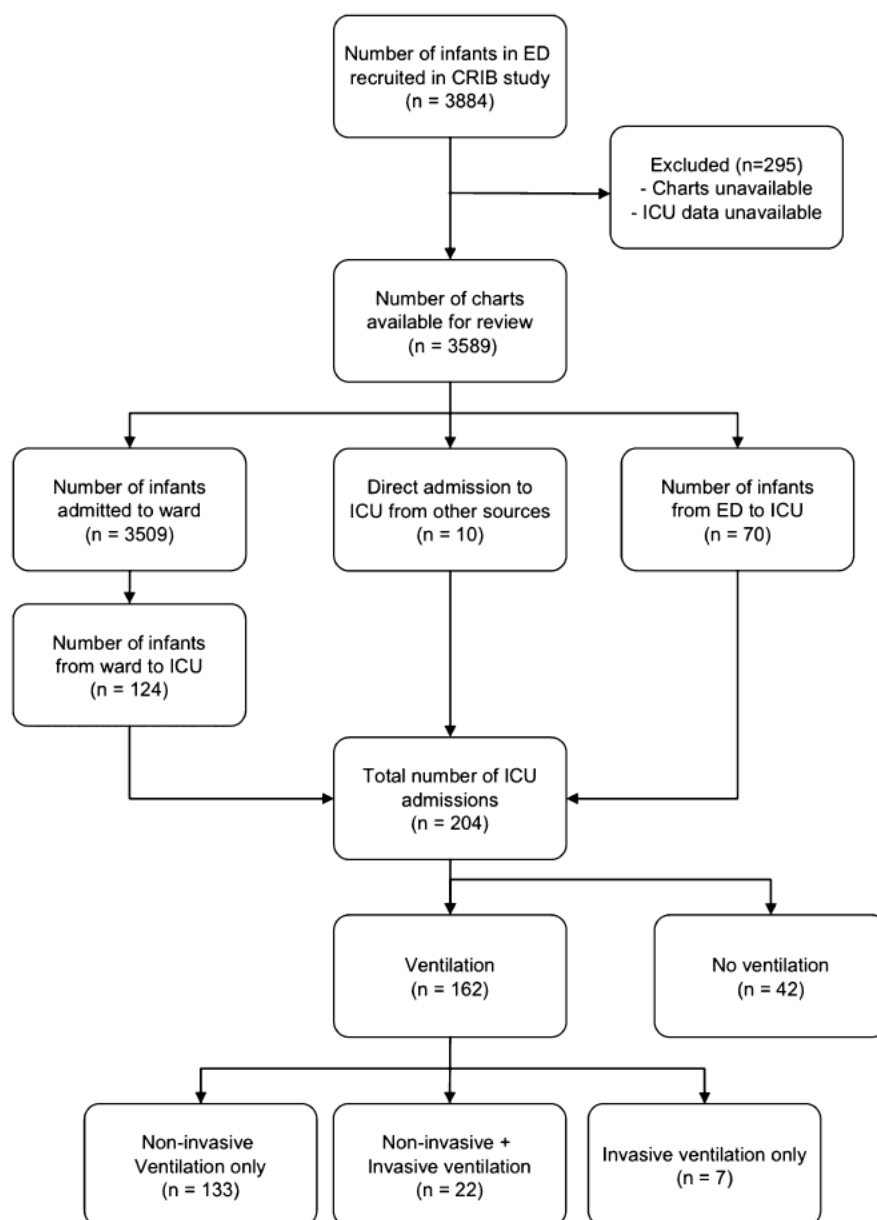
from 13/53 (24.5%) episodes in 39 infants ventilated in 2009 to 39/91 (42.9%) episodes in 64 infants in 2011 an absolute increase of 18.3% (95% CI 2.9–33.7%) (**Figure 4-2**).

Compared with infants not admitted to intensive care units those admitted to an intensive care unit were younger, had more co-morbidities, and a longer length of hospital stay (**Table 4-2**).

Limitations

As a retrospective study the limitations of documentation of management undertaken exists. There were a small number of medical records that were unavailable for review. The reviewers of the medical records were not blinded to the hypotheses leading to possible bias. As this study used infants identified through a previous randomised controlled study that only recruited infants in the bronchiolitis seasons of the years involved (April to October inclusive) it does not include all infants admitted in with bronchiolitis. No standard measurement of disease severity was used, with the need for intensive care unit admission or ventilation was decided by the clinician managing the infant. Infants under 8 weeks of age were excluded from the study making interpretation of the findings in this age group impossible. The study captured ventilation events per patient, but not the sequence in which they occurred, so no discussion about escalation from one ventilation strategy to another is possible.

Figure 4-1: Flow chart of study process and mode of ventilation of infants admitted to the intensive care unit with bronchiolitis.



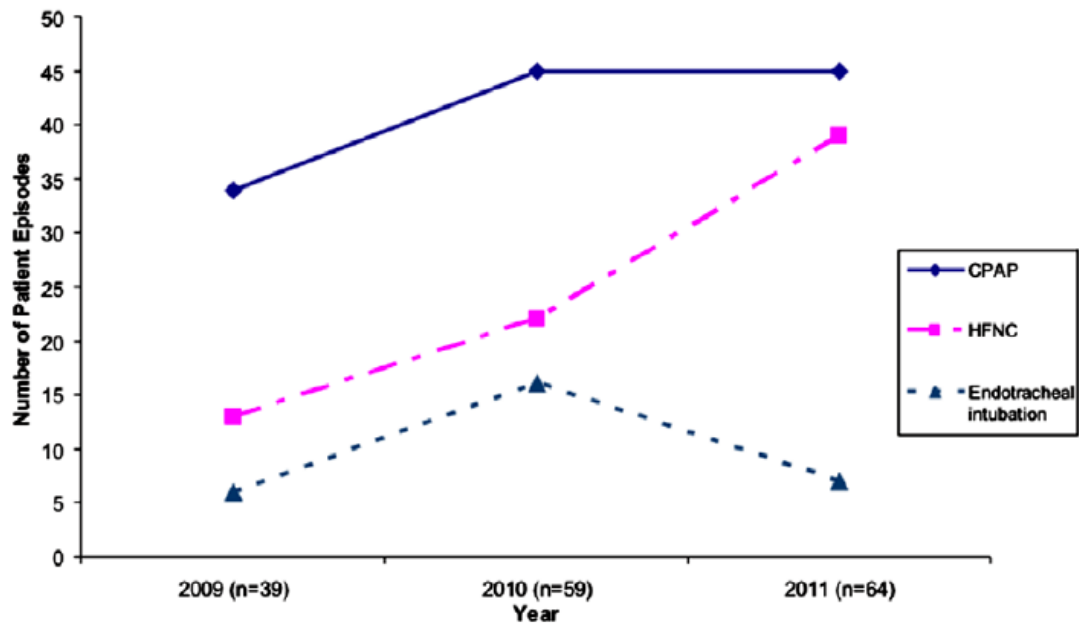
CRIB, comparative rehydration in bronchiolitis; ED, emergency department; ICU, intensive care unit

Table 4-1 Frequency of ventilation support of ICU infants with bronchiolitis by year (cumulative of all centres) from 2009 to 2011

Year	Infants with bronchiolitis		Infants with bronchiolitis admitted to ICU		Infants with bronchiolitis admitted to ICU requiring ventilation support		Infants admitted with bronchiolitis requiring ventilation support
	n	%	n	%	n	%	%
2009	1005	28.0	51	5.1	39	76.5	3.9
2010	1412	39.3	75	5.3	59	78.7	4.2
2011	1172	32.7	78	6.7	64	82.1	5.4
Total	3589	100	204	5.7	162	79.4	4.5

ICU intensive care unit

Figure 4-2 Graph of type of ventilation support by years (cumulative of all centres) from 2009 to 2011.



CPAP, continuous positive airway pressure; HFNC, high flow nasal cannula; ICU, intensive care unit; n = number of patients

Table 4-2: Demographics comparing non-ICU and ICU infants with bronchiolitis

	Non ICU infants	ICU infants	Total	Difference (95% CI)	OR 95% CI	P-value
Age (days) Mean (SD)	195.6 (84.5)	176.9 (85.7)	194.6 (84.7)	18.8 (6.8-30.7)	-	0.002
Age 2–6 months	1565	114	1679	—	1.5 (1.1–2.0)	0.007
Age ≥6 months	1820	90	1910	—		
LOS in hospital (h) mean (SD)	70.5 (95.2)	208 (172.3)	78.3 (106.1)	137.6 (113.6–161.6)	—	<0.001
LOS in ICU (h) median (IQR)	—	—	50.6 (28.3–78.3)	—	—	—
Male %	2103/3385 (62.1%)	116/204 (56.9%)	2219/3589 (61.8%)	—	1.2 (0.9–1.7)	0.13
Prematurity	492/3302 (14.9%)	41/199 (20.6%)	533/3501 (15.2%)	—	1.5 (1.0–2.1)	0.03
Chronic lung disease	238/3356 (7.1%)	22/199 (11.1%)	260/3555 (7.3%)	—	1.6 (1.0–2.6)	0.04
Neurological disorder	95/3356 (2.8%)	12/198 (6.1%)	107/3554 (3.0%)	—	2.2 (1.2–4.1)	0.01
Congenital heart disease	224/3357 (6.7%)	28/199 (14.1%)	252/3556 (7.1%)	—	2.3 (1.5–3.5)	<0.001
Previous bronchiolitis	1206/3357 (35.9%)	86/197 (43.7%)	1292/3554 (36.4%)	—	1.4 (1.0–1.9)	0.03
RSV+†	998/2140 (46.6%)	91/189 (48.1%)	1089/2329 (46.8%)	—	1.1 (0.8–1.4)	0.69

†Only 2329 of 3385 had viral studies done. CI, confidence interval; ICU, intensive care unit; IQR, interquartile range; OR, odds ratio; RSV, respiratory syncytial virus; SD, standard deviation; LOS, length of stay

Implications

Over the three years studied intensive care unit admission rate remained stable as did invasive and non-invasive ventilation rates. The invasive ventilation rate in this study (17.9% of infants requiring ventilatory support) is lower than that reported in a NSW cohort from 2000-2009 where 28.6% of ventilation episodes were invasive.[76] This decrease is in keeping with other recent data suggesting an increase in non-invasive ventilation and a decrease in invasive ventilation for infants with bronchiolitis.[69-73, 76] However over the three years of the study rather than demonstrating an decrease in invasive ventilation, we demonstrated an 18.3% increase in the use of high flow nasal cannula use for respiratory support with static invasive ventilation rates. Continuous positive airway pressure remained the most frequently used ventilation support accounting for 54.6% of all ventilation episodes. This study did not support other emerging evidence that high flow nasal cannula use can prevent invasive ventilation needs. [69-73, 76] Further recent evidence has suggested high flow nasal cannula therapy can reduce intensive care length of stay. These studies found a reduction from six days to four days in intensive care unit stay. In this seven site study our median length of intensive care unit stay was 50 hours with 75% of infants staying just over three days (78 hours), so Australasian management of bronchiolitis in intensive care units differs from that reported overseas.[73-75]

Risks for intensive care admission in infants with bronchiolitis have been reported previously. The data from this study supports these previous reports that indicate co-morbidities, prematurity and younger age are risk factors for increasing intervention and need for intensive care unit admission.[77, 78]

Making formal recommendations from this Australasian study is difficult. It was a retrospective review and attributing cause to any factors is not possible. The associations found support the suggestion in existing literature that high flow nasal cannula use is increasing and appears safe, but does not allow recommendations on its continued use or its role in managing bronchiolitis.

PDFs of Papers Chapter 4

Paper 4-1

Oakley E; Chong V; Borland M; Neutze J; Phillips N; Krieser D; Dalziel S; Davidson A; Donath S; Jachno K; South M; Fry A; Babl FE

Intensive care unit admissions and ventilation support in infants with bronchiolitis.

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The final approved manuscript submitted for publication is provided below

Title Page

ICU admissions and ventilation support in infants with bronchiolitis

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No reprints will be ordered

Abstract (word count 273)

Objectives: To describe the rate of Intensive Care Unit (ICU) admission, type of ventilation support provided and risk factors for ICU admission in infants with bronchiolitis.

Design: Retrospective review of hospital records and Australia & New Zealand Paediatric Intensive Care (ANZPIC) registry data for infants 2 to 12 months old admitted with bronchiolitis

Setting: 7 Australian and New Zealand hospitals. These infants were prospectively identified through the comparative rehydration in bronchiolitis (CRIB) study between 2009 - 2011.

Results: Of 3884 infants identified, 3589 charts were available for analysis. Of 204 (5.7%) infants with bronchiolitis admitted to ICU, 162 (79.4%) received ventilation support. Of those 133 (82.1%) received non-invasive ventilation (High Flow Nasal Cannula [HFNC] or Continuous Positive Airway Pressure [CPAP]) seven (4.3%) received invasive ventilation alone and 21 (13.6%) received a combination of ventilation modes.

Infants with comorbidities such as chronic lung disease (OR 1.6 [95% CI 1.0-2.6]), congenital heart disease (OR 2.3 [1.5-3.5]), neurological disease (OR 2.2 [1.2-4.1]) or prematurity (OR 1.5 [1.0-2.1]), and infants 2-6 months of age (OR 1.5 [1.1-2.0]) were more likely to be admitted to ICU. Respiratory Syncytial Virus positivity did not increase the likelihood of being admitted to ICU (OR 1.1 [95% CI 0.8 - 1.4]).

HFNC use changed from 13/53 (24.5% [95% CI 13.7-38.3]) patient episodes in 2009 to 39/91 (42.9% [95% CI 32.5-53.7]) patient episodes in 2011.

Conclusion: Admission to ICU is an uncommon occurrence in infants admitted with bronchiolitis, but more common in infants with co-morbidities and prematurity. The majority are managed with non-invasive ventilation, with increasing use of HFNC.

Introduction

Bronchiolitis is a common respiratory tract infection affecting infants under 1 year of age. Following an Emergency Department (ED) presentation, up to 40% of infants are admitted to hospital, and of these about 10% have intensive care unit (ICU) admission.^{1,2} Bronchiolitis is one of the most common causes of non-elective intensive care admissions.^{3,4}

There is no proven clinical benefit in administering medications to infants with bronchiolitis⁵ and the mainstay of treatment is supportive care with oxygen therapy and supplemental fluids. There are also no clearly effective medicinal therapies available to improve the outcome of critically ill infants with bronchiolitis.⁶

The aims of this multicentre study were to determine the number of patients over 2 months of age with bronchiolitis receiving intensive care, the type of ventilation support and to determine factors associated with infants with bronchiolitis requiring ICU admission, over 3 bronchiolitis seasons.

Methods

Study Design and Setting:

This was a retrospective chart review of data collected from 3884 infants, admitted with bronchiolitis at 7 Australian and New Zealand Hospitals who were prospectively assessed for eligibility as part of the comparative rehydration in bronchiolitis (CRIB) study conducted between 2009-2011.^{3,4} This was a National Health and Medical Research Council (NHMRC), Australia, funded randomised trial in Australia and New Zealand where infants between 2 and 12 months of age with bronchiolitis, requiring fluid therapy, were randomised to receive either nasogastric (NGT) or intravenous fluid (IVF) therapy^{3,4}. The study

received ethical approval at all participating sites.

Study Population, Inclusion and Exclusion:

There were 7 recruitment sites in this multi centre study: Royal Children's Hospital (RCH) Melbourne, Sunshine Hospital Melbourne, Monash Medical Centre Melbourne, Princess Margaret Hospital Perth, Royal Children's Hospital Brisbane, and Kidz First Hospital Middlemore, New Zealand and Starship Hospital Auckland, New Zealand. Of note, Sunshine Hospital Melbourne does not have an ICU, therefore infants with bronchiolitis requiring respiratory support were transferred to one of two other hospital with ICU facilities, which are both participating sites of this multicenter study.

Infants were between the ages of 2 months and 12 months presenting to the ED with bronchiolitis showing symptoms and signs of respiratory distress (tachypnoea, recessions, nasal flaring, and cyanosis) associated with symptoms of viral respiratory tract infection (cough, runny nose, blocked nose)^{22,23}.

Infants were excluded from final analysis if medical records or ICU data were unavailable.

Data Collection:

All infants were identified through the CRIB study^{3,4} or the Australia and New Zealand Paediatric Intensive Care (ANZPIC) database. The CRIB study prospectively identified all infants presenting to the emergency departments of participating hospitals and recorded this in a log. At each participating site, investigators reviewed CRIB study records to identify all admitted infants presenting during the CRIB study. This included infants that were missed, or excluded from the study, or refused participation. Baseline demographic variables including age, gender, prematurity, previous bronchiolitis, comorbidities (chronic respiratory disease, chronic neurological disease and congenital heart

disease), length of stay in hospital, medications received and investigations done were collected.

Data were obtained directly from medical records or from electronically scanned medical records (ESMR). Results of chest radiographs (CXR) and viral panel testing with nasal pharyngeal aspirates (NPA) or nasal swabs were obtained from radiology and pathology databases of participating hospitals. NPA/nasal swab results were any positive results throughout the admission. Data on infants admitted to ICU were obtained from medical records, ESMR and the ANZPIC database from the participating hospitals. Abstracted data included information on modes of ventilation support, duration of ventilation and length of stay in ICU. Investigators from participating sites recorded information for all infants on standardized clinical report forms (CRFs).

Investigators from each site were trained based on an operations manual to ensure that all data were collected in a standardized and defined fashion. All study materials were piloted at two sites. Completed CRFs were entered into an Epidata database at a single site.

Data Extraction and Analysis/ Synthesis:

Data were extracted from the combined Epidata database (Epidata, Odense, Denmark) and analysed with Stata (Statacorp, College Station, Tx, USA) using logistic regression, reporting odds ratios (OR) with 95% confidence intervals (95% CI). A p-value less than 0.05 was considered to denote statistical significance.

Results

From 3884 infants identified from the 7 sites, 295 infants were excluded, 293 due to unavailability of medical records and 2 due to unavailability of ICU data, leaving 3589 available records. There were 204 (5.7%) infants with bronchiolitis admitted to ICU with both

medical records and ICU data available. Eighty (39.2%) were direct admissions to ICU from ED or other sources while 124 (60.8%) were infants who were admitted to the wards from ED and subsequently to the ICU (**Figure 1**).

Of the 204 infants with bronchiolitis admitted to ICU, 162 (79.4%) received ventilation support. They comprised 133 (82.1%) receiving non-invasive ventilation only (NIV; HFNC or CPAP), 7 (4.3%) receiving invasive ventilation (endotracheal intubation) only, and 22(13.6%) receiving a combination of both non-invasive and invasive ventilation modes (**Figure 1**). Of infants admitted initially to hospital inpatient wards with bronchiolitis 0.8% (95% CI 0.5%-1.2%) received invasive ventilation; of infants admitted directly to ICU 14.2% (95% CI 9.7%-19.8%) received invasive ventilation; and of infants admitted to ICU receiving any ventilatory support 17.9% (95% CI 12.3%-24.7%) received invasive ventilation. No infants received nitric oxide, high-frequency ventilation or extracorporeal membrane oxygenation and there were no deaths.

Baseline patient demographic and clinical characteristics, risk factors for ICU admission are presented in Table 1. Infants admitted with bronchiolitis requiring ICU care, compared to those not requiring ICU care, were younger (mean age ($\pm$ SD) non-ICU care 195 ($\pm$ 85) days, ICU care 177 ($\pm$ 86) days, difference (95% CI) 18.8 (6.8-30.7) days, $p=0.002$) and had a longer mean length of hospital stay (mean length of stay ($\pm$ SD) ICU care 8.7 ($\pm$ 7.2) days, non-ICU care 2.9 ($\pm$ 4.0) days, difference (95% CI) 5.7 (4.7-6.7) days, $p<0.001$). Overall, 62% of infants were male, with no difference between those requiring or not requiring ICU care. The median length of stay in ICU was 2.1 days (IQR 1.2- 3.3 days).

Infants with co-morbidities such as chronic lung disease (OR 1.6 [95% CI 1.0-2.6]), congenital heart disease (OR 2.3 [95% CI 1.5-3.5]), neurological disease (OR 2.2 [95%CI 1.2-4.1]), prematurity (OR 1.5 [95% CI 1.0-2.1]) or age between 2-6 months (OR

1.5 [95% CI 1.1-2.0]) were more likely to be admitted to ICU. Viral testing was performed on 2329 out of 3385 (68.8%) infants. RSV positivity did not increase the likelihood of being admitted to ICU (OR 1.1 [95% CI 0.8 - 1.4]).

There was some evidence of a difference between sites in rates of admission to ICU for the six sites which have an ICU ($p=0.03$). ICU admission rates ranged from 4.1% to 9.1% with an average of 5.7%. There was evidence of a difference between sites in the rates of ventilatory support use ($p<0.001$). Ventilatory support rates ranged from 2.8% to 5.9% across the sites with an average of 4.5%. There was no evidence of a difference between the sites in rates of ETI for all patients admitted with bronchiolitis (**Table 2**). For the 162 infants receiving ventilatory support admitted to ICU there was evidence of a difference between sites for the non-invasive ventilatory support use (HFNC and CPAP; $p<0.001$), but no evidence of a difference between sites for the use of invasive ventilatory support (ETI) (**Table 3**).

Frequency of ventilatory support in ICU by year from 2009 to 2011, cumulative for all sites over the study period is shown in Table 4. There was no evidence of a change in the proportion of infants admitted to ICU over the study period, with percentages ranging from 5.1% in 2009 to 6.7% in 2011 ($p=0.21$). Over the 3 years of the study period, there was no evidence that the proportion of infants admitted to ICU requiring ventilatory support changed ($p=0.73$).

Figure 2 shows the number of episodes of use of each ventilation strategy in each study year. Ventilation assistance increased from 53 episodes in 39 patients admitted to ICU in 2009 to 91 episodes in 64 infants in 2011, with the proportion of infants requiring NIV varying slightly from 47/53 (88.7%) episodes to 84/91 (92%) episodes over the study period. Whilst there is no evidence of a change in the proportion of infants requiring NIV over the study period, there is evidence of a change in the type of non-

invasive support method, with HFNC use increasing from 13/53 (24.5%) patient episodes in 39 infants ventilated in 2009 to 39/91 (42.9%) patient episodes in 64 infants in 2011 an absolute increase of 18.3% (95% CI 2.9%, 33.7%).

Discussion

The overall rate of ICU admission for infants 2-12 months was 5.7% which remained stable across the 3 study years, and is similar to that reported from Australia previously.³

The ICU admission rate across sites ranged from 4.3% to 9.1%. This likely reflects the differing resources available between hospitals with some hospitals having high-dependency units (HDU) capable of looking after infants with bronchiolitis requiring non-invasive ventilation in a ward based setting rather than an ICU. This variation is also likely due to other factors including bed availability, local guidelines, patient and clinician factors.

Compared with a study from New South Wales looking at a 10 year period from 2000-2009, our ventilation rate for infants admitted to ICU was 79.4% (compared with 76.7%) with 17.9% requiring invasive ventilation (compared with 28.6%).¹⁶ These changes are consistent with recent data showing a high rate of ventilation support in ICU admissions for bronchiolitis (>70%) with an increasing number receiving non invasive ventilation (NIV).^{12,16} NIV has been shown to be an effective ventilation strategy preventing clinical deterioration, avoiding endotracheal intubation (ETI), and shortening ICU length of stay.^{17 18 19 20 21} NIV has become the preferred initial ventilation strategy with ETI reserved predominantly for failure of NIV.

We demonstrated there was no increase in the proportion of infants requiring NIV over the years of the study, however there was a noticeable and escalating increase in the use of HFNC (18.3% increase). In contrast to previous reports of a reduction in invasive ventilation with the institution of HFNC our rate of invasive ventilation did not decline with increasing use of NIV.²⁴ One postulated reason for this is that with increasing experience and comfort with use of HFNC, patients on this mode of ventilation assistance are more likely to be managed on the ward and an ICU admission avoided, however we did not analyze HFNC in non-ICU settings. What we have demonstrated is that the rate of HFNC usage is increasing over the years of the study. There is emerging evidence that HFNC can not only prevent ETI but shorten ICU and hospital length of stay with few complications (21, 23, 24). HFNC therapy has been shown to decrease respiratory rate more than other forms of respiratory support, and infants with the greatest decrease in respiratory rate were least likely to be intubated.²⁵ In addition, the introduction of HFNC has decreased median PICU length of stay for infants with bronchiolitis from 6 to 4 days.²⁵ Short and longer-term follow up data did not identify any adverse effects related to NIV.^{24,26} Risk factors for NIV failure were apnea, prematurity, pneumonia, and bacterial co-infection.

This study showed infants with comorbidities (chronic lung disease, congenital heart disease, neurological disease) and that were younger (between 2 to 6 months of age), were more likely to have ICU admission supporting research by Richard *et al* showing that infants with a history of prematurity, chronic lung disease, congenital heart disease and other comorbidities are more at risk of requiring interventions such as supplemental fluids and oxygen or ICU treatment.⁸ In a prospective multicentre study from the US comparing ward and ICU admissions in infants with bronchiolitis, predictors of ICU admission were age <2 months, an ED visit the past week, moderate or severe retractions

and inadequate oral intake. Unlike previous studies, no association with male gender, socioeconomic factors, insurance status, breast-feeding, or parental asthma was found to be associated with ICU admission. ¹³

In our study 69% patients were tested for respiratory viruses. Our data indicate a lower rate of RSV positivity (50%) compared with earlier French (76%) ¹² and New South Wales (66%) ¹⁶ studies in infants with bronchiolitis admitted to ICU. There is conflicting information about whether RSV positivity increased ⁹⁻¹² or had no effect on ^{27,28} the likelihood of ICU admission and length of ICU stay. In this study RSV positivity was not associated with an increase likelihood of ICU admissions.

Limitations

There were several limitations to this study. This is a multicentre retrospective study which relied on medical record reviews. Based on Gilbert et al ²⁹ we defined inclusion criteria, determined the variables being analysed, trained the abstractors, used standardised and piloted abstraction forms and had periodic abstractor monitoring. However, the abstractors were not blinded to the study hypotheses. A strength was the prospective identification of patients with bronchiolitis (that is diagnosis on admission) rather than a discharge diagnosis, as we have picked up all patients initially treated as bronchiolitis, representing a real world view of the management of this clinically diagnosed disease.

Infants were pre-identified from the CRIB study which did not include all bronchiolitis admissions to hospital and intensive care during the annual study period. In particular it excluded infants seen between the end of one bronchiolitis season and the bron-

chiolitis season of the following year (November to March). The definition of bronchiolitis season was based on the perceived volume of maximum recruitment with a defined cutoff. There were a small proportion of medical charts and ICU data missing during the study period.

There was no standardised measure of disease severity used, and the need for admission to ICU and initiation of ventilation support was made by individual clinicians. Infants less than 2 months corrected gestational age were not included in this study. The CRIB trial studied hydration methods in non neonatal patients with bronchiolitis so no prospective log of these patients was available and we did not include a retrospective identification of these patients in this study. This age group has been previously shown to be have an increased risk of ICU admission.¹³

Some infants received more than one method of ventilation; therefore we captured ventilation events per patient episode. We were unable to describe the sequence of ventilation modes, escalation or step-down of ventilation modes and length of ventilation episodes as many infants had multiple episodes of ventilation within the same admission to ICU. A prospective study would obtain more accurate information on ventilation support usage.

Conclusion

Infants admitted to hospital with bronchiolitis requiring intensive care support represent a small but significant proportion of bronchiolitis admissions with the rate of ICU admission increasing over the study period. Comorbidities and younger age were risk factors for ICU admission. The use of NIV is increasing with HFNC ventilation becoming the strategy of choice, and reduces the need for invasive ventilation.

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Conflicts of Interest

The authors declare they have no conflicts of interest.

Author Contribution:

All authors contributed to the design and implementation of the study, or analysis and interpretation of the study results. EO, FB, MB, NP, JN, DK, MS, AD, AW contributed to all stages of the study. SDa contributed to the implementation of the study. EO was the principal investigator. SDo, and KJ performed the statistical analysis. KJ controlled the database. VC ensured appropriate data collection. EO, VC, FB, MB, SDa, DK, NP contributed to interpretation of the results. All authors contributed to the manuscript preparation and review, and approved the final version. The report was written by EO.

Figure Legends

Figure. 1. Flow chart of study process and mode of ventilation of infants admitted to ICU with bronchiolitis

ED, emergency department; CRIB, comparative rehydration in bronchiolitis; ICU, intensive care unit

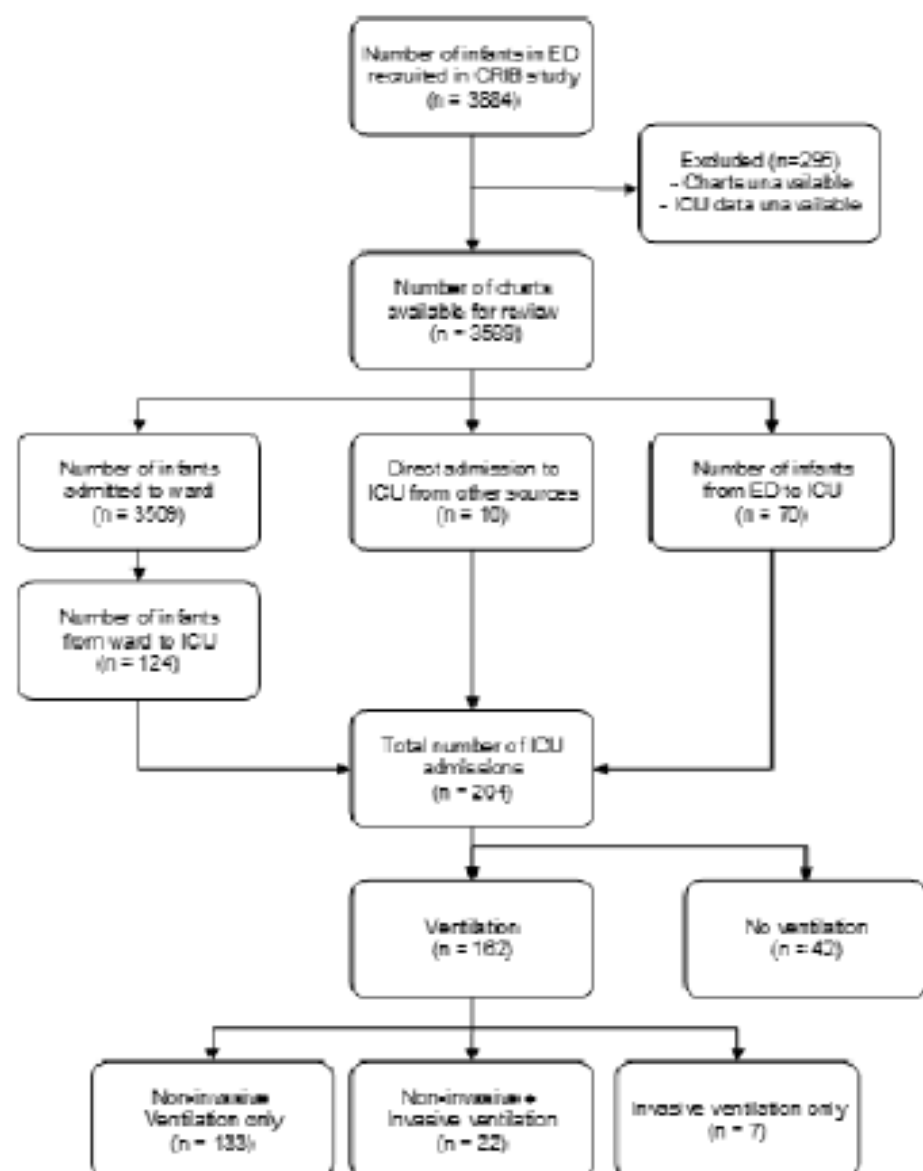
Figure. 2. Graph of type of ventilation support by years (cumulative of all centres) from 2009 – 2011

ICU, intensive care unit; HFNC, high flow nasal cannula; CPAP, continuous positive airway pressure

n = number of patients

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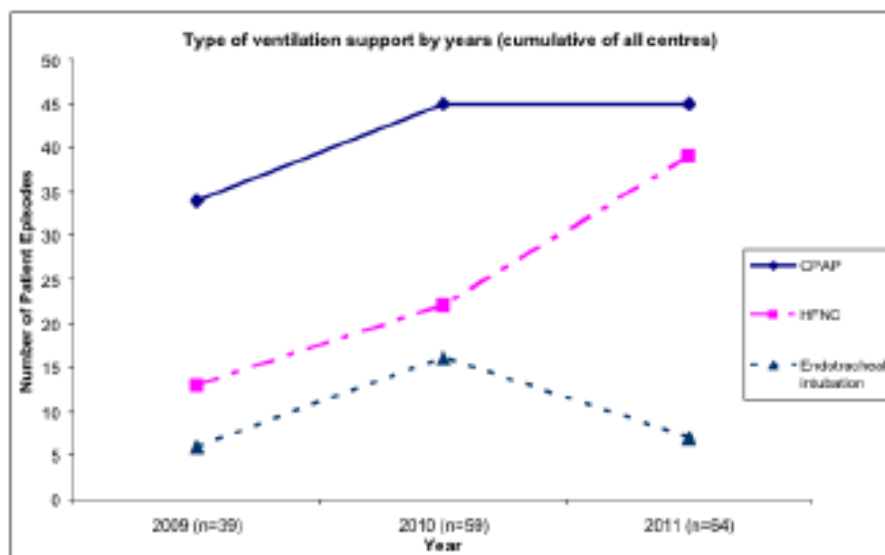


Table 1. Demographics comparing non-ICU and ICU infants with bronchiolitis

	Non-ICU infants	ICU infants	Total	Difference (95% CI)	OR (95% CI)	P-value
Age in days (mean $\pm$ SD)	195.6 $\pm$ 84.5	176.9 $\pm$ 85.7	194.6 $\pm$ 84.7	18.8 (6.8-30.7)	-	0.002
Age 2-6 months	1565	114	1679	-	1.5 (1.1 – 2.0)	0.007
Age $\geq$ 6months	1820	90	1910	-		
Length of stay in hospital in hours (mean $\pm$ SD)	70.5 $\pm$ 95.2	208.0 $\pm$ 172.3	78.3 $\pm$ 106.1	137.6 (113.6-161.6)	-	<0.001
Median length of stay in ICU in hours (IQR)	-	50.6 (28.3-78.3)	-	-	-	-
Male %	2103/3385 (62.1%)	116/204 (56.9%)	2219/3589 (61.8%)	-	1.2 (0.9 - 1.7)	0.13
Pre-maturity	492/3302 (14.9%)	41/199 (20.6%)	533/3501 (15.2%)	-	1.5 (1.0 - 2.1)	0.03
Chronic lung disease	238/3356 (7.1%)	22/199 (11.1%)	260/3555 (7.3%)	-	1.6 (1.0 - 2.6)	0.04
Neurological disorder	95/3356 (2.8%)	12/198 (6.1%)	107/3554 (3.0%)	-	2.2 (1.2 - 4.1)	0.01
Congenital heart disease	224/3357 (6.7%)	28/199 (14.1%)	252/3556 (7.1%)	-	2.3 (1.5 - 3.5)	<0.001
Previous bronchiolitis	1206/3357 (35.9%)	86/197 (43.7%)	1292/3554 (36.4%)	-	1.4 (1.0 - 1.9)	0.03
RSV+ *	998/2140 (46.6%)	91/189 (48.1%)	1089/2329 (46.8%)	-	1.1 (0.8 - 1.4)	0.69

* Only 2329 of 3385 had viral studies done

ICU, intensive care unit; RSV, respiratory syncytial virus; OR, odds ratio; CI, confidence interval; IQR, inter-quartile range; SD, standard deviation

Table 1. Number of infants admitted to hospital with bronchiolitis and requiring ICU admission and ventilation support

Hospital	Infants admitted with bronchiolitis		Infants with bronchiolitis admitted to ICU		Infants with bronchiolitis admitted to ICU receiving ventilation support		Infants admitted with bronchiolitis receiving ventilation support	Infants admitted with bronchiolitis receiving invasive ventilation support (ETI)	
	n	%	n	%	N	%	%	N	%
Site 1	814	22.7	61	7.5	48	78.7	5.9	8	1.0
Site 2	1077	30.0	57	5.3	55	96.5	5.1	5	0.5
Site 3	466	13.0	19	4.1	13	68.4	2.8	1	0.2
Site 4	206	5.7	10	4.9	9	90.0	4.4	4	1.9
Site 5	274	7.6	25	9.1	13	52.0	4.7	3	1.1
Site 6	525	14.6	32	6.1	24	75.0	4.6	8	1.5
Site 7	227	6.3	0		0		-	-	-
Total	3589	100	204	5.7	162	79.4	4.5	29	0.9

Note: Site 7 does not have an ICU

ICU, intensive care unit

Table 1. Type of ventilation support by hospitals in infants with bronchiolitis admitted to ICU

Hospital (n=patients/episodes)	Types of ventilation support (n=patient episodes)					
	HFNC		CPAP		Endotracheal intubation	
	n	%	n	%	n	%
Site 1 (n=48/57)	10	17.5	39	68.4	8	14.0
Site 2 (n=55/90)	35	38.9	50	55.6	5	5.6
Site 3 (n=13/15)	4	26.7	10	66.7	1	6.7
Site 4 (n=9/17)	9	52.9	4	23.5	4	23.5
Site 5 (n=13/15)	3	20.0	9	60.0	3	20.0
Site 6 (n=24/33)	13	39.4	12	36.4	8	24.2
Total (n=162/227)	74	32.6	124	54.6	29	12.8

Some infants received a combination of ventilation modes

ICU, intensive care unit; HFNC, high flow nasal cannula; CPAP, continuous positive airway pressure

Table 1. Frequency of ventilation support of ICU infants with bronchiolitis by year (cumulative of all centres) from 2009 to 2011

Year	Infants with bronchiolitis		Infants with bronchiolitis admitted to ICU		Infants with bronchiolitis admitted to ICU receiving ventilation support		Infants admitted with bronchiolitis receiving ventilation support
	n	%	n	%	n	%	
2009	1005	28.0	51	5.1	39	76.5	3.9
2010	1412	39.3	75	5.3	59	78.7	4.2
2011	1172	32.7	78	6.7	64	82.1	5.4
Total	3589	100	204	5.7	162	79.4	4.5

ICU, intensive care unit

CHAPTER 5

Exploring low value care in bronchiolitis in Australia and New Zealand

Problem

Bronchiolitis remains a clinical diagnosis indicated by a cluster of clinical symptoms and signs including rhinorrhoea, cough, crackles and wheeze.[2, 4] As previously outlined, the treatment of bronchiolitis remains supportive, with no medication having been shown to clearly effect the clinical outcomes.[2, 4, 10, 13, 14, 51, 67, 79] There is a body of evidence indicating a lack of benefit from salbutamol, corticosteroids, adrenaline, hypertonic saline and antibiotics[11, 12, 28, 49, 80-89] and existing international guidelines recommend against their use in.[2, 4, 67, 90] Despite this, research continues to show ongoing high rates and wide variation in the use of medication and chest x-rays (with rates of use over 70% in some North American Hospitals).[45, 47, 91-93] Reducing rates of use of both chest x-rays and medication has been suggested to be cost saving[47] and is a recommendation of the Royal Australasian College of Physicians' Choosing Wisely Australia® campaign.[27]

In New Zealand a review of bronchiolitis management in five hospitals revealed significant variation in medication and chest x-ray use between hospitals, with between 18% and 45% of infants receiving antibiotics, 35% and 48% receiving bronchodilators, and 42% and 78% receiving a chest x-ray.[47] A survey performed of paediatric emergency physicians in Australia and New Zealand, and reported in **Chapter 1 (Paper 1-1)** of this thesis suggested more uniform practice with bronchodilators and steroids used only in older infants with more severe disease. Further evidence is needed to determine if there is a need to invest effort in improving bronchiolitis management in Australia.

Questions

What is the rate, variability and pattern of medication use in emergency departments in Australia and New Zealand?

Answers

What is the rate, variability and pattern of medication use in emergency departments in Australia and New Zealand?

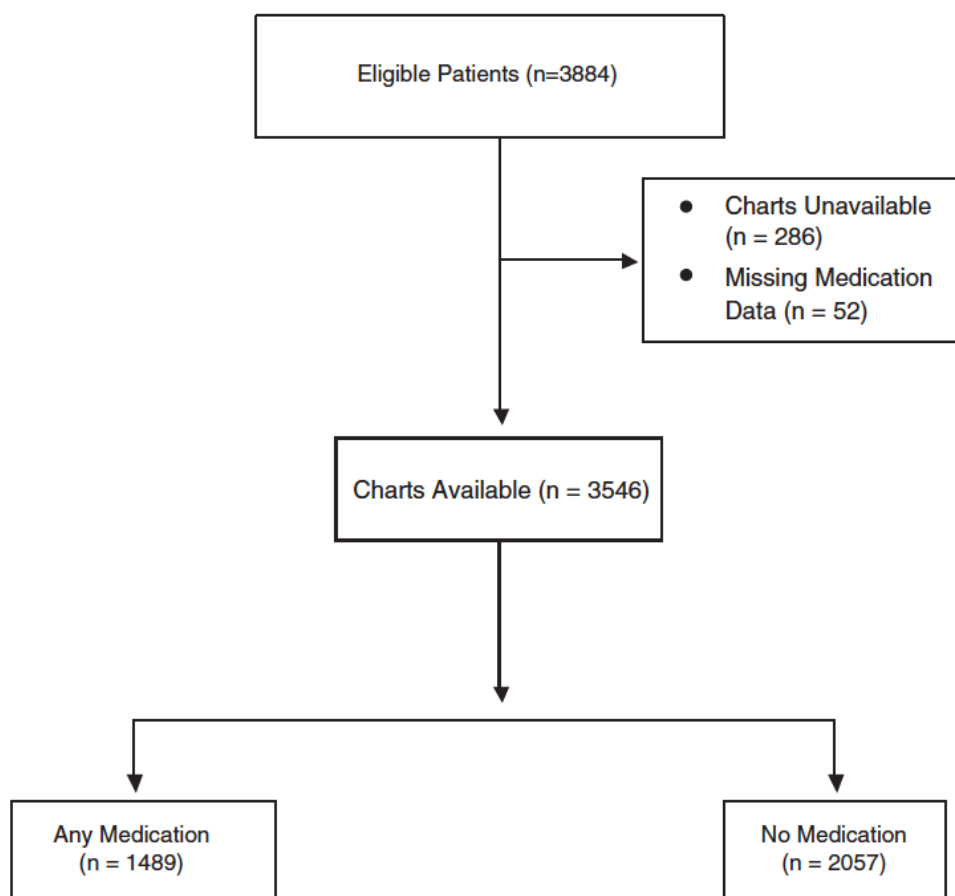
Paper 5-1:

Oakley E; Brys T; Borland M; Neutze J; Phillips N; Krieser D; Dalziel SR; Davidson A; Donath S; Jachno K; South M; Williams A; Babl FE; Paediatric Research in Emergency Departments International Collaborative (PREDICT).

Medication use in infants admitted with bronchiolitis.

Emergency Medicine Australasia. 2018;30(3), 389-397

This paper reports a multicentre retrospective observational study of 3884 infants between 2 and 12 months of age admitted to hospital with bronchiolitis. The population is the same population used in the report on intensive care admission and ventilation use in **Chapter 4 (Paper 4-1)**. The infants were prospectively assessed as part of the CRIB study (**Chapter 1 Papers 1-1 and 1-2**) and include the 759 infants randomised to the CRIB study and all other infants between 2 and 12 months of age admitted to hospital via the emergency departments of the seven participating hospitals in bronchiolitis seasons (April to November) of the years 2011 to 2013 inclusive. The primary outcome was the rate of medication use in infants admitted to hospital with bronchiolitis. Secondary outcome measures included cross site variation in medication use, the effect of investigations on medication use (Chest x-ray and nasopharyngeal aspirate), and the effect of increasing age on medication use. The medications specifically of interest were salbutamol, ipratropium bromide, adrenalin, hypertonic saline and normal saline, corticosteroids, and antibiotics.

Figure 5-1: Patient recruitment and medication use

Of the 3884 infants identified meeting the inclusion criteria adequate medication data was available for 3456 infants (**Figure 5-1**). Forty-two percent (1489) of the infants received at least one medication. Rates of medication use varied between sites ranging from 27% and 49%. (**Table 5-1**). Salbutamol was the most commonly administered medication (25.5% of infants). Infants older than 6 months of age were more likely to receive medication than those 2-6 months old (Odds Ratio (OR) 4.1 95% CI 3.6 to 4.7). The effect of age on medication use was analysed with regression analysis. After 4 months of age there was a relatively linear increase in medication use with total medication use increasing by 8.2% (95% CI 7.7 to 8.6) per month of age, meaning that by 11 months of age 80% of infants received some medication. Salbutamol followed a

similar linear age related increase, increasing by 9.3% (95% CI 8.4 to 10.2) per month of age (**Figure 5-2**).

Intensive care unit admission was associated with an increase in medication use with 81.6% receiving some medication. Compared with infants not admitted to intensive care, intensive care unit admission had an OR of 6.8 (95% CI 4.8 to 9.7) for medication use. Antibiotics were the most commonly used medication in intensive care, administered in 68.6% of infants. Having a chest x-ray was associated with increased antibiotic use (OR 10.9 95% CI 8.9 to 13.3). Infants who had a nasopharyngeal aspirate to assess for viral pathogens were more likely to receive antibiotics than infants who did not have an aspirate performed (OR 2.5 (95% CI 2.0 to 3.0). Isolation of any viral pathogen did not reduce the rate of antibiotic use.

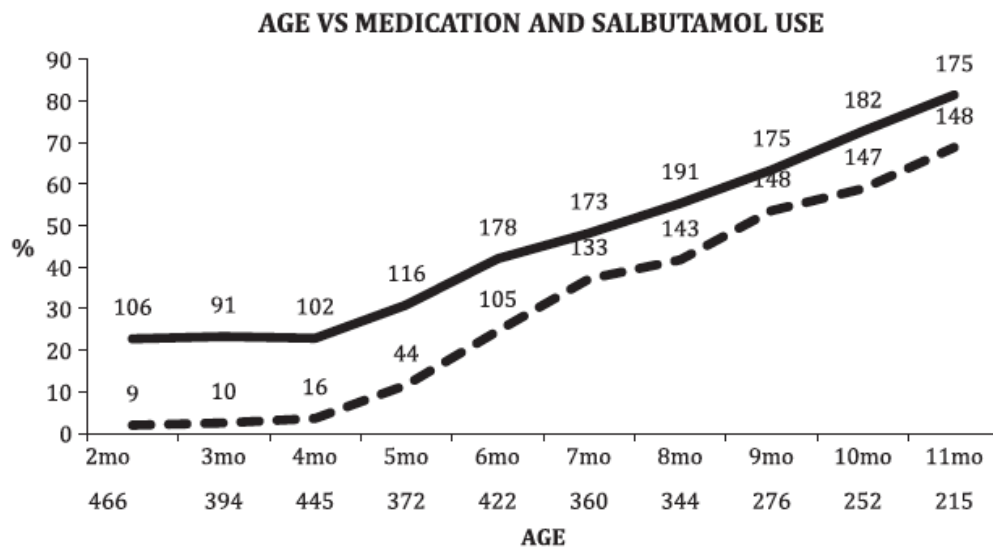
Limitations

As this was a retrospective review of medical records the data depends on accurate recording of the events in the medical record. Some information – such as family or previous patient history - were not recorded accurately enough to be included in the study. The medical records document the medication used but not the location in which it was given, so the study cannot report of medication use in the emergency department or the inpatient ward specifically. The data set recorded only if the medication was used, not the frequency or duration of administration. We also did not record severity of illness or change in severity of illness so cannot report whether medication use improved or did not improve the illness.

Table 5-1: Medication use in management of infants with bronchiolitis by site and medication type

	Any medication		Salbutamol		Ipratropium Bromide		Adrenaline		Hypertonic Saline		Normal Saline		Steroids		Antibiotics		Adrenaline + steroids		No medication	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Site 1 (<i>n</i> = 798)	369	46.2	253	31.7	39	4.9	44	5.5	3	0.4	32	4.0	170	21.3	121	15.2	39	4.9	429	53.8
Site 2 (<i>n</i> = 1078)	472	43.8	253	23.5	5	0.5	34	3.2	0	0.0	1	0.1	22	2.0	259	24.0	1	0.1	606	56.2
Site 3 (<i>n</i> = 463)	125	27.0	61	13.2	5	1.1	1	0.2	0	0.0	2	0.4	21	4.5	72	15.6	1	0.2	338	73.0
Site 4 (<i>n</i> = 205)	76	37.1	56	27.3	4	2.0	1	0.5	1	0.5	3	1.5	31	15.0	20	9.8	1	0.5	129	62.9
Site 5 (<i>n</i> = 273)	133	48.7	96	35.2	11	4.0	9	3.3	2	0.7	15	5.5	38	13.9	37	13.6	6	2.2	140	51.3
Site 6 (<i>n</i> = 204)	66	32.4	44	21.6	5	2.5	8	3.9	1	0.5	5	2.5	21	10.3	20	9.8	7	3.4	138	67.6
Site 7 (<i>n</i> = 525)	248	47.2	140	26.7	8	1.5	3	0.6	3	0.6	3	0.6	28	5.3	128	24.4	2	0.4	277	52.8
Total (<i>n</i> = 3546)	1489	42.0	903	25.5	77	2.2	100	2.8	10	0.3	61	1.7	331	9.3	657	18.5	57	1.6	2057	58.0

Figure 5-2: Medication and salbutamol use by age



*

mo, months. (—), Medication; (- -), salbutamol.

Implications

This study identified that despite widespread agreement that antibiotics, steroids, bronchodilators, hypertonic saline and combinations of these medications are not currently indicated for the management of bronchiolitis,[2, 4, 66, 67] there remains significant use of these medications in Australian and New Zealand emergency departments. As has been reported previously from New Zealand and North America[4, 5, 45, 47, 51, 93] this study revealed significant variation in medication use across sites ranging from 27% to 49%.

Factors associated with increased medication use in this study were admission to an intensive care unit, having a chest x-ray performed, having a nasopharyngeal aspirate performed, and age over 6 months. Admission to an intensive care unit is an indicator of more serious illness, and these infants may not meet the clinical diagnostic pattern for typical bronchiolitis, warranting further investigation. However, the finding that over 80% of these infants received medication with almost 70% receiving antibiotics was surprising. This association was also found by Damore *et al* who

showed an OR of 2.6 for use of antibiotics in infants admitted to the intensive care unit.[78]

As has been previously reported our study demonstrated a relationship of increasing antibiotic use with having a chest x-ray performed.[94-96] Our study did not record the indications for x-ray or the number of doses of medication used, but showed a nine-fold increase in use of antibiotics when a chest xray is performed despite a diagnostic rate of pneumonia of only 7.6%. This would indicate an over use of both chest x-ray and of antibiotics, supporting calls for reduction in chest x-ray use in bronchiolitis[97, 98].

A nasopharyngeal aspirate is usually undertaken to identify viral pathogens as the cause of the illness. It is not recommended in typical bronchiolitis but may be used to exclude pertussis or influenza.[4] It would be expected that finding a viral pathogen would reduce antibiotic use, but our data indicate this did not happen, and that having a nasopharyngeal aspirate performed increased the risk of receiving antibiotics. We did not record the duration of treatment so cannot determine if these were single doses or ongoing treatments, but our data further support evidence that nasopharyngeal aspirates are not indicated in typical bronchiolitis. Medication use was also shown to increase with age. This was dominated by the use of salbutamol. Clinical practice guidelines available at the time of this study suggested a trial of salbutamol could be considered in older infants with a diagnosis of bronchiolitis.[9, 67] This may be the driver for this increased use and as we did not record duration of use or number of medication doses we cannot determine how many of these infants received ongoing salbutamol.

The Choosing Wisely movement highlights the challenges faced when trying to implement evidence that requires clinicians to reduce intervention with medications and investigations when caring for their patients. Worldwide experience suggests that despite high quality evidence that medications are not helpful in managing bronchiolitis, and may be harmful, ongoing use remains high. Research is beginning to highlight some of the reasons for clinicians intervening in infants with bronchiolitis, with parental pressure and concern for their child shown to be a major driver in one study.[99] Studies are needed that delineate clearly the drivers of intervention in bronchiolitis in Australian and New Zealand emergency departments, to allow better strategies to implement evidence to be devised, as we have confirmed that use of medication and some interventions remains high.

PDFs of Papers Chapter 5

Paper 5-1

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The final approved manuscript submitted for publication is provided below

TITLE PAGE

Medication use in infants admitted with bronchiolitis

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ABSTRACT

BACKGROUND: There are no medications known that improve the outcome of infants with bronchiolitis. Studies have shown the management of bronchiolitis to be varied.

AIMS: To describe medication use at the seven study hospitals from a recent multi-centre randomized controlled trial on hydration in bronchiolitis (Comparative Rehydration in Bronchiolitis (CRIB)).

METHODS: A retrospective analysis of extant data of infants between 2 months (corrected for prematurity) and 12 months of age admitted with bronchiolitis identified through the CRIB trial. CRIB study records, medical records, pathology and radiology databases were used to collect data using a standardized form and entered in a single site database. Medications investigated included salbutamol, adrenaline, steroids, ipratropium bromide, normal saline, hypertonic saline, steroids and antibiotics.

RESULTS: There were 3,456 infants available for analysis, of which 42.0% received at least one medication during hospitalization. Medication use varied by site between 27.0% and 48.7%. The most frequently used medication was salbutamol (25.5%). Medication use in general, and salbutamol use in particular, increased by 8.2% and 9.3% respectively per month after 4 months of age; from 22.9% and 3.6% at 4 months to 81.4% and 68.8% at 11 months. In infants admitted to the Intensive care Unit (ICU) compared with those not admitted to ICU 81.6% and 39.5% respectively received medication at one point during the hospital stay.

CONCLUSIONS: Medication was used for infants with bronchiolitis frequently and variably in Australia and New Zealand. Medication use increased with age. Better strategies for translating evidence into practice are needed.

BACKGROUND

Bronchiolitis is the leading cause of hospitalization during the first year of life.¹⁻³ Bronchiolitis remains a clinical diagnosis with a cluster of symptoms and signs including rhinorrhoea, cough, crackles and wheeze constituting the clinical picture.^{4,5} There are no clearly effective medications known to improve the outcome of infants with bronchiolitis. Although several medications might work in theory, and some may offer short-term symptomatic relief, none have been shown to conclusively alter the course of the disease or its major outcomes.⁴⁻⁶ Effective treatment is limited to supportive therapies such as oxygen and fluids.^{4,5,7-15}

Despite a large body of evidence and acceptance by international guidelines that salbutamol, adrenaline, steroids and antibiotics offer no clinical benefit to the infant with bronchiolitis,^{4,5,13,16-23} and no agreed benefits from hypertonic saline,²⁴⁻³² international evidence continues to reveal both overuse and wide variation in use of medications.³³⁻³⁶ Reducing the number of unnecessary chest radiographs, antibiotics or bronchodilator use has been suggested to be cost saving.³⁷ An Australian and New Zealand senior physician survey in 2008 at 11 sites revealed similar theoretical practice across sites in the management of bronchiolitis. Inhaled beta-agonists and steroids were only advised for severe cases of bronchiolitis at all sites.³⁸ However, a New Zealand study reviewing actual management of bronchiolitis in 5 major hospitals revealed significant variation in management between hospitals.³⁷

This study explores medication prescribing in infants with bronchiolitis in seven centres across Australia and New Zealand, including the impact that age, co-morbidities, and severity of illness have on medication use.

METHODS

DESIGN AND SETTING

This was a multi-centre retrospective observational study of extant data from 3,884 infants, admitted with bronchiolitis at 7 Australian and New Zealand Hospitals, who were prospectively assessed for eligibility as part of the comparative rehydration in bronchiolitis (CRIB) study conducted between 2009-2011.^{14,15} This was a National Health and Medical Research Council (NHMRC), Australia, funded randomised trial where infants between 2 and 12 months of age with bronchiolitis, requiring fluid therapy, were randomised to receive either nasogastric (NGT) or intravenous fluid (IVF) therapy.^{14,15} The research ethics committees of all hospitals approved the study.

STUDY POPULATION

There were 7 recruitment sites, five tertiary paediatric and two large mixed hospitals. All members of the Paediatric Research in Emergency Departments International Collaborative.³⁹

Infants were between the ages of 2 months and 12 months presenting to the ED with bronchiolitis showing symptoms and signs of respiratory distress (tachypnoea, recessions, nasal flaring, and cyanosis) associated with symptoms of viral respiratory tract infection (cough, runny nose, blocked nose).^{11,12}

Infants were excluded from final analysis if medical records or medication charts were unavailable.

STUDY PROCEDURE AND DATA COLLECTION

All infants were identified through the CRIB study.^{14,15} At each participating site, investigators reviewed CRIB study records to identify all admitted infants presenting during the CRIB study period. This included infants that were missed, or excluded from the study, or refused participation. Baseline demographic variables including age, gender, prematurity, previous bronchiolitis, comorbidities (chronic respiratory disease, chronic neurological disease and congenital heart disease), length of stay in hospital, medications received and investigations done were collected.

Medical records, pathology and radiology databases were used to collect epidemiological data, co-morbidities, relevant medical history, prematurity, admission characteristics, medication and oxygen use, chest x-ray (CXR) and nasopharyngeal aspirate results (NPA), discharge diagnoses and details of ICU admissions. Investigators at each site,

using a standardised form, reviewed medical records and result databases. These were entered into a database at a single site. The standardised data collection form was piloted at two sites. Medications investigated in the study included inhaled agents (salbutamol, adrenaline, steroids, ipratropium bromide, normal saline and hypertonic saline), and oral and intravenous agents (steroids and antibiotics), with data collected on any use of these medications from the time of ED presentation to time of discharge from the inpatient ward.

OUTCOME MEASURES

The primary outcome measure was the use of medication in patients admitted with bronchiolitis. Secondary outcome measures included variations in use of drugs according to age, investigations, co-morbidities, hospital site, intensive care unit (ICU) patients, infants with past medical history and ex-premature infants.

DATA ANALYSIS

All data were entered at a single site into an Epidata database (Epidata, Odense, Denmark) and analyzed using Stata (Statacorp, College Station, Tx, USA). Median values were reported with interquartile range. Relevant percentages are reported with 95% confidence interval.

We used odds ratios (OR) with 95% confidence interval (95% CI) and chi square testing to compare proportions. We used linear regression to obtain a measure of the effect of increasing age on the outcome variable of medication use.

RESULTS

Of the 3,884 patients identified during the CRIB study, 3,456 (89.0%) charts were available for analysis, as 286 charts were missing and 52 had missing medication data (**Figure 1**).

Forty two percent of the study population received at least one medication with rates of medication use varying between the seven sites from 27.0% to 48.7% (**Table 1**). The most commonly used medications were salbutamol (administered most frequently at five sites), antibiotics (most frequently at two), and steroids. Salbutamol use ranged from 13.2% to 35.2%, steroid use from 2.0% to 21.3%, and antibiotic use from 9.8% to 24.4% across sites.

Patients >6 months of age were more likely to receive medication than those 2-6 months old (Odds Ratio (OR) 4.1, 95% Confidence Interval (CI) 3.6-4.7). Specifically, older patients were more likely to receive salbutamol (OR 17.3, 95% CI 13.4-22.3), ipratropium (OR 13.1 95% CI 5.3-32.5) and steroids (OR 5.6, 95% CI 4.1-7.7) (**Table 2**). The effect of the age of the infant with bronchiolitis on medication use was also examined in regression analysis (**Figure 2**). After 4 months of age, medication use overall increased by 8.2% (95% CI 7.7%-8.6%) per month of age ($p<0.001$), and salbutamol use increased by 9.3% (95% CI 8.4%-10.2%) per month of age ($p<0.001$).

Of 207 patients admitted to ICU, 81.6% received medication compared with 39.5% of patients not admitted to ICU (OR 6.8 95% CI 4.8-9.7). Of the 169 ICU patients who received medication 116 (68.6%) received antibiotics, 73 (43%) received salbutamol, 59 (35%) received steroids and 54 (32%) received adrenaline (**Table 3**). ICU admission increased the likelihood of receiving any medication, with the largest influence on use of adrenaline (OR 25.2, 95% CI 16.5-38.6), hypertonic saline (OR 11.0, 95% CI 3.1-39.2) and antibiotics (OR 6.6, CI 4.9-8.8).

There was little difference in medication use in patients receiving fluids or oxygen when compared to those patients not receiving these supportive therapies (data not shown).

The association between investigations and medication use is displayed in **Table 4**. The likelihood of receiving antibiotics increased with having a CXR performed (OR 10.9, 95% CI 8.9-13.3), and with nasopharyngeal aspirate (NPA) collection (OR of 2.5, 95% CI 2.0-3.0). Infants who were NPA positive for a virus received antibiotics at similar rates to all patients who had an NPA performed (24% vs. 23%). Of the 657 (18.5%) of infants who received antibiotics 151 (23.0%) had discharge diagnoses that included pneumonia. Of the 541 non-ICU admissions receiving antibiotics 41 (7.6%) had diagnoses that included pneumonia.

Infants with comorbidities had an OR of 1.3 (95% CI 1.1-1.5) for receiving any medication compared with those with no co-morbidities; ex-premature infants had an OR of 1.1 (95% CI 0.9-1.3) compared with babies born at term.

DISCUSSION

There is widespread agreement that steroids, bronchodilators, adrenaline and antibiotics have no role in treating typical bronchiolitis^{4, 5, 13} and that there is insufficient evidence to recommend the use of adrenaline and steroids in combination, or hypertonic saline.^{4, 5, 13}

This study found that 42% of patients admitted with bronchiolitis during the study period were given at least one medication at some point during their hospitalisation. This was higher than suggested by a senior physician survey within the paediatric emergency medicine research network in Australia and New Zealand³⁹. The most frequently used medications were salbutamol, antibiotics and steroids.

Studies have shown wide-ranging and variable use of medications in the management of bronchiolitis, even within the same region.^{4, 6, 34, 35, 37, 40} We confirm variation in rates of medication use in Australia and New Zealand (range between sites: 27% to 49%). The largest variation was seen in the use of steroids (10 fold), adrenaline and nebulized normal saline (each 20 fold). Although not frequently used, three hospitals used a combination of adrenaline and steroid more commonly than other sites, these hospitals were geographically co-located. This combination was used at a higher frequency in patients admitted to ICU compared with ward patients.

A key finding is that medication use, and particularly salbutamol use, increased with age. Linear regression models found a significant increase in medication use and salbutamol use with increasing age after 4 months. Patients >6 months of age were more likely to receive salbutamol, ipratropium and steroids which are medications routinely used to treat asthma. We did not collect data on the frequency of drug administration, so are unable to ascertain whether bronchodilators were administered once as a therapeutic trial, or used repeatedly. Guidelines in practice at the time of data collection for this study recommended a trial of salbutamol was appropriate for older infants.¹¹ Subsequent guidelines have recommended against any use of salbutamol in bronchiolitis.^{4, 5, 13} In patients 2-6 months of age, antibiotics were the most frequently used medication.

Twice as many patients admitted to ICU received medication when compared with patients not admitted to ICU. Patients admitted to ICU with bronchiolitis most commonly

received antibiotics followed by salbutamol, steroids and adrenaline. These more unwell infants may not fit the definition for typical bronchiolitis that the guidelines refer to, and consideration of alternative diagnoses and treatments may be warranted.

Prematurity had little impact on medication use in bronchiolitis, which is surprising as prematurity is a recognized risk factor for more severe disease. Comorbidities, also a recognized risk factor for more severe disease, were associated with only a small increase in medication use.

An association between investigations and antibiotic use was found. Patients who had any investigation, specifically CXR and/or NPA collection, received antibiotics more frequently than patients who did not have these investigations. However there was very little difference in antibiotic use in patients who had positive and negative NPA. As performing an NPA/nasal swab is often stated as a means of limiting antibiotic use, these results were unexpected. Also unexpected was the small proportion (7.6%) of infants not admitted to ICU who received antibiotics that were diagnosed with pneumonia. However, as we did not record the duration of medication use it is possible an initial dose of antibiotic was administered at the time of performing the NPA or CXR, and treatment was subsequently altered by the result.

All infants enrolled in the study were diagnosed with bronchiolitis on the cluster of clinical symptoms. The clinical **indications** for the investigations have not been recorded. It is reasonable to assume a CXR is to exclude a diagnosis of pneumonia or cardiac failure (especially in the very young), and an NPA or nasal swab is to either confirm the presence of respiratory viruses (making other diagnoses **less likely**) or to make another diagnosis such as influenza **or pertussis**. Evidence from systematic reviews suggests that in the absence of non-typical features (such as severe illness, other signs of cardiac failure, or lack of typical clinical signs of bronchiolitis) that such investigations are of little value. Our data on CXR and antibiotic use, **showing** a nine fold increased risk of receiving antibiotics if a CXR is performed, **yet** only a 7.6% rate of diagnosis of pneumonia supports **the conclusion that CXR and antibiotics are over utilised. This is also supported by the Choosing Wisely Australia campaign. This campaign is aimed at improving the quality and safety of health care in Australia by removing unnecessary test, and lists performing CXR, prescribing salbutamol and prescribing steroids to infants with bronchiolitis as treatments that should not be routinely performed**⁴¹

De Brasi et al demonstrated a real or perceived pressure from parents of infants with bronchiolitis to provide a medical intervention of some kind.⁴² Parents in their desire to advocate for their sick infant are likely to believe that investigations or medication are going to be of benefit. If this is a driver of care in infants with bronchiolitis it is likely that clinicians

need to have more confidence in the evidence base and better strategies and techniques for discussing interventions (especially limiting interventions), when having management discussion with parents.

If there is a desire to minimise the use of medications shown to be of no benefit, efforts to determine the drivers of clinician behavior in Australian and New Zealand hospitals, and the development of interventions tailored to address these, are required.

Limitations

This was a retrospective chart review of infants prospectively identified during the CRIB study. While we attempted to utilise the strategies set out by Gilbert et al,⁴³ we depended on data elements being accurately recorded in the medical records. For example, consistent history of atopy or a family history of asthma or atopy to correlate with salbutamol use was not possible. It was not possible to differentiate between medication given in the ED, the ward and ICU. Similarly we did not record if medication was given once or was ongoing during admission. We did not review hospital practice guidelines for bronchiolitis so it is not known whether medication was administered according to hospital practices. We did not record the severity of the illness of the infants (other than ICU admission) and cannot comment whether medication use changed with severity of disease outside the ICU.

Conclusion

Almost half of all infants admitted with bronchiolitis at 7 large hospitals in Australia and New Zealand were given at least one medication. Medication use varied across sites. Salbutamol use increased in a linear fashion after 4 months of age. This study suggests that, compared with international recommendations, medications are overused in infants with bronchiolitis and better strategies to impement evidence are needed.

Contributors

All authors contributed to the design and implementation of the study or analysis and interpretation of the study results. EO was the principal investigator. SDo and KJ did the statistical analysis. KJ controlled the database. TB supervised data collection. All authors contributed to the report preparation and review, and approved the final version. The report was written by EO.

Conflicts of interest

We declare that we have no conflicts of interest.

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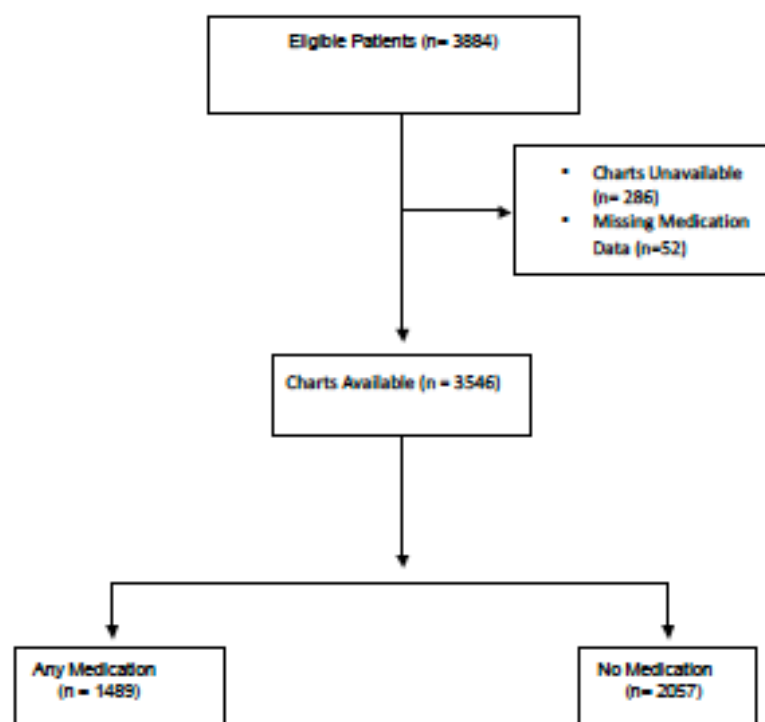
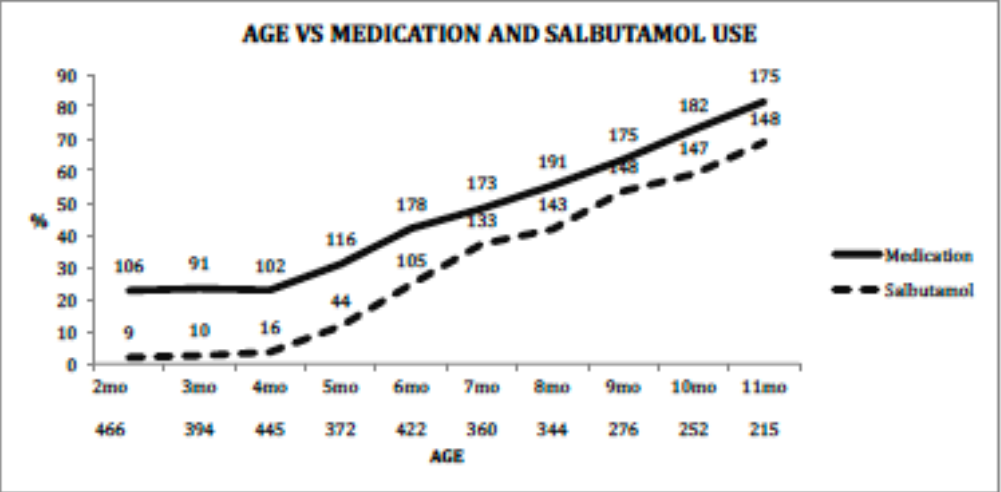


Figure 1. Flow chart of patient recruitment and medications used in bronchiolitis



mo=months

Figure 2: Medication and Salbutamol Use by Age

Table 1. Medication use in management of infants with bronchiolitis by site and medication type

	Any Medication		Sal		Ipra		Ad		H-Sal		N-Sal		Ster		Ab		Ad+Ster		No Medication	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Site 1 (n=798)	369	46.2	253	31.7	39	4.9	44	5.5	3	0.4	32	4.0	170	21.3	121	15.2	39	4.9	429	53.8
Site 2 (n=1,078)	472	43.8	253	23.5	5	0.5	34	3.2	0	0.0	1	0.1	22	2.0	259	24.0	1	0.1	606	56.2
Site 3 (n=463)	125	27.0	61	13.2	5	1.1	1	0.2	0	0.0	2	0.4	21	4.5	72	15.6	1	0.2	338	73.0
Site 4 (n=205)	76	37.1	56	27.3	4	2.0	1	0.5	1	0.5	3	1.5	31	15.0	20	9.8	1	0.5	129	62.9
Site 5 (n=273)	133	48.7	96	35.2	11	4.0	9	3.3	2	0.7	15	5.5	38	13.9	37	13.6	6	2.2	140	51.3
Site 6 (n=204)	66	32.4	44	21.6	5	2.5	8	3.9	1	0.5	5	2.5	21	10.3	20	9.8	7	3.4	138	67.6
Site 7 (n=525)	248	47.2	140	26.7	8	1.5	3	0.6	3	0.6	3	0.6	28	5.3	128	24.4	2	0.4	277	52.8
Total (n=3,546)	1489	42.0	903	25.5	77	2.2	100	2.8	10	0.3	61	1.7	331	9.3	657	18.5	57	1.6	2057	58.0

Sal=Salbutamol, Ipra=Ipratropium Bromide, Ad=Adrenaline, H-Sal=Hypertonic Saline Neb, N-Sal=Normal Saline Neb, Ster=Steroids, Ab=Antibiotics, Ad+Ster=Adrenaline+Steroids, n=number of patient

Table 2. Medication use in management of infants with bronchiolitis stratified by age

		2-6 mo		>6 mo		Odds Ratio	P Value
		n	%	n	%		
Any Medication	YES	407	24.6	1082	57.2	4.1 (3.6 - 4.7)	p<0.001
	NO	1249	75.4	808	42.8		
Salbutamol	YES	72	4.3	831	44.0	17.3 (13.4 - 22.3)	p<0.001
	NO	1584	95.7	1058	56.0		
Ipratropium	YES	5	0.3	72	3.8	13.1 (5.3 - 32.5)	p<0.001
	NO	1651	99.7	1815	96.2		
Adrenaline	YES	57	3.4	43	2.3	0.7 (0.4 - 1.0)	p=0.037
	NO	1598	96.6	1844	97.7		
Hypertonic Saline Nebulizers	YES	5	0.3	5	0.3	0.9 (0.3 - 3.0)	p=0.837
	NO	1650	99.7	1880	99.7		
Normal Saline Nebulizers	YES	25	1.5	36	1.9	1.3 (0.8 - 2.1)	p=0.364
	NO	1630	98.5	1850	98.1		
Steroids	YES	50	3.0	281	14.9	5.6 (4.1 - 7.7)	p<0.001
	NO	1606	97.0	1606	85.1		
Antibiotics	YES	293	17.7	364	19.3	1.1 (0.9 - 1.3)	P=0.064
	NO	1363	82.3	1524	80.7		
Adrenaline+ Steroids	YES	25	1.5	32	1.7	1.1 (0.7 - 1.9)	P=0.081
	NO	1630	98.5	1854	98.3		

mo=months n=number of patients

Table 3. Medication use in management of infants with bronchiolitis stratified by intensive care unit admission

		ICU admission		No ICU admission		Odds Ratio	P Value
		n	%	n	%		
Any Medication	YES	169	81.6	1,320	39.5	6.8 (4.8 - 9.7)	P<0.001
	NO	38	18.4	2,019	60.5		
Salbutamol	YES	73	35.3	830	24.9	1.6 (1.2 - 2.2)	P=0.001
	NO	134	64.7	2,508	75.1		
Ipratropium	YES	12	5.8	65	1.9	3.1 (1.7 - 5.9)	P<0.001
	NO	194	94.2	3,272	98.1		
Adrenaline	YES	54	26.1	46	1.4	25.2 (16.5 - 38.6)	P<0.001
	NO	153	73.9	3,289	98.6		
Hypertonic Saline Nebulizers	YES	4	1.9	6	0.2	11.0 (3.1 - 39.2)	P<0.001
	NO	202	98.1	3,328	99.8		
Normal Saline Nebulizers	YES	15	7.3	46	1.4	5.6 (3.1 - 10.2)	P<0.001
	NO	191	92.7	3,289	98.6		
Steroids	YES	59	28.6	272	8.2	4.5 (3.3 - 6.3)	P<0.001
	NO	147	71.4	3,065	91.8		
Antibiotics	YES	116	56.0	541	16.2	6.6 (4.9 - 8.8)	P<0.001
	NO	91	44.0	2,796	83.8		
Adrenaline+ Steroids	YES	32	15.5	25	0.7	24.3 (14.1 - 42.0)	P<0.001
	NO	174	84.5	3,310	99.3		

ICU=Intensive Care Unit n=number of patients

CHAPTER 6

Providing evidence for the use of high flow nasal cannula in bronchiolitis

Problem

Current guidelines recommend only supportive therapy for the treatment of infants with bronchiolitis, including oxygen therapy for hypoxemia, respiratory support, and the maintenance of hydration.[2, 4] Respiratory support as provided in emergency and ward settings has been limited to oxygen delivered through a standard nasal cannula, at a rate of up to 2 litres of 100% oxygen per minute, to treat hypoxemia.[100] Bronchiolitis is characterised by small airway inflammation resulting in hypoxaemia, hypercarbia and increased use of accessory muscles for breathing.[101] All these respond to the provision of positive airway pressure,[4, 72, 102] however the provision of all forms of positive airway pressure has usually been restricted to the intensive care unit. Mechanisms of action of high flow nasal cannula therapy are uncertain, although they are thought to involve some aspects of the following: washout of nasopharyngeal dead space, reduced upper airway resistance and provision of a degree of positive pressure.[100]

As found in **Chapter 5 (Paper 5-1)** high flow nasal cannula use has become more commonly used for treating infants with bronchiolitis. In this therapy humidified and heated air that is blended with oxygen is delivered through nasal cannula providing a degree of positive airway pressure.[103, 104] Studies to date have been observational and physiological, and suggest that decreased work of breathing,[105] improved oxygenation, and reduced rates of intubation are associated with high flow nasal cannula therapy.[106] As there remained little evidence to describe the indication or clinical outcomes for high flow nasal cannula therapy we conducted a multicentre randomized trial to test whether early treatment with high flow therapy in infants with bronchiolitis and hypoxemia in emergency departments and general paediatric wards would result in fewer infants having treatment failure that leads to the escalation of care.[35] (**Appendix 1, Oakley senior Australian author**))

This trial was conducted in 17 emergency departments and inpatient paediatric units in Australia and New Zealand. Infants younger than 12 months were randomised to receive either standard supplemental oxygen via nasal prongs at a rate of up to 2 litres per minute, or heated and humidified high flow oxygen at a rate of 2 litres per kilogram of body weight per minute. Oxygen was titrated to keep saturations between 92% and 98%. Infants were randomised only when oxygen saturations fell to a level that required oxygen delivery at the institution (ranging between 92% and 94%). Oxygen was weaned as required and

high flow therapy was ceased after 4 hours on 21% oxygen. Exclusion were critically ill infants who had an immediate need for respiratory support and intensive care unit admission; infants with cyanotic heart disease, basal skull fracture, upper airway obstruction, or craniofacial malformation; and infants who were receiving oxygen therapy at home.

The primary outcome was a composite outcome of treatment failure (defined in the protocol) resulting in escalation of care during that hospital admission. Prespecified secondary outcomes included the proportion of infants who were transferred to an intensive care unit; the duration of hospital stay; the duration of intensive care unit stay; the duration of oxygen therapy; intubation rates; and adverse events.

As high flow nasal cannula therapy had become part of routine care, sites indicated that randomisation not allowing this intervention would limit the recruitment to the trial. Therefore as part of the standard oxygen arm protocol, escalation of care to high flow nasal cannula therapy was possible once need for escalation of treatment had been determined by the treating clinician. A total of 1638 infants with bronchiolitis were randomised. Consent in some institutions was deferred, and after deferred consent refusals 1472 were available for analysis.

Treatment failure with escalation of care occurred in 87 of 739 infants (12%) in the high flow group, as compared with 167 of 733 (23%) in the standard-therapy group (risk difference, -11 percentage points; 95% CI, -15 to -7; $P < 0.001$). There were no significant between-group differences in the duration of hospital stay, the duration of stay in the intensive care unit, or the duration of oxygen therapy. In all 167 infants in the standard oxygen therapy group who had escalation of care clinicians chose to escalate to high flow nasal cannula therapy. Of these 167 infants 102 (61%) had a response to high flow rescue therapy, leaving 67 (39%) needing intensive care admission.[35] **(Appendix 1, Oakley senior Australian author).**

At the time this study was being conducted other evidence emerged on the use of high flow nasal cannula therapy so a formal systematic review of the literature was undertaken.

Question

What is the evidence for high flow nasal cannula use in infants with bronchiolitis?

Answers

What is the evidence for high flow nasal cannula use in infants with bronchiolitis?

Paper 6-1:

O'Brien S; Craig S; Babl FE; Borland ML; Oakley E; Dalziel SR; Paediatric Research in Emergency Departments International Collaborative (PREDICT) Network, Australasia.

'Rational use of high-flow therapy in infants with bronchiolitis. What do the latest trials tell us?' A Paediatric Research in Emergency Departments International Collaborative perspective.

Journal of Paediatrics & Child Health. 2019;55(7), 746-752

A systematic review of the literature regarding high flow nasal cannula use in infants with bronchiolitis was conducted as part of developing the Australasian Bronchiolitis Guideline[37] (**Oakley senior Australian author**) with evidence found to be low-level. Subsequent to this a number of randomised controlled trials had been published, so an update of this systematic literature review was undertaken. The aim was to summarise and critique the new evidence and provide updated recommendations for the use of high flow nasal cannula in infants with bronchiolitis in the emergency department and inpatient ward settings. The search strategy is shown in **Table 6-1**, the following databases were searched: Ovid Medline, Ovid Embase, PubMed, Cinahl (EBSCO), Cochrane Library, Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials (CENTRAL) for systematic reviews and randomised controlled trials from 1 January 2000 to 27 June 2018.

Table 6-1 Literature Search Strategy

Data Sources	MEDLINE (OvidSP); EMBASE (OvidSP); PubMed; The Cochrane Library; CINAHL(EBSCO)	
MeSH terms (MEDLINE OvidSP)	Population bronchiolitis/ bronchiolitis, viral/ respiratory syncytial viruses/ respiratory syncytial virus, human/ respiratory syncytial virus infections/ AND Intervention / Area of interest natural history/ epidemiology/ exp "reproducibility of results"/ "severity of illness index"/ diagnosis, differential/ physical examination/ exp auscultation/ blood pressure determination/ exp palpation/ percussion/ pulse/ exp vital signs/ exp *respiratory tract infections/ risk factors/ "length of stay"/ patient admission/ patient discharge/ exp intensive care units, pediatric/ respiratory care units/ morbidity/ prevalence/ exp mortality/ exp diagnostic imaging/ radiography, thoracic/ exp hematologic tests/ urinalysis/ nasal lavage fluid/ emergency service, hospital/ asthma/ or hypersensitivity, immediate/ exp albuterol/ad, tu epinephrine/ad,tu bronchodilator agents/ad, tu steroids/ad, tu exp cholinergic antagonists/ or receptors, adrenergic, beta-2/	exp anti-inflammatory agents/ exp adrenal cortex hormones/ leukotriene antagonists saline solution, hypertonic/ad, tu exp aerosols/ exp sodium chloride/ exp "nebulizers and vaporizers"/ exp oxygen inhalation therapy/ *oxygen/ad, st exp oximetry/ home care services/ home care services, hospital-based/ exp blood gas analysis/ continuous positive airway pressure/ positive pressure respiration/ positive end respiratory pressure/ exp physical therapy modalities/ physical therapy specialty/ exp physiotherapy/ suction/ administration, intranasal/ exp fluid therapy/ rehydration solutions/ enteral feeding/ parenteral feeding/ intubation, gastrointestinal/ exp bacterial infections/ exp otitis media/ exp meningitis/ exp *antibacterial agents/tu exp sepsis/ exp urinary tract infections/ tracheitis/ infection control/ exp primary prevention/ patient isolation/
Keywords (PubMed/Cochrane Library)	Population (bronchiolit* OR wheez* OR (Respiratory Syncytial Virus*) OR rsv AND Intervention / Area of interest history OR epidemiolog* OR "severity of illness" OR "disease severity" OR scoring system* OR diagnosis OR physical exam* OR auscultation OR "blood pressure" OR palpation* OR percussion OR pulse OR vital sign* OR Respiratory Tract Infection* OR risk factor* OR "length of stay" OR admission OR discharge OR "intensive care" OR ICU OR "respiratory care" OR morbidit* OR prevalence OR mortalit* OR "diagnostic imaging" OR ((chest OR thorac*) AND (x-ray* OR xray* OR "x ray" OR radiograph*)) OR ((hematolog* OR haematolog* OR blood OR virolog* OR urine) AND (test OR tests OR exam* OR investigation*)) OR urinalys* OR "nasal lavage" OR ((nose OR nasal) AND (mucosa OR mucus)) OR emergency department* OR asthma* OR atopy OR atopic OR hypersensitiv* OR salbutamol OR albuterol OR ventolin OR levalbuterol OR adrenalin* OR	

	epinephrin* OR beta2 adrenergic* OR beta2 agonist* OR ics OR corticosteroid* OR cortico steroid* OR cortico-steroid* OR glucocorticoid* OR gluco corticoid* OR gluco-corticoid* OR montelukast OR bronchodilat* OR steroid OR steroids OR cholinergic antagonist* OR cholinergic receptor* OR anti inflammatory agent* OR adrenal cortex hormone* OR leukotriene antagonist* OR leukotriene receptor* OR "hypertonic saline" OR (("sodium chloride" OR saline) AND (nebuliz* OR nebulis* OR vaporiz* OR vaporis* OR aerosol* OR intranasal OR "intra nasal" OR intra-nasal OR nasal)) OR oxygen OR "home oxygen" OR ((oximetry OR oximeter*) AND ("reproducibility of results" OR reliability OR validity OR function* OR technical specification* OR percutaneous measurement* OR blood gas analys*)) OR CPAP OR "continuous positive airway pressure" OR "positive pressure respiration" OR "positive end respiratory pressure" OR supplementa* oxygen OR "oxygen saturation" OR oxygen therap* OR oxygen treatment* OR physical therap* OR physiotherap* OR ((nasal* OR nose OR naso) AND (suction* OR toilet OR irrigation)) OR suction* OR saline drop* OR "nasal saline" OR "intranasal saline" OR deep suction* OR ((non-oral OR oral) AND (feed* OR hydration OR fluid* OR solution* OR therap*)) OR azithromycin OR fluid therap* OR intravenous infusion* OR "non-oral" OR rehydrat* OR "enteric feeding" OR "parenteral nutrition" OR "parenteral feeding" OR "enteral nutrition" OR oral* administ* OR bacterial infection* OR "otitis media" OR meningitis OR antibacterial agent* OR anti-bacterial agent* OR anti bacterial agent* OR antimicrobial agent* OR anti-microbial agent* OR anti microbial agent* OR antibiotic* OR sepsis OR septic OR urinary tract infection* OR tracheitis OR serious bacterial infection* OR "infection control" OR "primary prevention" OR isolation OR "patient care"
Search dates	The following databases were searched on the 27 June 2018 for references back to 1 January 2000: Medline (Ovid), Embase (Ovid) and The Cochrane Library. Ebsco Host Cinahl was searched back to 2000 for studies relating to chest physiotherapy and bronchiolitis only. PubMed was searched back to 2013 to capture E-pubs not available in Medline and back to 2000 to capture journals not indexed in Medline.
Other information sources checked	Reference lists of included studies were searched to identify additional relevant papers (i.e. snowballing references)
Inclusion criteria	(Publication type = clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or controlled clinical trial or guideline or meta analysis or practice guideline or randomized controlled trial or "review" or systematic reviews) or exp evidence-based medicine/ English language yr="2000 -current" age limit = ("newborn infant (birth to 1 month)" or "infant (1 to 23 months)") or infant* or newborn* or neonat* or babies or baby
Exclusion criteria	(Publication type = case reports or comment or editorial or letter) or exp bronchiolitis obliterans/ or bronchiolitis obliterans

Copies of the identified articles were retrieved and then reviewed by three authors for eligibility, and data were extracted. The search strategy identified 35 new articles since 2015, including four randomised controlled trials and no systematic reviews relevant to high flow nasal cannula use in infants with bronchiolitis.

There have now been four randomised controlled trials of high flow nasal cannula including 1891 infants with bronchiolitis. One of these studies involves infants treated only in intensive care units in France, while the other three involve infants treated in emergency departments and/or inpatient paediatric wards in Australia, New Zealand and Spain. The studies are summarised in **Table 6-2** noting important differences in inclusion criteria, definition and application of high flow nasal canula, and definitions of treatment failure.

Outcomes are summarised in **Table 6-3**. Both Franklin *et al.*[35] and Kepreotes *et al.*[107] ($n = 1674$) reported fewer treatment failures (although using different definitions, **Table 6-2**) with high flow nasal cannula than with standard care. However, these randomised controlled trials found no difference in intensive care unit admission rates, intubation rates, duration of oxygen therapy or hospital length of stay between those initially commenced on standard sub-nasal oxygen therapy and those commenced on high flow nasal cannula. In the 200 infants who failed standard sub-nasal oxygen in these two studies, high flow nasal cannula effectively rescued (no need for intensive care admission) 61%. Similarly, Milesi *et al.*[108] report in their intensive care unit study, that for the 22 infants who failed nasal continuous positive airway pressure, high flow nasal cannula rescued (with no need for other respiratory support) 82%. (**Table 6-4**)

These results provide robust evidence for when clinicians should use high flow nasal cannula. While more infants will require escalation of care if started on standard oxygen therapy, over two thirds of those started on standard sub-nasal oxygen therapy will require no further escalation of treatment. Of those requiring escalation they will all be able to escalate to high flow nasal cannula, with about 60% of these requiring no further escalation in care (and being able to remain on the ward). Kepreotes *et al.*[107] provided a health economic analysis that shows cost benefit to the treatment strategy of initial sub nasal oxygen with high flow nasal cannula as rescue therapy. Recommendation was therefore made that initial treatment for infants with bronchiolitis and hypoxemia should be sub-nasal oxygen therapy up to 2 litres per minute to maintain oxygen saturations, with high flow nasal cannula reserved for cases of deterioration after the use of standard sub-nasal oxygen therapy (**Figure 6-1**).

Table 6-2 Summary of randomised controlled trials on the use of high flow nasal cannula for bronchiolitis

Citation	Campana <i>et al.</i> [109]	Kepreotes <i>et al.</i> [107]	Franklin <i>et al.</i> [35]	Milesi <i>et al.</i> [108]
Setting	Two hospitals in Spain (paediatric ward)	One hospital in Australia (ED and paediatric ward)	17 tertiary and regional hospitals in Australia and New Zealand (EDs and paediatric wards)	Five tertiary hospitals in France (PICUs)
Eligibility	Infants aged ≤6 months with moderate acute bronchiolitis (RDAI ≥4)	Infants aged <24 months with a clinical diagnosis of bronchiolitis of moderate severity and requiring supplemental oxygen (at least one of the following: Abnormal heart rate, abnormal respiratory rate, decreased SpO ₂ , or increased work of breathing)	Infants aged <12 months with a clinical diagnosis of bronchiolitis and need for supplemental oxygen therapy to maintain SpO ₂ ≥92 or ≥94 (dependent on individual sites oxygen guidelines)	Infants aged ≤6 months with a clinical diagnosis of bronchiolitis and moderate to severe respiratory distress, defined by an mWCAS
Key exclusion criteria	Those requiring immediate intubation and ventilation. Prematurity, chronic lung disease, cystic fibrosis, congenital heart disease, neuromuscular disease, airway anomalies and Immunodeficiency	Severe or life-threatening bronchiolitis, including SpO ₂ < 90% on room air	Critically ill infants who had an immediate need for respiratory support and ICU admission, cyanotic heart disease, basal skull fracture, upper airway obstruction, craniofacial malformation, infants receiving home oxygen	Indication for imminent intubation, cardiac or neuromuscular disease and pneumothorax on chest radiograph
Study design	Open-label RCT	Open-label RCT	Open-label RCT	Open-label RCT
HFNC intervention	6–8 L/min based on the following calculation: Tidal volume x respiratory rate x9, via Precision Flow (Vapotherm Inc. Stevensville, MD, USA) or RT329 (Fisher and Paykel Healthcare, Auckland, New Zealand) AND nebulised epinephrine 1:1000 0.5 mL/kg (maximum 3 mL) + 2 mL 0.9% saline every 4 h	1 L/kg/min (max 20 L/min) via Optiflow Junior nasal cannula and the MR850 humidifier (Fisher and Paykel Healthcare) using a 1:1 air–oxygen ratio, resulting in a maximum FiO ₂ of 0.6	2 L/kg/min (max 25 L/min) via Optiflow Junior cannula and the Airvo 2 high flow system (Fisher and Paykel Healthcare) with FiO ₂ titrated to maintain SpO ₂	2 L/kg/min via Optiflow (Fisher and Paykel, Villebon, France) with FiO ₂ titrated to maintain SpO ₂ at 94–97%
Comparison group	Nasal cannula (max 3 L/min) AND nebulised epinephrine 1:1000 0.5 mL/kg (maximum 3 mL) + 2 mL 3% saline every 4 h	Nasal cannula (max 2 L/min)	Nasal cannula (max 2 L/min)	Nasal CPAP (7 cm H ₂ O) via Infant Flow Ventilator (Electro Medical Equipment, Brighton, UK) or FlexiTrunk infant interface (Fisher and Paykel)

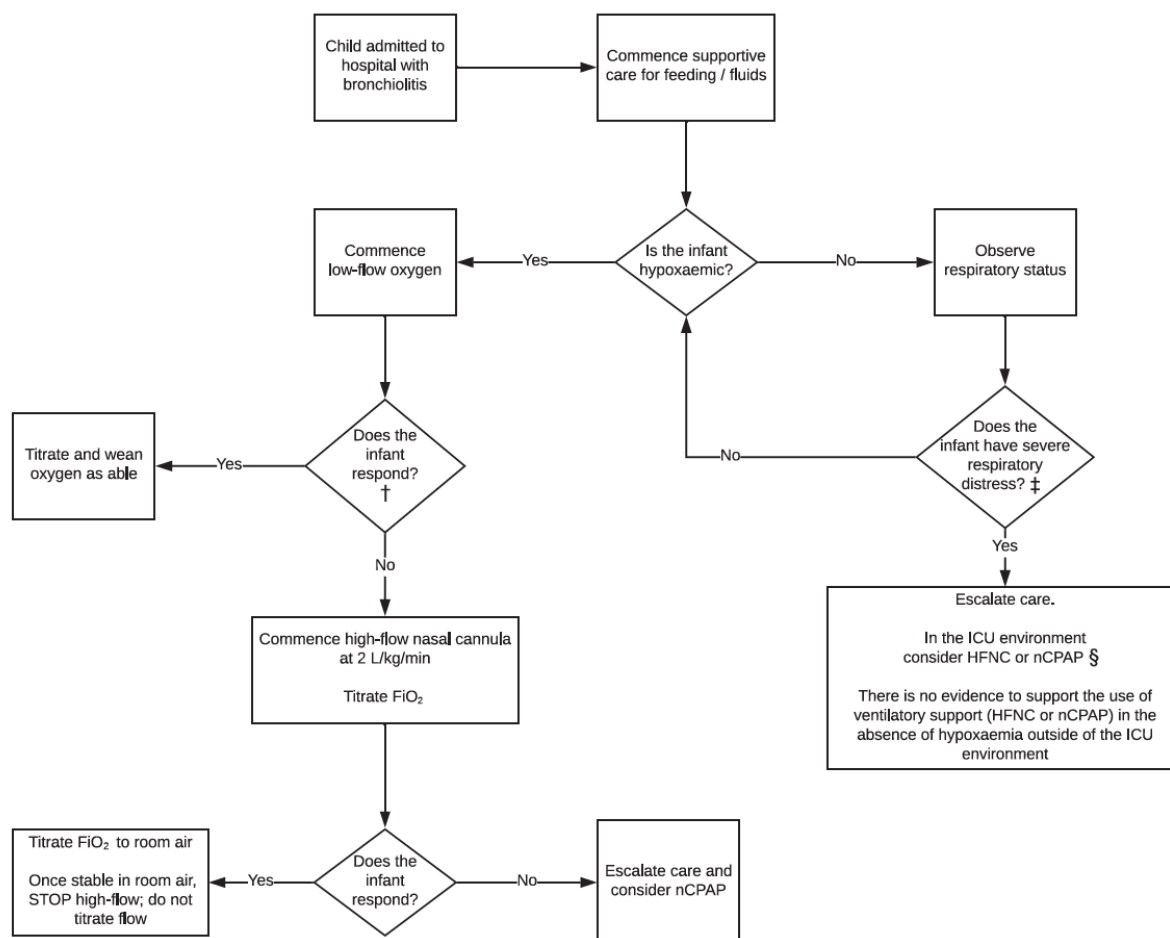
Citation	Campañā <i>et al.</i> [109]	Kepreotes <i>et al.</i> [107]	Franklin <i>et al.</i> [35]	Milesi <i>et al.</i> [108]
Number of participants	75	202	1472	142
Primary outcome	Mean RACS (based on RDAI)	Duration of oxygen therapy	Treatment failure that results in escalation of care	Treatment failure within 24 h of randomisation
Definition of 'treatment failure'	NA	Critically abnormal observations that fell within the red zone on an age-appropriate SPOC for heart rate (age dependent), respiratory rate (age dependent), SpO2 (<90%) or respiratory distress score (severe) while on maximum therapy, AND a clinical decision by the treating physician or medical delegate that the current treatment was insufficient to reverse the deterioration	Meeting ≥3 of 4 clinical criteria: (i) persistent or increased tachycardia; (ii) persistent or increased tachypnoea; (iii) hypoxemia (requiring FiO2 of ≥0.4 if on HFNC, or flow of >2 L/min if on nasal cannula, to maintain SpO2 ≥ 92–94%); (iv) medical review triggered by a hospital early-warning tool, AND escalation of care (increase in respiratory support or transfer to an ICU)	One of the following criteria: (i) a 1-point increase in mWCAS compared with baseline; (ii) RR rise >10 bpm compared with baseline, with RR >60 bpm; (iii) a 1-point increase in the EDIN score compared with baseline, with EDIN >4 despite the use of hydroxyzine (1 mg/kg); or (iv) more than two severe apnoea episodes per hour (i.e. requiring bag and mask ventilation), despite a loading dose of caffeine (20 mg/kg) after the first apnoea
Secondary outcomes	Comfort score, LOS, rate of ICU admission	Time from randomisation to treatment failure; treatment failure; serious adverse events; ICU admission; LOS; baseline-adjusted heart rate and respiratory rate at 4 and 24 h; delayed serious adverse events; subsequent medical care; parental	concern with therapy; and parental rating of their child's comfort, ability to feed and sleep	ICU admission, LOS, length of ICU stay, duration of oxygen therapy, intubation rate and adverse events Predictors of failure, success rate after crossover, intubation rate, skin lesions, LOS and serious adverse events (air leak syndrome and death)
Risk of bias	Open study, small sample size, no control arm of standard clinical care (both arms experimental), primary outcome measured at five different times points without adjustment for multiple comparisons, primary outcome a non-validated and not routinely used measure	Open study, single centre, few patients in the study had a true oxygen requirement (median (interquartile range) of SpO2 in both groups was 96% (93–98%), <25% of participants had an SpO2 of <94%)	Open study, primary outcome reported in manuscript different from primary outcome defined in protocol, primary outcome effect size different in sites with and without an ICU	Open study, primary outcome a composite end-point that includes the use of an asthma score

CPAP, continuous positive airway pressure; ED, emergency department; EDIN, neonatal pain and discomfort scale²¹; HFNC, high-flow nasal cannula; ICU, intensive care unit; LOS, length of stay; mWACS, modified Wood's clinical asthma score; NA, not applicable; PICU, paediatric intensive care unit; RACS, Respiratory Assessment Change Score; RCT, randomised controlled trial; RDAI, Respiratory Distress Assessment Instrument; RR, respiratory rate; SPOC, standard paediatric observation chart

Table 6-3 Results of randomised controlled trials of high flow nasal cannula in bronchiolitis

Citation	Campaña <i>et al.</i> [109]			Kepreotes <i>et al.</i> [107]			Franklin <i>et al.</i> [35]			Milesi <i>et al.</i> [108]		
	Nasal cannula Oxygen + epinephrine + 3% saline	HFNC + epinephrine + 0.9% saline	P value	Nasal cannula oxygen	HFNC	P value	Nasal cannula oxygen	HFNC	P value	Nasal CPAP	HFNC	P value
Duration of oxygen therapy, hours	NR	NR		24.0 (18.0–28.0)	20.0 (17.0–34.0)	0.61	44.9 ± 50.2†	43.4 ± 52.3†	0.61	NR	NR	
Hospital length of stay, days	4.5 (3–6)	5 (3–7)	0.80	2.0 (1.0–3.0)	2 (1–3)	0.99	2.94 ± 2.73	3.12 ± 2.43	0.19	NR	NR	
ICU transfer	5/42 (12)	5/32 (16)	0.50	12/101 (12)	14/101 (14)	0.41	65/733 (9)	87/739 (12)	0.08	NA	NA	
Treatment failure as defined in study protocol	NR	NR		33/101 (33)	14/101 (14)	0.002	115/733 (16)	53/739 (7)	<0.001	22/71 (31)	36/71 (51)	0.001
Intubation	NR	NR		NR	NR		4/733 (1)	8/739 (1)	0.39	3/71 (4)	5/71 (7)	0.72
Pneumothorax	NR	NR		0/101 (0)	0/101 (0)	NC	1/733 (1)	1/739 (1)	NC	0/71 (0)	0/71 (0)	NC

†Reported in days in original paper; values multiplied by 24 to enable comparison. Data are median (interquartile range), mean ± standard deviation, or n (percentage). HFNC, high flow nasal cannula; CPAP, continuous positive airway pressure; ICU, intensive care unit; NA, not applicable; NC, not calculated; NR, not reported

Figure 6-1 Suggested evidence-based approach to the use of high flow nasal cannula for bronchiolitis.

†Response to therapy (low flow oxygen or HFNC) is determined by a reduction in respiratory rate, heart rate, or paediatric early warning score within 4 h of commencing therapy. ‡If at any time the infant has severe respiratory distress, escalate care. Respiratory distress is a subjective finding. We define severe respiratory distress as a level where a senior clinician determines that escalation of care is required; transferring to emergency department/paediatric ward resuscitation area, high dependency unit or intensive care. Junior staff should escalate concerns regarding severe respiratory distress to senior colleagues. §For infants aged <6 months in intensive care, nasal continuous positive airways pressure (nCPAP) appears to be superior to HFNC.

ICU, intensive care unit; HFNC, high flow nasal cannula; nCPAP, nasal continuous positive airway pressure; FiO₂, fractional concentration of inspired oxygen

Implications

For the first time clinicians have some compelling evidence, that is consistent across more than one clinical trial for the use of high flow nasal cannula for the treatment of bronchiolitis. This evidence from randomised controlled trials and a health economic analysis does not support primary treatment with high flow nasal cannula therapy in the emergency department or inpatient ward setting. Given the ease with which care can be escalated from standard sub-nasal oxygen therapy to high flow nasal cannula, and that two thirds of infants are unlikely to require escalation past standard sub-nasal oxygen therapy, initial treatment for infants with bronchiolitis and hypoxemia should be sub-nasal oxygen therapy up to 2 litres per minute. High flow nasal cannula should be reserved for cases of deterioration after the use of standard sub-nasal oxygen therapy. If high flow nasal cannula is ineffective then transfer to a higher level of care and consideration of nasal Continuous Positive Airway Pressure is a reasonable next step.

The use of high flow nasal cannula for the work of breathing in the absence of hypoxaemia, or severe disease is not currently supported by the evidence and should only be undertaken in the context of clinical research trials.

PDFs of Papers for Chapter 6

Paper 6-1

O'Brien S; Craig S; Babl FE; Borland ML; Oakley E; Dalziel SR; Paediatric Research in Emergency Departments International Collaborative (PREDICT) Network, Australasia.

'Rational use of high-flow therapy in infants with bronchiolitis. What do the latest trials tell us?' A Paediatric Research in Emergency Departments International Collaborative perspective.

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The final approved manuscript submitted for publication is provided below

Rational use of high-flow oxygen for infants with bronchiolitis. What do the latest trials tell us? A PREDICT perspective.

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"One of the general methods to be adopted in the treatment of acute bronchiolitis is that these children should be nursed in warm moist air, with an adequate oxygen supply." ¹

- D Hubble and GR Osborn. BMJ, 1941

Bronchiolitis, caused by viral lower respiratory tract infections, is the most common reason for infants aged less than one year of age to be admitted to hospital. Various therapies have been studied over the years, with little demonstrable benefit. A multidisciplinary committee systematically reviewed the bronchiolitis literature in 2015 and using the robust Grading of Recommendations Assessment, Development and Evaluation (GRADE) and the National Health and Medical Research Council (NHMRC) methodologies developed the Australasian Bronchiolitis

Guideline² for the management of infants presenting to and admitted into Australasian hospitals with bronchiolitis. This guideline recommended against the use of beta-agonists, corticosteroids, adrenaline, antibiotics, antivirals and hypertonic saline in infants with bronchiolitis, with the pillars of recommended therapies being support of hydration and respiration.²

Over the last decade high flow nasal cannula (HFNC) therapy has been increasingly used for respiratory support in infants admitted to hospital with bronchiolitis. HFNC use was initially confined to the intensive care unit (ICU) setting but has now broadened to include emergency departments (EDs) and general paediatric wards. At the time of writing the Australasian Bronchiolitis Guideline,² studies on the use of HFNC in bronchiolitis were limited to low quality and observational evidence, mainly confined to the ICU setting, with very limited studies on the utility of HFNC use in EDs and inpatient wards. As such, Guideline recommendations regarding the use of HFNC for bronchiolitis were: (1) in non-hypoxic infants, its use should be confined to randomised controlled trials (RCTs), and (2) in hypoxic infants (oxygen saturations less than 92%) a low level recommendation (NHMRC: C, GRADE: Conditional) to consider HFNC. Subsequent to the 2015 systematic literature search for the Australasian Bronchiolitis Guidelines, a number of RCTs have published their results, in particular three major studies.³⁻⁵ This paper updates the systematic literature review regarding HFNC use in bronchiolitis used for the Australian Bronchiolitis Guideline, summarizes and critiques the new RCTs, and provides evidence-based recommendations for the use of HFNC to manage bronchiolitis in ED and ward settings.

What is high-flow nasal cannula therapy?

HFNC therapy is a form of respiratory support in which flow rates of humidified, heated gas are delivered into the nasal passages at higher rates of flow than that which is traditionally delivered via standard sub nasal oxygen therapy. HFNC therapy can be delivered at a rate of up to 2-3 L/kg/min, with a maximum of 60 L/min,⁶ whilst traditional sub nasal oxygen therapy is usually delivered up to a maximum of 2-3 L/min. With HFNC therapy flow rates can exceed peak inspiratory flow and efficiently deliver oxygen to the terminal airways, leading to improved gas exchange

and reduced work of breathing.^{7,8} Mechanisms of action are unclear, but are thought to involve the following: washout of nasopharyngeal dead space, reduced upper airway resistance, provision of an amount of continuous positive airway pressure (CPAP), while reducing the damage to the upper airway mucosa caused by other modes of gas delivery.⁹ As bronchiolitis is a disease of the small and medium airways, HFNC is an attractive modality to overcome hypoxia and potentially increased respiratory work associated with bronchiolitis.

Literature search

Using the same search strategy (Appendix 1 and 2) and methodology¹⁰ as the current Australasian Bronchiolitis Guideline² the following databases were searched: Ovid Medline, Ovid Embase, PubMed, Cinahl (EBSCO), Cochrane Library, Cochrane Database of Systematic Reviews (CDSR) and Cochrane Central Register of Controlled Trials (CENTRAL) for systematic reviews and RCTs from 1 Jan 2000 to 27 June 2018. Once studies were identified, one author (SOB) screened the title and abstracts of the articles identified for systematic reviews and RCTs relevant to HFNC use in infants with bronchiolitis. Copies of the identified articles were retrieved, then reviewed by three authors (SOB, SC, SD) for eligibility and data extracted. The search strategy identified 34 new articles since 2015, three RCTs and no systematic reviews, relevant to HFNC use in infants with bronchiolitis.

Evidence for high-flow nasal cannula therapy in bronchiolitis

The evidence base for the recommendations regarding HFNC in the Australasian Bronchiolitis Guideline was based upon a 2014 Cochrane systematic review,⁹ one evidence based guideline,¹¹ one RCT,¹² two prospective studies,^{13,14} four non-systematic reviews,¹⁵⁻¹⁸ and one retrospective cohort review.¹⁹ The single RCT identified was a small trial of HFNC vs. hypertonic saline in 75 infants with bronchiolitis from two Spanish hospitals. In our subsequent systematic literature search three further RCTs have been identified involving 1,816 participants. Thus, there have now been four RCTs, in 1,891 participants, of HFNC in infants with bronchiolitis: three of these studies involved infants treated in EDs and inpatient paediatric wards in Spain, Australia and New Zealand,^{3,5} and one study involved infants treated in paediatric ICUs in France⁴ (*Table 1*).

The three studies conducted outside of ICU differed in important areas. Franklin *et al.* enrolled patients with oxygen saturations < 92-94% (depending on individual institution cut offs for hypoxia) and used flow rates of 2 L/kg/min. Kepreotes *et al.* excluded infants with saturations < 90%, mainly enrolled infants with oxygen saturations > 94% and used flow rates of 1 L/kg/min. Campaña *et al.* used a non-validated clinical score (which includes oxygen saturations as one component) to define eligibility, but do not report the final oxygen saturation of the included participants, and used a calculation of tidal volume and respiratory rate to determine the flow rate of HFNC delivered, although the delivered flow at 6-8 L/min is likely approximately 1 L/kg/min. The primary outcomes and the definition of treatment failure itself also differed between the three studies. Franklin *et al.* used treatment failure as the primary outcome, defined as escalation of care and ≥ 3 out of 4 pre specified physiological endpoints. Kepreotes *et al.* used time on oxygen therapy as the primary outcome, and defined treatment failure as escalation of care and the presence of one of four slightly different physiological endpoints to those used by Franklin *et al.* Meanwhile, Campaña *et al.* used a non-validated, not routinely used, clinical score as their primary end-point and did not define or report treatment failure. Additional concerns regarding the quality of the RCT evidence include the small sample size, lack of a comparison arm of standard clinical care, and multiple comparisons in the Campaña *et al.* trial; single centre design in the Kepreotes *et al.* trial; and the reporting of the main primary outcome in the Franklin *et al.* study differing from the protocol (however, both outcomes clearly reported), with a differing effect size between sites with and without an ICU (Table 1).

The Milesi *et al.* trial enrolled infants with bronchiolitis requiring ICU admission⁴ comparing HFNC therapy and nasal continuous positive airway pressure (nCPAP) therapy. The authors used a validated asthma clinical score (which includes oxygen saturations as one component) to define infants for enrolment, using HFNC at 2 L/kg/min. Their primary outcome was treatment failure based on deterioration in the asthma clinical score, comfort score, respiration rate, or presence of two apnoeas in an hour (Table 1).

All RCTs evaluating HFNC are open studies. While this design feature is not avoidable due to the nature of the experimental therapies being compared, it introduces a potential for bias.

Results of the RCTs are presented in **Table 2**. Notably, both Franklin *et al.* and Kepreotes *et al.* (n=1,674) reported fewer treatment failures with HFNC than with standard care. However, these RCTs found no difference in ICU admission rates, intubation rates, duration of oxygen therapy, or hospital length of stay between those initially commenced on standard sub nasal oxygen therapy and those commenced on HFNC. In the ICU setting Milesi *et al.* (n=142) found that nCPAP was superior to HFNC with less treatment failures.⁴ All three RCTs allowed the use of rescue HFNC. In the 200 infants who failed standard sub nasal oxygen in the two non ICU RCTs, HFNC effectively rescued (no ICU admission) 61%. Similarly, in the ICU RCT, for the 22 infants who failed nCPAP, HFNC rescued (no need for further respiratory support) 82% (**Table 3**). HFNC appears safe to use with only one case of a pneumothorax being reported in total, in each of the combined HFNC and comparison arms for the three RCTs that reported this outcome (n=1,816).

Kepreotes *et al.*³ undertook a health economic analysis comparing initial treatment of standard sub nasal oxygen with rescue HFNC in ED and the ward environment. Although the cost differential for consumables favours standard therapy, once intention to treat was factored into the analysis and allowing for 19 fewer treatment failures in HFNC therapy, they demonstrated HFNC was more cost effective than standard sub nasal oxygen therapy.

Updated evidence tables using GRADE and NHMRC methodologies

The addition of the new RCT evidence has allowed for more definitive recommendations to be formulated using the GRADE and NHMRC approaches (**Table 4; Appendix 3 and 4**).

When should I use high-flow nasal cannula therapy for a child with bronchiolitis?

The usual clinical course for infants with bronchiolitis is worsening symptoms over 3 to 5 days followed by improvement over the next 7 to 10 days. Within this predictable clinical course there is further variation in clinical appearance with at times minute-by-minute clinical variation.¹¹ This variation can be attributed to discomfort, hunger, hypoxia or mucus plugging, and makes prediction of clinical projection problematic. Thus, there will be times when clinical observations breach “acceptable” physiologic parameters and lead to medical review, for the physiologic parameters to self-settle, while other breaches will reflect true clinical deterioration.

The definition of “treatment failure” in the two largest RCTs conducted in the ED and paediatric ward setting was based on escalation of care in response to clinical parameters; however, there were differences in this definition between studies, and differences in interpretation between sites with and without an ICU in Franklin *et al.*,⁵ reflecting a lack of objective consensus between clinicians on this topic. In these two RCTs all patients in the standard sub nasal oxygen therapy arm who failed therapy escalated initially to HFNC (with the exception of one infant in Kepreotes *et al.*³ who was changed to room air and did not need a change in treatment location). Both these studies utilised paediatric early warning scores as part of their definitions of failure. Without a better alternative, and until further evidence is available regarding the utility of paediatric early warning scores, utilising these widely used tools, and their components, appears appropriate to define failure. The two large non-ICU RCTs demonstrated a good “success” rate of standard sub nasal oxygen therapy of 67%³ to 77%⁵, and a relatively high ability of high flow to “rescue” those “failing” standard oxygen therapy (61%)^{3 5}.

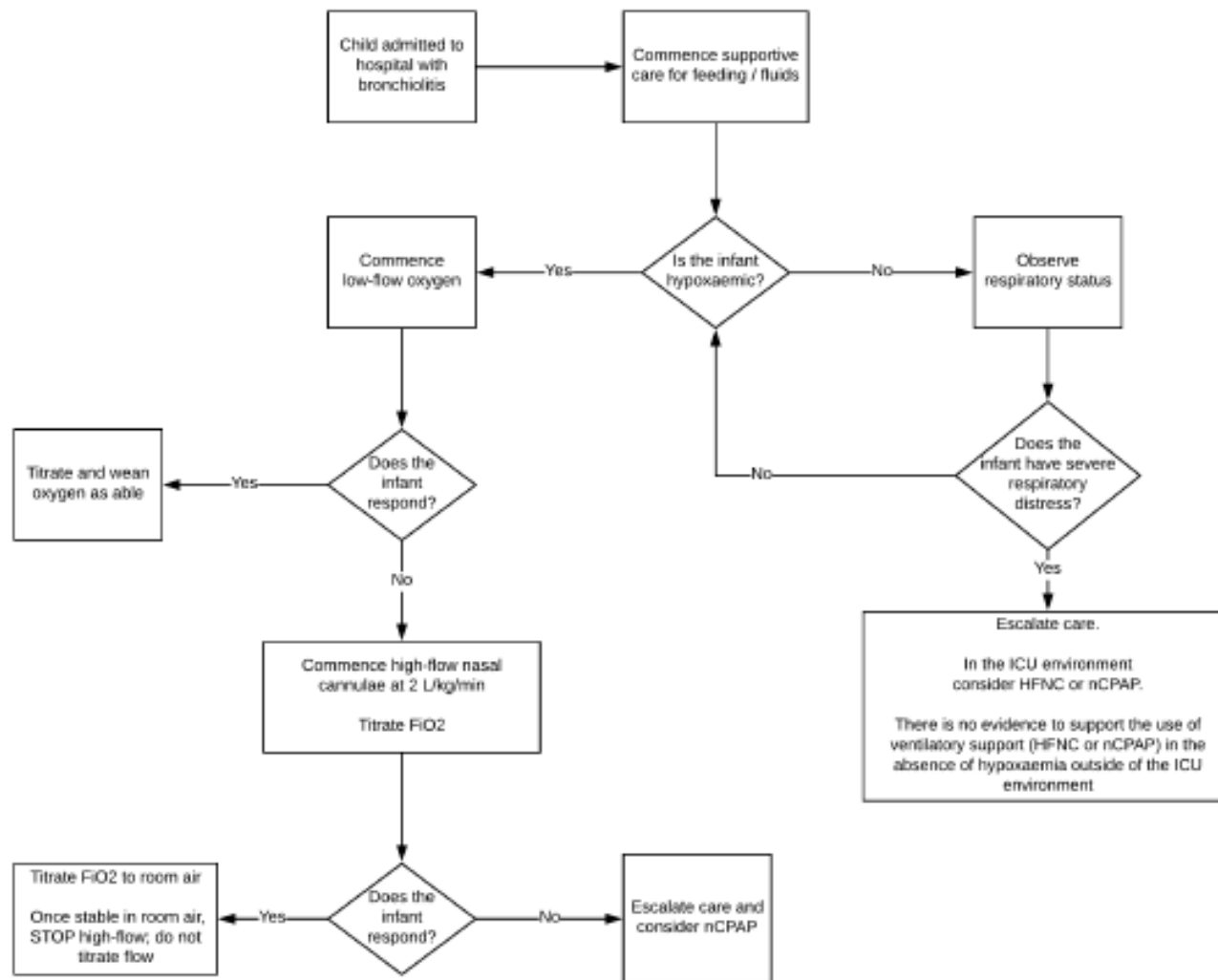
When infants with bronchiolitis are initiated on standard sub nasal oxygen therapy response to therapy is not going to be immediate. However, observational evidence supports that by 4 hours clinicians should see reduction in heart rate, respiratory rate and paediatric early warnings scores.²⁰

Clinical Bottom line

Given the ease with which care can be escalated to HFNC if needed, and that two thirds of infants in the largest studies did not require escalation past standard sub

nasal oxygen therapy, we believe that it remains logical to commence infants with bronchiolitis and hypoxaemia on sub nasal oxygen therapy up to 2 L/min to maintain oxygen saturations, and reserve HFNC for cases of deterioration (**Figure 1**). This approach appears to be the most cost effective. If HFNC is ineffective in the ward setting, then transfer to a higher level of care, and consideration of nCPAP appear to be reasonable next steps. The use of HFNC for work of breathing in the absence of hypoxaemia, and severe disease, is not currently supported by the evidence, and should only be considered in the context of an appropriate research trial.

Figure 1. Suggested evidence-based approach to the use of HFNC for bronchiolitis.



Notes:

- (1) Response to therapy (low flow oxygen or HFNC) is determined by a reduction in respiratory rate, heart rate, or paediatric early warning score within 4 hours of commencing therapy.
- (2) If at any time the infant has **severe respiratory distress**, escalate care. Respiratory distress is a subjective finding. We define severe respiratory distress as a level where a senior clinician determines that escalation of care is required; transferring to emergency department/paediatric ward resuscitation area, high dependency unit or intensive care. Junior staff should escalate concerns regarding severe respiratory distress to senior colleagues.
- (3) For infants aged <6 months in intensive care, nCPAP appears to be superior to HFNC.

F_iO_2 = Fractional concentration of inspired oxygen, nCPAP = nasal Continuous Positive Airways Pressure, HFNC = High-flow nasal cannulae.

Table 1. Summary of randomised controlled trials of the use of high-flow nasal cannula for bronchiolitis.

Citation	Campaña 2014	Kepreotes 2017	Franklin 2018	Milesi 2017
Setting	2 hospitals in Spain (paediatric ward).	1 hospital in Australia (ED and paediatric ward).	17 tertiary and regional hospitals in Australia and New Zealand (EDs and paediatric wards).	5 tertiary hospitals in France (PICUs).
Eligibility	Infants aged ≤ 6 months with moderate acute bronchiolitis (RDAI ≥ 4).	Infants aged < 24 months with a clinical diagnosis of bronchiolitis of moderate severity and required supplemental oxygen (at least one of the following: abnormal heart rate, abnormal respiratory rate, decreased SpO ₂ , or increased work of breathing).	Infants aged < 12 months with a clinical diagnosis of bronchiolitis and need for supplemental oxygen therapy to maintain SpO ₂ ≥ 92 or ≥ 94 (dependent on individual sites oxygen guidelines).	Infants aged ≤ 6 months with a clinical diagnosis of bronchiolitis and moderate to severe respiratory distress, defined by a mWCAS.
Key exclusion criteria	Those requiring immediate intubation and ventilation, prematurity, chronic lung disease, cystic fibrosis, congenital heart disease, neuromuscular disease, airway anomalies, and immunodeficiency.	Severe or life-threatening bronchiolitis, including SpO ₂ $< 90\%$ on room air.	Critically ill infants who had an immediate need for respiratory support and ICU admission, cyanotic heart disease, basal skull fracture, upper airway obstruction, craniofacial malformation, infants receiving home oxygen.	Indication for imminent intubation, cardiac or neuromuscular disease, and pneumothorax on chest radiograph.
Study design	Open-label RCT	Open-label RCT	Open-label RCT	Open-label RCT
HFNC intervention	6-8 L/min based on the following calculation: Tidal volume x respiratory rate $\times 9$, via Precision Flow (Vapotherm Inc. Stevensville, Maryland, US) or RT329 (Fisher and Paykel Healthcare, Auckland, New Zealand). AND nebulised epinephrine 1:1,000 0.5 mL/kg (maximum 3 mL) + 2 mL 0.9% saline every 4 hours.	1 L/kg/min (max 20 L/min) via Optiflow Junior nasal cannula and the MR850 humidifier (Fisher and Paykel Healthcare, Auckland, New Zealand) using a 1:1 air-oxygen ratio, resulting in a maximum FiO ₂ of 0.6.	2 L/kg/min (max 25 L/min) via Optiflow Junior cannula and the Airvo 2 high-flow system (Fisher and Paykel Healthcare, Auckland, New Zealand) with FiO ₂ titrated to maintain SpO ₂ .	2 L/kg/min via Optiflow (Fisher and Paykel, Villebon, France) with FiO ₂ titrated to maintain SpO ₂ at 94-97%.

Comparison group	Nasal cannula (max 3 L/min) AND nebulised epinephrine 1:1,000 0.5 mL/kg (maximum 3 mL) + 2 mL 3% saline every 4 hours.	Nasal cannula (max 2 L/min).	Nasal cannula (max 2 L/min).	Nasal CPAP (7 cm H ₂ O) via Infant Flow Ventilator (Electro Medical Equipment, Brighton, UK) or FlexiTrunk infant interface (Fisher and Paykel, Villebon, France).
Number of participants	75	202	1,472	142
Primary outcome	Mean RACS (based on RDAI).	Duration of oxygen therapy.	Treatment failure that results in escalation of care.	Treatment failure within 24 hours of randomisation.
Definition of "treatment failure"	N/A	Critically abnormal observations that fell within the red zone on an age-appropriate SPOC for heart rate (age dependent), respiratory rate (age dependent), SpO ₂ (<90%), or respiratory distress score (severe) while on maximum therapy, AND a clinical decision by the treating physician or medical delegate that the current treatment was insufficient to reverse the deterioration.	Meeting ≥3 of 4 clinical criteria: (1) persistent or increased tachycardia; (2) persistent or increased tachypnea; (3) hypoxemia (requiring FiO ₂ of ≥0.4 if on HFNC, or flow of >2 L/min if on nasal cannula, to maintain SpO ₂ ≥92-94%); (4) medical review triggered by a hospital early-warning tool, AND escalation of care (increase in respiratory support or transfer to an ICU).	One of the following criteria: (1) a 1-point increase in mWCAS compared with baseline; (2) RR rise >10 bpm compared with baseline, with RR >60 bpm; (3) a 1-point increase in the EDIN score compared with baseline, with EDIN >4 despite the use of hydroxyzine (1 mg/kg); or (4) more than two severe apnea episodes per hour (i.e., requiring bag and mask ventilation), despite a loading dose of caffeine (20 mg/kg) after the first apnea.
Secondary outcomes	Comfort score, LOS, rate of ICU admission.	Time from randomisation to treatment failure, treatment failure, serious adverse events, ICU admission, LOS, baseline-adjusted heart rate and respiratory rate at 4 hr and 24 hr, delayed serious adverse events, subsequent medical care, parental concern with therapy, and parental rating of their child's comfort, ability to feed, and sleep	ICU admission, LOS, length of ICU stay, duration of oxygen therapy, intubation rate, and adverse events.	Predictors of failure, success rate after crossover, intubation rate, skin lesions, LOS, and serious adverse events (air leak syndrome and death).

Risk of bias	Open study, small sample size, no control arm of standard clinical care (both arms experimental), primary outcome measured at five different times points without adjustment for multiple comparisons, primary outcome a non-validated and not routinely used measure.	Open study, single centre, few patients in the study had a true oxygen requirement (median (interquartile range) of SpO ₂ in both groups was 96% (93% to 98%), <25% of participants had an SpO ₂ of <94%).	Open study, primary outcome reported in manuscript different from primary outcome defined in protocol, primary outcome effect size different in sites with and without an ICU.	Open study, primary outcome a composite end-point that includes the use of an asthma score.
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ED = emergency department, PICU = paediatric intensive care unit, RDAI = Respiratory Distress Assessment Instrument, RCT = randomised controlled trial, SPOC = standard paediatric observation chart, LOS = length of stay, mWACS = modified Wood's clinical asthma score, EDIN – neonatal pain and discomfort scale,²¹ RACS = Respiratory Assessment Change Score, CPAP = Continuous Positive Airway Pressure.

Table 2. Results of randomised controlled trials of high-flow nasal cannula in bronchiolitis

Citation	Campaña 2014			Kepreotes 2017			Franklin 2018			Milesi 2017		
	Nasal cannula oxygen + epinephrine + 3% saline	HFNC + epinephrine + 0.9% saline	P value	Nasal cannula oxygen	HFNC	P value	Nasal cannula oxygen	HFNC	P value	Nasal CPAP	HFNC	P value
Duration of oxygen therapy, hours	NR	NR		24.0 (18.0–28.0)	20.0 (17.0–34.0)	0.61	44.9±50.2†	43.4±52.3†	0.61	NR	NR	
Hospital length of stay, days	4.5 (3–6)	5 (3–7)	0.80	2.0 (1.0–3.0)	2 (1–3)	0.99	2.94±2.73	3.12±2.43	0.19	NR	NR	
ICU transfer	5/42 (12%)	5/32 (16%)	0.50	12/101 (12%)	14/101 (14%)	0.41	65/733 (9%)	87/739 (12%)	0.08	N/A	N/A	
Treatment failure as defined in study protocol	NR	NR		33/101 (33%)	14/101 (14%)	0.0016	115/733 (16%)	53/739 (7%)	<0.001	22/71 (31%)	36/71 (51%)	0.0

Intubation	NR	NR		NR	NR		4/733 (1%)	8/739 (1%)	0.39	3/71 (4%)	5/71 (7%)	0.7
Pneumothorax	NR	NR		0/101 (0%)	0/101 (0%)	NC	1/733 (1%)	1/739 (1%)	NC	0/71 (0%)	0/71 (0%)	NC

Data are median (interquartile range), mean ± standard deviation, or n/N (percentage).

†Reported in days in original paper; values multiplied by 24 to enable comparison.

ICU = intensive care unit, HFNC = high flow nasal cannula, CPAP = continuous positive airway pressure, NR = not reported, NC = not calculated.

Table 3. Outcomes of “rescue therapy” with HFNC or nCPAP.

Citation	Treatment failure n/N (%)	Successful “rescue” n/N (%)	ICU transfer from treatment failure n/N (%)
Kepreotes 2017 – standard oxygen arm	33/101 (33%)	20/33 (61%)	12/32 (38%)
Franklin 2018 – standard oxygen arm*	167/733(23%)	102/167 (61%)	65/167 (39%)
Milesi 2017 – HFNC arm	36/71 (51%)	26/36 (72%)†	N/A
Milesi 2017 – nCPAP arm	22/71 (31%)	18/22 (82%)‡	N/A

Treatment failure not reported in Campaña 2014.

*Treatment failure in Franklin 2018 is given as those who received escalated care (n=167), and not the protocol definition of escalated care AND ≥ 3 of 4 clinical criteria.

† Those failing HFNC were “rescued” by nCPAP.

‡ Those failing nCPAP were “rescued” by HFNC.

ICU = intensive care unit, HFNC = high flow nasal cannula, nCPAP = nasal continuous positive airway pressure, NR = not reported.

Table 4. New GRADE and NHMRC recommendations regarding the use of high flow nasal cannula therapy in infants with bronchiolitis

Question: In infants hospitalised with bronchiolitis does the use of heated humidified high flow oxygen, or air, via nasal cannula improve clinically relevant end-points?		
Clinical recommendation: In hypoxic infants presenting to hospital heated humidified high flow oxygen, or air, via nasal cannula therapy should only be used as a rescue therapy when standard sub nasal oxygen has failed. Its use in children without hypoxia should be limited to the Randomised Controlled Trial setting only.	Strength of recommendation	
	NHMRC B	GRADE CONDITIONAL
Research recommendations: A large RCT comparing heated humidified high flow oxygen via nasal cannula at 2 L/kg/min with standard oxygen therapy, or no-oxygen therapy, in infants with respiratory distress without hypoxia outside of the PICU setting is required.		

RCT = randomised controlled trial, PICU = paediatric intensive care unit.

CHAPTER 7

Improving bronchiolitis care – Knowledge mobilisation and translation

Problem

As has been demonstrated in this thesis, in the management of bronchiolitis there is widespread use of medication and investigations for which there is international agreement of no clinical benefit.[2, 4, 67, 90] This is highlighted in **Chapter 5 (Paper 5-1)** where I have demonstrated high, and variable, use of medication for managing bronchiolitis, and high use of some investigations, which might actually be erroneously driving medication use. In **Chapter 4 (Paper 4-1)** I have demonstrated an increasing use of high flow nasal cannulae in managing bronchiolitis. This had developed without adequate evidence for indications for use or evidence for benefit in this patient population. The challenge that presents itself is to understand why existing evidence is not being put into practice, and to know what interventions in changing clinician practice might be effective in emergency departments. This is important as use of unproven interventions can lead to sub-optimal outcomes for patients, lead to unnecessary adverse events. and increase health-care costs.[39]

The emergency department setting presents unique challenges to the effective translation of knowledge into practice.[110] Time pressures to meet demand and large patient volumes contribute to a challenging environment, and are accompanied by substantial child and parent anxiety due to acute health concerns, and frequent staff rotations making system wide knowledge retention difficult. Paediatric emergency medicine has on top of this further challenges. Most children are cared for in mixed emergency departments that are focussed primarily on adult care and may not have specific paediatric emergency medicine expertise. A literature scan revealed that there is no repository, nor existing systematic reviews of knowledge translation studies and interventions in emergency medicine or paediatric emergency medicine. Knowledge translation requires appropriate levels of evidence, appropriate and agreed evidence summaries (that are accepted by the clinician end users) to mobilise the knowledge, an understanding of the barriers and drivers of existing care to allow education and behaviour change strategies to be appropriately targeted, and well designed and targeted implementation tools such as education material, process redesign, and clinician engagement.[39, 111]

The survey reported in **Chapter 1 (Paper 1-1)** highlighted multiple bronchiolitis clinical practice guidelines used across the Australia and New Zealand, with heterogeneity in some recommendations for clinical practice. Further, surveys of the paediatric emergency medicine workforce in Australia and New Zealand highlighted a desire for

unified guidelines and indicated bronchiolitis as a priority area.[29] This suggested that existing international bronchiolitis guidelines were not adequate to engage our emergency medicine clinicians, and that different means of mobilising this evidence was needed.

This left a series of problems to be overcome to improve the care of infants with bronchiolitis in Australian and New Zealand emergency departments. An effective means of mobilising existing evidence that would be accepted by our clinicians was needed. An understanding of what evidence there is for effective clinical practice improvement in emergency departments and whether there are gaps in this science of improvement implementation was needed.

After broad discussion within Australia and New Zealand and with international emergency medicine knowledge translation experts in Canada (Prof. T Klassen, Prof. D Johnson and Prof. J Grimshaw), it was decided that the way to mobilise the evidence was to develop a bi-national Australian and New Zealand bronchiolitis clinical practice guideline. Although high quality international clinical practice guidelines for children with bronchiolitis exist for practitioners in the United States[4] and the United Kingdom[2, 67] these guidelines are not completely applicable to the Australasian setting as they do not take into consideration the differing environmental factors, prevalence and variance of respiratory diseases, the indigenous population risk or the health service delivery mode.[112]

This bi-national Australian and New Zealand bronchiolitis clinical practice guideline was developed as a collaborative systematic review of the literature, producing recommendations for a series of management questions. The scope was for the management of infants with bronchiolitis, younger than one year of age, being managed in an emergency department or inpatient ward. A structured guideline development process was utilised. The guideline development process is outlined in **Paper S1 (Oakley senior Australian author)**. [35] A Guideline Advisory Group led the development process. A guideline development committee was convened to formalise the clinical questions, review the literature, and develop the recommendations for management. This committee was convened in accordance with the National Health and Medical Research Council (NHMRC) recommendations for guideline development.[113] This committee comprised of 22 individuals, including; eight General Paediatricians, one Paediatric Respiratory Physician, eight Paediatric Emergency Medicine Physicians, one Paediatric Intensive Care Physician, one Paediatric Nurse Practitioner, two Paediatric Nurses, and one Paediatric Emergency Nurse from a mixture of Australian and New Zealand metropolitan and nonmetropolitan centres, (including representatives from six of the eight Australian States and Territories). The Australian and New Zealand Paediatric Societies were also approached seeking their representation for this committee. This committee defined 33 questions. A systematic literature review was undertaken by the Guideline Advisory Group using the services of a

librarian skilled in database searches. The search strategy is outlined in the paper in

Appendix 1.[35]

The literature search identified 12,535 papers. After filtering of the literature by the Guideline Advisory Group the remaining 8,722 were assessed by the Guideline Development Committee. This committee was broken up into four groups each dealing with a specific and related group of questions. Papers were allocated to each question (and hence each group) when reviewed by the Guideline Advisory Group. Each group assessed the evidence and summarised it using both Grading of Recommendations Assessment, Development and Evaluation (GRADE) and NHMRC methodologies, [113, 114] with clinical recommendations agreed by the group. All evidence tables and clinical recommendations were presented to the entire Guideline Development Committee and agreement of recommendations was reached. The guideline and recommendations are available at "www.predict.org.au/download/Australasian-bronchiolitis-guideline.pdf." [66] and are presented in **Appendix 2.**[37] The recommendations broadly align with the American Academy of Paediatrics[4] evidence-based recommendations, undertaken a few years prior, and those from the National Institute for Health and Care Excellence[2] in the UK, undertaken at the same time as the Australasian guideline.

To translate this new guideline into clinical practice an understanding of what evidence there is for effective clinical practice improvement in emergency departments was still needed.

Question

What are the effective methods for implementing existing evidence into practice (changing practice) in paediatric emergency medicine?

Answer

What are the effective methods for implementing existing evidence into practice (changing practice) in paediatric emergency medicine?

Paper 7-1

Catherine L Wilson, David Johnson, and Ed Oakley on behalf of the Paediatric Research in Emergency Departments International Collaborative (PREDICT) network

Knowledge translation studies in paediatric emergency medicine: A systematic review of the literature.

Journal of Paediatrics and Child Health. 2016;52, 112–125

This paper represents a systematic review of published clinical knowledge translation studies undertaken in emergency departments and dealing with the care of children. The search strategy was created in conjunction with a library literature search expert and targeted research studies of any design related to knowledge translation in emergency departments and research involving paediatric populations. We allowed translational research involving children that included environments other than emergency departments, and emergency department translational research that involved both adult and paediatric populations. The search strategy followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[115] Papers published in English and within the ten year prior to the search date were included. The search and selection strategy is outlined in **Table 7-1**.

There were 1305 publications identified through the search strategy. After the removal of duplicates, and screening 26 papers were identified. These papers were individually reviewed for inclusion by two authors and 15 papers were included in the analysis: four cluster controlled trials,[116-119] two patient-level randomised controlled trials[120, 121] two interrupted time series, one descriptive study[122] and six before and after intervention studies.[123-128] The included papers are described in detail in **Table 7-2**, including patient populations, study location, knowledge translation aims and tools used, study design, knowledge translation interventions, outcome measures and findings. The knowledge translation interventions used were aimed at health care professionals. They identified clinician engagement and involvement in formulating the methods and tools as vital. They included education regarding both the need for the change and tools, how to use the tools, and the changed behaviour or practice.[116-128] Interventional studies included those aiming at stopping an existing practice.[116, 117, 125, 128]

Table 7-1 Search and selection strategy

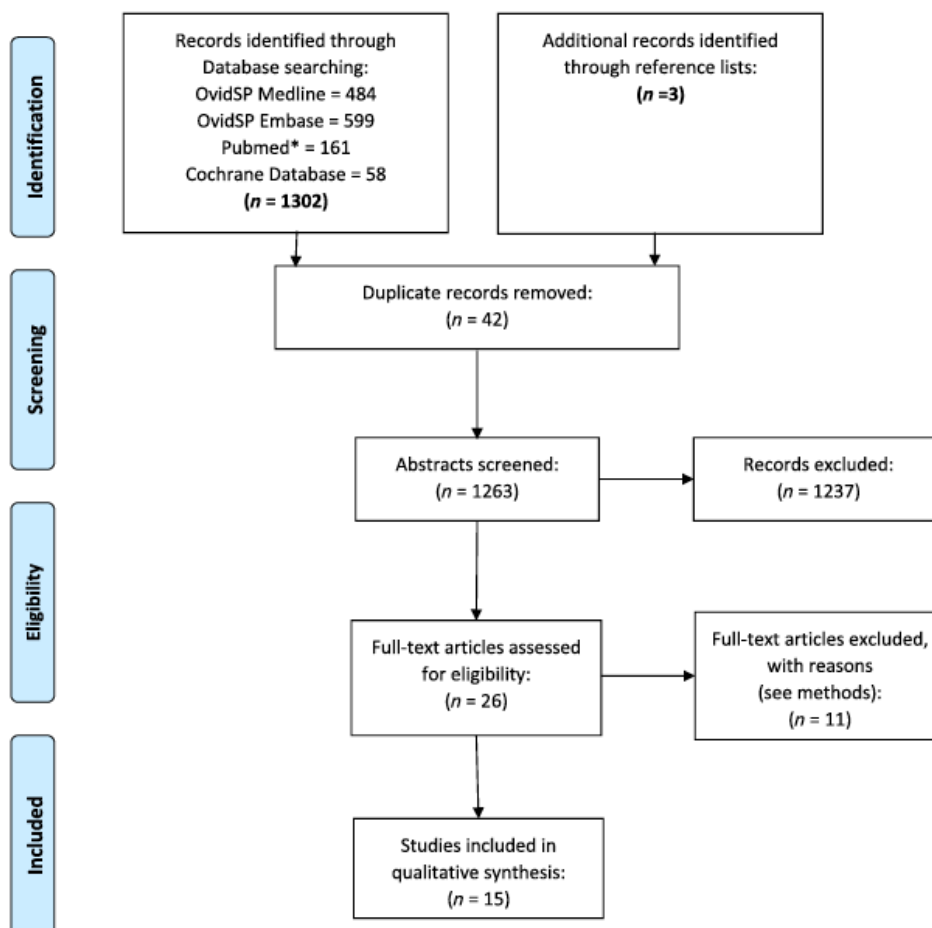
Data sources	Medline (OvidSP); EMBASE (OvidSP); PubMed; The Cochrane Database
Thesaurus terms	Broad searches were performed using the relevant thesaurus terms: (emergency care OR emergency medicine OR emergency service, hospital OR emergency ward), and (information dissemination OR knowledge OR translational medical research OR 'diffusion of innovation' OR professional knowledge OR translational research OR evidence based medicine OR evidence based emergency medicine OR randomized controlled trial OR randomised controlled trial (topic)) AND pediatrics
Keywords	Emergency AND (knowledge translation OR dissemination OR innovation) AND (child* OR infant* OR adolesc* OR neonat* OR pediatric* OR paediatric*)
Search dates	1 January 2004 to 19 January 2015
Other information	Reference lists of included studies were searched to identify additional relevant papers (i.e. snowballing references)
Sources checked	Studies published in English language in peer reviewed journals
Inclusion criteria	Studies undertaken in an emergency department setting (but not limited to the emergency department ie other departments could be involved) Studies which described knowledge translation interventions adequately The knowledge translation interventions were mostly professional interventions targeted to staff rather than patients Studies included paediatrics but were not limited to paediatric populations
Exclusion criteria	Studies which did not describe knowledge translation interventions sufficiently Studies carried out in settings that did not included the emergency department

Some studies identified the clinicians' reasons for using or not using the intervention tools. One study[121] implemented a computer system designed to support clinical decision making for the ordering of diagnostic blood tests in febrile children, and reported only 49% compliance with the advice supplied. Staff reported non-compliance due to difficulty in agreeing to order blood tests on children who appeared perfectly well. Two trials by Stiell[116, 117] provide unique insight into the complexities of implementing clinical guidelines into an emergency department. The trials designed to implement imaging guidelines to assist clinician decision making for the use of computed tomography (CT) scans in adults and teenagers with head injury and with cervical spine injury. These two studies used identical implementation methods yet the ability to change CT head imaging was greatly lower than the ability to reduce CT use in cervical spine injuries. To understand this difference the authors went back to the clinicians to understand the barriers to reducing

head CT scans. The barriers included underlying clinician beliefs about the need for CT scans and the local practices that allowed faster discharge of a patient if a CT scan was performed. Two studies looked retrospectively at the effect of guideline implementation[129, 130] Johnson[129] found no change in use of interventions known to be of no benefit over a 4 year period post the publication of the American Academy of Pediatrics Bronchiolitis guideline. Knapp[130] looked at implementation of two guidelines, one by simple publishing of a National guideline (for croup), and one by a planned implementation approach to dissemination (for asthma), and found no difference in the degree of practice change.

In general, the description of the knowledge translation interventions was highly variable, and often inadequate to allow the implementation to be accurately reproduced at other sites. The reported outcomes tended to concentrate on the clinical interventions and practice change rather than the means used and effectiveness of different means to produce the practice change.

Figure 7-2 Preferred reporting items for systematic reviews and meta-analyses (PRISMA) information flow diagram for the systematic review.



*PubMed search only completed for 2014–2015 to obtain Epubs

Table 7-2 Summary of Studies Selected for Review

Author and year	Knowledge translation Aims and tools	Location and setting	Design, study period and sample	Knowledge translation Interventions	Outcome measures	Findings
Ambroggio[124] 2013	Aim: Improve compliance with the community acquired pneumonia in children national antibiotic prescribing guideline Tool: Local guideline based on National antibiotic prescribing guideline for community acquired pneumonia	Cincinnati, USA: Single tertiary children's hospital; ED and hospital medical (HM) department.	Single site before and after study; 6 months before data (n = 67) compared with 9 months post data (n = 150). Quality improvement, plan-do-study-act methodology, with ongoing interventions. Sample: (n = 217) patients aged 3 months to 19 years.	Organisational: Multidisciplinary team designed the interventions using a process map; Professional: Interactive seminar about guidelines; Summary of guidelines emailed; reminder prescribing card; default link to guideline in electronic medical record; weekly audit of eligible patients for success or failure.	Proportion of eligible patients receiving appropriate first line antibiotic therapy; and length of stay (LOS)	ED had an 82% absolute improvement in correct prescribing (0 vs. 82%); HM department had a 60% absolute improvement (30 vs. 90%). Ongoing interventions improved rates to 100% after 3 months in both locations. Pre intervention median LOS <1 day, IQR: 0–1 day, post intervention median LOS: 1 day; IQR: 0–2 days < .001.
Bernstein[122] 2009	Aim to implement a high risk drug and alcohol screening intervention in emergency departments across the state using 'SBIRT', Screening, brief intervention and referral to treatment.	Massachusetts, USA: Seven hospital EDs in urban, suburban and rural community settings.	Descriptive study; 18 months data collection prospectively over implementation period with 15,383 patients screened across seven sites. Qualitative semi-structured interviews of	Organisational: 12 health promotion advocates (HPA) were employed in seven EDs to do screening of at risk patients; ED and HPA staff identified at risk groups to be screened. Professional: Peer educators at each site	RE-AIM (Reach, effectiveness, adoption, implementation and maintenance). Quantitative: total patients screened; % positive; % negative; % referred to other	SBIRT required a team focused model of delivery customised to each ED. Overcoming staff attitudes to SBIRT was best addressed by

Author and year	Knowledge translation Aims and tools	Location and setting	Design, study period and sample	Knowledge translation Interventions	Outcome measures	Findings
	Tools to assess the intervention in the ED were based on the RE-AIM theory (Reach, effectiveness, adoption, implementation and maintenance).		staff (n = 24) to determine reach and success. Data from this state-based study was compared with Federal data; sample age was not stated, assumed to include adolescents	delivered education and training to HPAs which included quarterly workshops and monthly monitoring of performance for accuracy.	resources. Qualitative: identification of barriers, challenges and successes to the intervention.	local staff champions who intervened when problems arose. The intervention relies on continued funding of the staff to implement SBIRT at each site.
Boutis[128] 2013	Aim to reduce use of radiography in management of ankle injuries in children. Tool:- Clinical decision support rule - 'The Low Risk Ankle Rule' and computerised decision support system (CDSS) to support the rule.	Ontario, Canada: Two urban children's hospitals, two urban general hospitals, two community-based suburban hospitals; all in ED.	Multisite controlled before and after study; 18-month study period with three consecutive 26 week phases at the intervention sites (one 18 month period for Controls); prospective data collection. Sample: (n = 2151); patients aged 3–16 years.	Professional: Intervention sites only: Phase 1 – internal control phase that is clinical data collection re ankle injury management and assessment of physician satisfaction. Phase 2 – physician teaching sessions; pocket cards and posters of the rule; flagging of charts for ankle injuries; physician champions; use of CDSS; training of physicians in management of low risk ankle injury; Phase 3 – use of CDSS only.	Proportion of eligible children who received ankle radiography; proportion of children with missed significant fractures; proportion of children who did not have radiology in ED but did so subsequently; length of stay. Patient satisfaction and ED physician satisfaction were assessed. All were compared with the control group.	In comparison with control group, there was an absolute reduction of 21.9% in radiography between Phase 1 and 2 and 23.9% between Phases 2–3. No increase in clinically important fractures missed. Use of the rule did not affect patient or physician satisfaction or length of stay.
Cunningham[118] 2008	Aim: Assess effectiveness of implementing an integrated care	Edinburgh, Scotland: Single, tertiary paediatric hospital; ED and hospital	Cluster randomised controlled trial; 26-week	Organisational: Multidisciplinary team	Difference in length of hospital stay; rate of	Physiological recovery or length of stay did not

Author and year	Knowledge translation Aims and tools	Location and setting	Design, study period and sample	Knowledge translation Interventions	Outcome measures	Findings
	Pathway (ICP) on the management of asthma Tool: Local Integrated Care Pathway based on the United Kingdom asthma management guidelines.	respiratory department.	trial of 7-day trial periods randomly assigned to either standard care or care delivered using the ICP in blocks of 8 weeks. Sample: (n = 298); patients aged 2–16 years.	developed an integrated care pathway (ICP) for acute asthma/wheeze which involved development of a single document for use by whole team incorporating guidelines and reducing variation. Professional: Tutorials were given in the use of these tools and underpinning knowledge.	asthma improvement in physiological variables, and bronchodilator requirements; bronchodilator and prednisolone use. Discharge process: time to complete discharge criteria; provision of education to family; parent questionnaire to determine receipt and understanding of discharge information. Proportion of prescribing errors.	improve. There was an absolute reduction of 30% in prescribing errors and an absolute increase of 39% (33% vs 72%) in prednisolone prescribing. Patient education and discharge planning improved by 48% (41% vs 89%).
Dexheimer[120] 2014	Aim: Implement evidence based guidelines for the management of asthma: Tool: Integrated computerised asthma detection and management system in the ED.	Cincinnati, USA: Single tertiary paediatric hospital; ED.	Randomised controlled trial to intervention or standard care (paper based) over a 5-month period Sample: (n = 788); patients aged 2–18 years.	Organisational: Multidisciplinary team refined evidence based practice guideline, care flow sheet and severity based order sheets which informed the computerised and paper based systems 2-years prior. Use of the computerised asthma management system was used to detect patients with	Time from ED triage to disposition decision; adherence to guidelines including asthma education ordered; asthma scoring performed; ED length of stay; hospital admissions. Survey to evaluate staff awareness of study.	The absolute difference between the two groups median time to disposition decision was 5 min, which was not significant, P = 0.362. ED median length of stay was 15 min longer in the

Author and year	Knowledge translation Aims and tools	Location and setting	Design, study period and sample	Knowledge translation Interventions	Outcome measures	Findings
				asthma exacerbation and used computer driven work flow, tracking asthma scores at triage and onwards and delivering re-scoring reminders and relevant order sets. Professional: Physician, nurse and respiratory therapist education sessions at meetings, in two months prior; divisional email restudy.		intervention group, but this was not significant. Admission rates were also very similar. There was no difference between the two groups in any of the guideline adherence measures.
Diaz[123] 2004	Aim: 1. Implement evidence based guideline for diagnosis and management of pharyngitis. 2. Reduce antibiotic prescription. Tool: Locally created clinical practice guideline for pharyngitis	Akron, USA: Single tertiary paediatric hospital; ED.	Single site before and after study; retrospective medical record review of pre-intervention and post-intervention randomly selected cohorts, over a 4-month period, using standardised data collection. Sample: (n = 443); patients aged 1.5–19 years.	Professional: Development of a pharyngitis pathway by ED physicians in form of a document which contains reminders re guidelines. Organisational: Triage nurse adds the pathway document to appropriate patient's notes.	Compliance with guideline as indicated by appropriate diagnosis and antibiotic prescribing.	An absolute improvement in diagnosis procedure and appropriate antibiotic treatment of 47% (44% to 91%).
Doherty[119] 2006	Aim: To assess if an evidence-based approach to implementation	New South Wales, Australia: Eight rural district hospitals; EDs.	Cluster randomised controlled study; four matched pairs of rural	At intervention sites only Organisational:	Changes in six targeted areas: asthma severity;	An absolute improvement of 26% (36%

Author and year	Knowledge translation Aims and tools	Location and setting	Design, study period and sample	Knowledge translation Interventions	Outcome measures	Findings
	of an asthma guideline improved compliance with evidence-based care Tool: Evidence based approach to implementing an established asthma guideline		hospitals. Retrospective medical record review of pre-intervention (n = 52) and post-intervention (n = 47) cohorts, over 7-month periods, using standardised data collection. Sample: (n = 187); patients aged 14 + years.	Identification of practice gaps; identification of barriers to change in ED at each hospital prior to implementing the EBI tool. Professional: Guideline reformatting to useable format – incorporated in medical record; reminders with site visits twice during study period; education sessions for medical and nursing staff; audit and feedback twice per 7 months; study coordinator/Knowledge broker led change.	use of spirometry; use of ipratropium; use of corticosteroids; use of antibiotic; documentation of short- term asthma management plan.	vs. 62%) in the adherence to the aggregate of all six indicators.
Fong[125] 2008	Aim: Improve appropriate use of computerised tomography (CT) scans in the management of head injury. Tool: A locally developed head injury guideline based on the Canadian CT Head Rule (CCTHR)	Melbourne, Australia: Single tertiary hospital; mixed ED.	Single site before and after study; comparison of pre-intervention period (n = 311) over 5 months, and post-intervention period (n = 326) over 7 months, using standardised data collection from medical records. Retrospective pre-intervention data	Professional: Development of a local guideline with a focus group; training of medical staff in prospective application of the local head injury rule.	CT head ordering rates in head injury; appropriateness of ordering CT scan. Comparison of the detection of clinically significant head injury abnormalities on CT (local rule vs. CCTHR.).	An absolute increase of 27% (32% vs. 59%) in the ordering of Head CT. No abnormalities were missed versus four that would have been missed using CCTHR alone.

Author and year	Knowledge translation Aims and tools	Location and setting	Design, study period and sample	Knowledge translation Interventions	Outcome measures	Findings
Johnson[129] 2013	Aim: To assess change in bronchiolitis management after publication of American Academy of Paediatrics Guideline on management of bronchiolitis Tools: non-intervention study	U.S.A.: nationally representative group of EDs across the country.	collection; prospective data-collected postintervention. Patient follow-up questionnaire used. Sample: (n=637); patients >16years. Interrupted time series; retrospective review of a subset of survey data from the US National Hospital ambulatory Medical Care Survey during 2001–2009, pre (5 years) and post (4 years) comparison of data in relation to introduction of a guideline in November 2006. Sample: (n=678); patients aged 0–2 yrs.	National: Publication of national guideline in November 2006.	Use of bronchodilators, steroids, antibiotics and chest X-ray for bronchiolitis.	No change in use of nonrecommended therapies (bronchodilators, steroids, antibiotics). Absolute reduction of 19.7% (65.3% vs. 48.6%). for CXR.
Knapp[130] 2014	Aim: To compare knowledge transfer in the emergency department management of	U.S.A.: nationally representative group of EDs across the country.	Interrupted time series; retrospective cross-sectional study of a subset of survey data from the US National	National: Publication and dissemination of asthma guidelines in 1991 with expert panel review and update in 1997, 2001 and	Use of corticosteroids in for asthma or croup, administered in the ED.	From 1995 to 2009: absolute increase of 23% in use of corticosteroids for management of asthma. Absolute

Author and year	Knowledge translation Aims and tools	Location and setting	Design, study period and sample	Knowledge translation Interventions	Outcome measures	Findings
	paediatric asthma and croup by measuring trends in corticosteroid use. Tools: national paediatric asthma guidelines versus only passive diffusion for croup.		Hospital ambulatory Medical Care Survey during 1995–2009. Comparison of trends in corticosteroid usage between the two groups over 15-year period. Asthma sample: (n = 1829); patients aged 2–18 years. Croup Sample: (n = 1075); patients aged 6 months–6 years.	2006.		increase of 24% in use of corticosteroids for management of croup. There was no difference in the trend between the two groups, or interaction term was 0.99.
Pannifex[127] 2013	Aim: To develop and implement standardised approach to procedural sedation for children in the emergency department to improve safety. Tools: development of a training and documentation tool; And Clinical governance self-assessment checklist.	Victoria, Australia: 10 urban hospitals and four regional/ rural hospitals; EDs.	Multi-site uncontrolled before and after study; comparison of baseline data with 6-months postintervention qualitative data review per ED department. Convenience sample: (n = 215); patients (age was not stated but conducted within paediatric patients)	Organisational: Development of a clinical governance checklist; review and update of training materials; development of information sheets, risk assessment and documentation forms; materials about family centred approach; development of audit tool. Professional: Workshop and training of staff.	Comparison of clinical governance; number of staff trained during intervention period; compliance with and documentation of risk assessment procedures; qualitative feedback from staff on their satisfaction with the intervention and perception of impacts.	An average 33% (54 vs. 87%) absolute improvement with compliance with all governance measures. Staff feedback very positive, increase teamwork reported.
Roukema[121] 2008	Aim: Assess compliance	Rotterdam, The Netherlands: single	Randomised controlled	Organisational:	Compliance with the	Compliance with using

Author and year	Knowledge translation Aims and tools	Location and setting	Design, study period and sample	Knowledge translation Interventions	Outcome measures	Findings
	with clinical decision support system recommendations; time spent in ED and test ordering. Tool: clinical decision support system (CDSS) developed locally for risk assessment of febrile young children.	tertiary paediatric ED.	trial; enrolments were over a 28-month period. Sample: (n = 164); patients aged 1–36 months.	Implement CDSS – based upon prediction rules to identify high risk patients – then randomised the high risk patients to immediate diagnostic tests or clinician review and ordering of tests (control group); Professional: Training for nursing staff in use of CDSS.	CDSS in registration of febrile children and recommendation for testing. Time at the ED; diagnostic tests in high risk group in comparison with control group.	CDSS 49%. Compliance with CDSS randomisation 82%. There was an absolute increase of 38% (44% vs 82%) of using CDSS to order blood tests in high risk patients. There was an absolute increase of 15 min (123 vs 138 min) in time in the ED.
Stiell[116] 2009	Aim: To evaluate the Effectiveness of an active strategy of implementing the Canadian C-Spine Rule for appropriate ordering of cervical spine imaging; test the impact of the rule on use of imaging. Tools: the Canadian Cspine rule and active implementation strategies at intervention sites.	Canada: 12 hospitals, (six teaching and six community sites); EDs.	Cluster randomised controlled study; matched pairs of 12 hospital sites. Data captured during 12 months preintervention And 12 months postintervention. Sample: (n = 11 824); patients aged 16–100 years.	Professional: Discussion of rule with physician team and agreement on use of rule; education including pocket cards, posters; 1 hour teaching sessions; reminders of the rule when imaging requested.	Proportion of eligible patients referred for imaging of C-spine; number of clinically important injuries not identified on initial ED visit; adverse outcomes. Performance of the C spine rule at the intervention sites; accuracy of interpretation of and compliance with the rule.	An absolute reduction of 8.4% (61.7% vs. 53.3%) of patients referred for imaging in the intervention group, compared with an absolute increase of 7.1% (52.8% vs. 58.9%) at control sites. No fractures were missed.
Stiell[117] 2010	Aim: To evaluate the effectiveness and safety of an active	Ontario, Alberta and British Columbia, Canada: 12 hospitals (six teaching sites	Cluster randomised controlled study; matched pairs of 12 hospital sites. Data captured during	Organisational: Assessed barriers prior to intervention and tailored interventions	Proportion of eligible patients referred for CT head scan; number of	At intervention sites an absolute increase of 13.3% (62.8% vs. 76.2%) in

Author and year	Knowledge translation Aims and tools	Location and setting	Design, study period and sample	Knowledge translation Interventions	Outcome measures	Findings
	implementation strategy for the Canadian CT Head Rule. (Aim to reduce use of CT Imaging) Tools: The Canadian CT Head Rule. An active implementation strategy.	and six community sites); EDs.	12 months preintervention (n = 1049) and 12-months postintervention (n = 1531). Qualitative interviews of staff; Sample: (n = 2580); patients aged 16–99 years.	accordingly at sites; adherence to the rule was checked via the radiology dept. review of requests. Professional: Education sessions were held for physicians and information distributed; Use of pocket reminder cards and posters; real time reminder when requisitioning CT scans	clinically important brain injuries not identified; staff perception of using rule (and barriers and facilitators to using the rule); sensitivity and specificity of the rule (secondary outcome).	rates of CT imaging. At control sites an absolute increase of 6.7% (67.5% vs. 74.1%). Sensitivity of the Canadian head CT rule was 100%. Unforeseen barriers to effective implementation were identified in post study feedback.
To[126] 2010	Aim: To examine whether use of a paediatric acute asthma management guideline reminder card improves asthma management. Tools: A local guideline based on Canadian asthma consensus guideline. A reminder card with guideline information.	Toronto, Canada: Single tertiary paediatric hospital; ED.	Single centre before and after study; retrospective chart review of ED visits over 12 months prior to the intervention were compared with 154 prospective ED visits over 12 months following the intervention. Sample: (n = 432); patients aged < 7 years.	Professional: Development of acute asthma management guideline by local team at hospital; formatted in pocket sized reminder card; disseminated to multidisciplinary team by presentations and email, plus provision of reminder card.	Administration of systemic corticosteroids and bronchodilators during ED stay; delivery of asthma education to patient in ED; conduct of discharge planning.	An absolute increase of 23.7% in the use of corticosteroids (60.1%–83.8%). An absolute increase of 20.7% (50.7%–71.4%) in oxygen saturation reassessment. For discharge planning, there was an absolute increase of 8.6% (63.7% vs 2.3%) in a combined measure of discharge planning.

Implications

Knowledge translation in paediatric emergency medicine is a new field. It is only after realisation that producing evidence alone is not enough to change practice and that up to one quarter of patients receive care that is known to be of no benefit that research into how to effectively implement guidelines, and change behaviour has started.[40, 49, 131-133] Consequently the search in this systematic review produces only 26 trials for inclusion with a wide variation in study type and interventions used. The studies identified a number of actions that were generally thought to be beneficial – engaging clinician end users in discussion and implementation tool development; and development and modification of tools before implementation. Some but not all trials used education, feedback and audit to assist. The trials in general did not report detail on the way these interventions were implemented just that they were used. This lack of reporting on the knowledge translation interventions limits our capacity to understand how we should approach practice change, and has been identified in both the intensive care literature[134] and in the translation literature in general[135, 136]. This review highlighted success of the intervention in six of the twenty-six studies.[116, 119, 123, 124, 126] In the unsuccessful studies the level of reporting does not allow an understanding of how poor the performance was or what inhibited the desired change. The studies by Stiell[116, 117] give some insight to the importance of understanding clinician drivers of behaviour in clinical decision making, and that interventions need to specifically address these behaviours if practice change is to be successful. Studies by Johnson[129] and Knapp[130] highlight the inability of solely producing guidelines to produce material improvements in patient care.

This broader literature of knowledge translation reflects that audit and feedback has been extensively researched, is agreed to be beneficial, and should be incorporated wherever possible into translation interventions.[136] Evidence for other successful interventions in paediatric emergency medicine is sparse. The study designs are mostly before and after intervention designs. It is widely acknowledged that this study design is likely to overestimate the degree of effectiveness of interventions.[39, 137] The majority of these studies were also single-centre limiting the generalisability to other centres. Of the studies that used more rigorous designs – such as cluster controlled studies – many were poorly designed and used incorrect methods making interpretation of outcomes difficult. It remains unclear if there is a series of

knowledge translation interventions that will be effective (or able to be adapted) across regions or will translate between different professional, patient or disease populations.

Evidence for effective methods to translate knowledge into practice in paediatric emergency medicine is limited. If this remains unchanged our ability to improve outcomes for children in emergency departments will also be limited. Well designed, conducted and reported studies on knowledge translation in paediatric emergency medicine are needed. These studies should concentrate on describing interventions, measuring the effectiveness of different interventions and reporting these outcomes along with general clinical practice change.

As it is now accepted that simply providing a guideline to clinicians is insufficient to significantly change practice,[39, 118] an Australian and New Zealand cluster randomised trial of implementation of the developed clinical practice guideline (**Appendix 3, Oakley senior Australian author**) was designed (**Appendix 4, Oakley senior Australian author**) and implemented. This trial was designed to determine if tailored, theory informed knowledge translation interventions are effective in improving evidence-based practice in Australasian paediatric acute care settings. The aim of the study is to test the uptake of five evidence-based recommendations from the Australasian Bronchiolitis Guideline (**Appendix 3, Oakley senior Australian author**): that infants under one year of age with bronchiolitis who present to hospital receive none of the following: 1. Salbutamol; 2. Antibiotics; 3. Glucocorticoids; 4. Adrenaline; 5. A chest x-ray. The trial was designed to report the effectiveness of the tailored interventions on the delivery of the clinical care.

The interventions were designed after a series of qualitative interviews were conducted with clinicians of varying seniority at the included hospitals. These interviews identified key drivers and barriers to the desired care. Interventions were designed to address these issues using the Theoretical Domains Framework as the informing theory.[138, 139]. Twenty-six hospitals were included in the study (two more than the sample size required to allow for site drop out). The sites were randomised to intervention and control 1:1. Intervention sites received the guideline, had education on the use and modification of the interventional tools, and had a defined contact within the study group to advise as needed. Control sites received the guideline only. Data was recorded retrospectively for the use of the outcome clinical management interventions. Intervention sites audited twenty cases each month and supplies that information. This was then converted to feedback tables identifying the sites performance compared with other de-identified sites. Control sites did not review their

performance during the intervention period. Control sites received the interventions, and education on their use after completion of the study. **(Appendix 4, Oakley senior Australian author)** This study has been completed and is in final analysis.

PDFs of Papers for Chapter 7

Paper 7-1

Catherine L Wilson, David Johnson, and Ed Oakley on behalf of the Paediatric Research in Emergency Departments International Collaborative (PREDICT) network

Knowledge translation studies in paediatric emergency medicine: A systematic review of the literature.

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Abstract

Objective: Systematic review of knowledge translation studies focused on paediatric emergency care to describe and assess the interventions used in emergency department settings.

Method: Electronic databases were searched for knowledge translation studies conducted in the emergency department that included the care of children. Two researchers independently reviewed the studies.

Results: From 1305 publications identified, 15 studies of varied design were included. Four were cluster controlled trials, two patient-level randomized controlled trials; two interrupted time series, one descriptive study and six before and after intervention studies. Knowledge translation interventions were predominantly aimed at the treating clinician, with some targeting the organisation. Studies assessed effectiveness of interventions over 6 to 12 months in before and after studies, and 3 to 28 months in cluster or patient level controlled trials. Changes in clinical practice were variable, with studies on single disease and single treatments in a single site showing greater improvement.

Conclusion: Evidence for effective methods to translate knowledge into practice in paediatric emergency medicine is fairly limited. More optimal study designs with more explicit descriptions of interventions are needed to facilitate other groups to effectively apply these procedures in their own setting.

Key words: Emergency; knowledge translation; dissemination; evidence based medicine; paediatrics

Key Points

- Knowledge translation interventions in the emergency department setting, are predominantly aimed at the health professional, using before and after or cluster controlled trial designs.

- Thorough identification of potential barriers to implementation is critically important and needs to be undertaken early on so they can be addressed.
- Description of knowledge translation interventions needs to be made more explicit so that other groups can implement in their local setting.

Introduction

The capacity for generating new knowledge to address evidence gaps in paediatric emergency care is steadily improving. A critical mass of paediatric emergency medicine (PEM) specialists is now established and collaborative research is being conducted through several highly successful national and international research networks focusing on generating better evidence for how to manage children who are critically ill or injured. .

Whilst this is important, the capacity to generate new evidence is only the first step in improving emergency care outcomes for children. The second and arguably harder step is to translate new knowledge into practice. There are often significant gaps in time – upwards of fifteen years - between when evidence is first generated and when it is routinely used to treat patients. How to most effectively shorten the time period between discovery of new knowledge and its routine wide spread use in the emergency department (ED), is a critically important goal.

When clinicians who care for acutely ill and injured children do not utilise best evidence, outcomes are suboptimal with potential exposure to unnecessary interventions which increase health care costs and may also lead to unnecessary adverse events (1). Acute bronchiolitis, asthma, gastroenteritis, pneumonia and upper respiratory infections in children are all common conditions for which evidence on diagnosis and management exists (2-5). Despite this there is substantial variation in how these conditions are managed all around the world, as evidenced-based care is inconsistently provided.

There is general agreement that the ED setting presents many challenges to the effective translation of knowledge into practice (6). Large patient volumes, time pressures to meet

demand, frequent staff rotations and substantial child and parent anxiety, all contribute to a dynamic and demanding environment. The challenges are made even greater for paediatric emergency medicine as most children are cared for in mixed EDs that are focussed primarily on adult care, and may not have specific paediatric emergency medicine expertise.

Consequently, ED knowledge translation (KT) initiatives need to be tailored to address these and other potential barriers to delivering optimal care and to harness the inherent strengths of a flexible and capable workforce.

This paper aims to provide a systematic review of published clinical knowledge translation studies carried out in the ED setting and focused on paediatric care. Different approaches to knowledge translation, types of interventions and their overall impact on practitioners, work processes and clinical care outcomes will be reviewed.

Materials and Methods

Details of the data sources, search strategy and the study selection process for this review are summarised in Table 1.

Search strategy

Our systematic search followed PRISMA guidelines (7). A literature search was conducted in OvidSP Medline, OvidSP Embase, PubMed and the Cochrane Database. The search included thesaurus terms and key words relating to KT studies in EDs and research involving paediatric populations. The search strategy was broad to include studies of varied research design that used both quantitative and qualitative methods.

Study selection

Only papers published in the past ten years and in English were included. Because paediatric emergency medicine is our topic of interest, the search aimed to select translational studies carried out in an emergency department setting with paediatric

populations. However, we also included studies carried out with other departments and or mixed paediatric and adult populations.

Screening and quality assessment

All results from electronic databases and reference lists (n=1305) were reviewed, based on the inclusion and exclusion criteria in Table 1. After exclusion of duplicates and screening of the title and abstract, a further 1281 were excluded (see Figure 1). Full texts of 26 studies were obtained and each study was evaluated independently by two reviewers/authors (Wilson and Oakley). Fifteen of the 26 studies met both our inclusion and exclusion criteria and are presented in this review. The remaining 11 studies were excluded for the following reasons: two studies (8, 9) did not include any patients under 18 years of age in the sample; three papers (10-12) were protocols only; two studies did not include sufficient description of their knowledge translation interventions to add value to this review (13, 14); three studies focused heavily on patient mediated interventions (requiring change in patient behaviour) which were not of interest in this review (15-17) and one study by a different author (18) duplicated another already in this review (19). The included studies have been reported using the domains outlined by the Cochrane Effective Practice and Organisation of Care Review group (EPOC) (20).

Results

Selected studies and their characteristics are presented in Table 2.

Study Design:

A wide range of study designs have been used in ED paediatric knowledge translation research. The studies included in this review are: four cluster controlled trials (21-24), two patient-level randomized controlled trials (3, 25); two interrupted time series (2, 26), one descriptive study (19) and six before and after intervention studies (of which four were single site (5, 27-29), one multisite uncontrolled (30) and one multisite controlled (31)).

KT Interventions:

The KT Interventions were predominantly aimed at healthcare professionals. They included involving the clinicians in formulating the tools and methods to be implemented, and educating them in both the need for the tools and interventions, and how to use them (3, 5, 19, 21-25, 27-31). In all of these studies, staff engagement was perceived to be very important for success. Organisational interventions were also common and included: formation of new multidisciplinary teams to coordinate the writing and implementation of guidelines (3, 21, 27-29), development of clinical governance guidelines and checklists (30), implementing new clinical roles and redefining clinical boundaries (19), implementing clinical decision support software (3, 25), and prospective identification of practice and process gaps and barriers (22, 24).

Interventional studies were focussed on modification of existing management (5, 21, 22, 25, 27) with some aiming for a reduction of established management (23, 24, 28, 31) such as reduction in anti-biotic prescribing, and some aiming to establish new models of care (19).

Study intervention times varied across studies and intervention types. The mean study time in the before and after intervention studies was 7 months (range 4 to 12 months), and in the cluster controlled or patient level randomised trials was 14 months (range 7 to 28 months).

Ambroggio (27) was the only investigator to incorporate ongoing intermittent interventions over the period of the trial to improve antibiotic prescribing for community acquired pneumonia. These interventions included Grand Rounds presentation, distribution of a guideline summary, prescribing reminder lanyard cards, small group meetings with targeted clinicians and weekly audit. Each of the interventions was associated with an improvement in antibiotic prescribing and after the last intervention, compliance was 100% for the final 3 months of the trial.

When implementing the "Low Risk Ankle Rule", Boutis (31) incorporated a three staged approach to intervention that had a control period of no intervention followed by a period of intensive education plus use of the tool, followed by a period of use of the tool alone to simulate 'real' ongoing conditions. This strategy showed a progressive improvement in performance with absolute reduction in unnecessary ankle imaging of 21.9% between phase 1 to 2 and reduction of 23.9% between phases 1 – 3.

Outcomes:

Outcomes are shown in Table 2 with primary outcomes presented as absolute change from baseline.

Three trials reported clinicians or families experience with the study intervention.(19, 25, 30) Roukema (25) implemented a computer assisted clinical decision support system to support ordering of diagnostic blood tests in febrile children, and reported only 49% compliance with the advice supplied. The reason reported by staff for non-compliance was the difficulty in agreeing to order blood tests on children who appeared perfectly well. Pannifex (30) reported on the introduction and compliance with governance processes in relation to procedural sedation in children with 20-30 random charts audited at each site before and after the intervention. The compliance with best practice process, was markedly improved in the 6 month follow up period and staff satisfaction with impact of interventions and the outcomes was very high. Bernstein (19) collected interview data from staff in the ED where the model of care had been changed to deliver screening and health promotion information to patients at risk of drug and alcohol dependency. The staff described their initial resistance to the new process then gradual acceptance with unexpected improvements in patient flow through the ED and greater understanding of resources they could offer the patient group.

The trials by Stiell (23, 24) which focussed on implementing clinical imaging guidelines for cervical spine and head injuries using computerised tomography (CT), used identical

implementation methods yet had very different degrees of success. Stiell reviewed why the implementation of the Head CT rule was not so successful and discovered a number of barriers to implementation that were not identified prior to the implementation of the knowledge translation interventions but were raised later on.(24) These barriers related to underlying physician beliefs that opposed application of the rule because of concerns it might miss something clinically important and that CT scanning was a local standard of care that would likely lead to more timely discharge.

Johnson's (2) study investigating the effect of the publication of the 2006 American Academy of Pediatrics guideline for managing bronchiolitis on subsequent bronchiolitis hospital care, showed no difference in the utilisation of interventions known to be of no benefit over a 4 year post publication period. Knapp (26) retrospectively reviewed management documented in the US National Hospital Ambulatory Medical Care Survey and found that publishing a guideline (for croup) and disseminating a guideline with a planned implementation approach (for asthma) had no differential effect on the degree of practice change.

Discussion

Knowledge translation in paediatric emergency medicine is a relatively new field with its necessity only really being recognised in the last decade.(32-34) This has come after a realisation that producing high quality evidence does not in itself change practice; and knowledge that one third of patients do not receive care they could benefit from; and one quarter receive care that has been shown to be of no benefit (35-37).

There are varied approaches to knowledge translation that have arisen from different disciplinary or stakeholder groups and different contexts (1). The barriers and difficulties begin with the fact that effective treatment paradigms in one population or region may not translate to other populations or contexts due to cultural difference which affects attitudes and beliefs, and the way things are done. Add to this a lack of evidence on effective

methods to translate new knowledge into clinical practice in the emergency department, and the problem of a growing evidence-practice gap becomes understandable. (1, 34, 38)

In the ED the individual clinician often has power of decision making, especially in test ordering and treatment choice. This should be but is not always supported by systems and evidence. This is exemplified by over 80% of KT interventions targeting individual clinician behaviour in some way, despite there being little evidence on how this should be done, or the impact this may have on effectively translating knowledge (38, 39).

The studies identified in this systematic review undertook a range of processes for KT intervention with some similarities and with some different points of emphasis. They attempted to engage the clinician users, encouraged and undertook discussion, gained agreement and support, developed or modified tools before implementation and a few provided ongoing education, audit or feedback. These types of intervention process are supported by literature in relation to KT in other fields (40, 41). See Table 3 for a summary of potentially successful KT interventions (1, 40-44).

Unfortunately, description of these KT interventions in the studies reviewed is of variable quality and often insufficient to allow the process to be undertaken at other sites or in other studies. This is a significant impediment because effective translation of knowledge into practice requires a thorough understanding and assessment of the implementation processes used and barriers encountered, in order to allow them to be critically appraised and adapted locally. The paediatric emergency KT literature to date, tends to report on outcomes of the 'clinical' interventions, with success determined by the 'clinical outcomes' that the interventions desired to change, with inadequate reporting on and evaluation of the process or KT intervention that was used to bring about the change. A recent review of ICU-based knowledge translation studies highlighted similar issues with limited evidence

available to demonstrate any benefit of knowledge translation interventions or clinical outcomes in the studies undertaken (45).

Distinguishing between evaluation of KT interventions and clinical outcomes is an important distinction to make, and is highlighted by having successful implementation in only six studies. (5, 22, 23, 27, 29) In the unsuccessful studies, it is not clear whether this is because the practice was already reasonable in the participating institutions and hence they did not measure improvement, whether the KT intervention was not appropriate to bring about change, or whether the intervention was not implemented adequately to effect change. Thorough evaluation of KT interventions success or failure can be a very powerful way to better understand the complexities involved in a change initiative and how it relates to a particular setting. A study carried out by Kinsman (8) to implement a clinical pathway for management of acute myocardial infarction in rural areas, illustrates this very well. No change in clinical outcomes was measured in this study but significantly more insight was gained into what is potentially achievable in this context and what needs to be the area of focus for intervention in the future.

The two studies by Steill (23, 24) further highlight the importance of these distinctions. In these trials identical methods were used in similar institutions with different results. The C-Spine study was successful in bringing about a reduction in unnecessary ordering of cervical spine x-rays through implementation of the Canadian C-spine rule, but the equivalent study to implement the Canadian CT Head rule did not bring about the desired reduction in the ordering of unnecessary head CT scans. Further exploration of why this occurred revealed that in the unsuccessful CT Head trial there existed a number of barriers to clinicians using the intervention had not been identified or addressed at commencement of the study. Study designs that describe the provider specific factors that may be barriers to successful implementation of new knowledge, and methods used to address these, are needed to help future groups to learn more from existing KT evidence. (38) There are a number of

theoretical frameworks that can be used to explore and identify a range of factors that will potentially influence implementation such as the Theoretical Domains Framework (46, 47) or the Theory of Planned Behaviour (48).

As in many other fields, Johnson (2) showed that production of high quality evidence based guidelines is insufficient to change practice at a population level (41). To date the evidence of what is effective in implementing change in paediatric emergency medicine is also sparse. It is unclear if there is a series of KT interventions that will be effective (or able to be adapted) across regions or will translate between different professional, patient or disease populations.

There was a reasonable consistency in the timeframes of the assessment of the KT interventions in the identified trials, with approximately 6 to 12 months follow up and pre study data being the norm. However, there are potential issues with these short timeframes. The sustainability of the KT interventions in an environment where physician training requirements produce a regular turnover of clinical staff has not been adequately assessed. Furthermore, a slow and persistent practice change that has been underway since the evidence emerged may be overlooked. The change identified over a short study period that is attributed to the KT intervention, may be diminished if this longer term trend for improvement is uncovered. To be sure this scenario has not occurred, a period of 2-3 years data collection pre and post intervention is warranted.

The most popular trial design in the reviewed studies was a before and after KT intervention measure. Most of these studies were at single institutions and their generalisability to other settings is unclear.(5, 21, 27-29) Furthermore, it is well established that this study design can lead to overly optimistic estimates of the effectiveness of KT interventions due to extrinsic factors underlying trends. (49, 50). Four studies used cluster-controlled trial design which is widely considered to be the most rigorous method for determining the effectiveness of a KT

intervention (49, 50). However one of these trials (21), inappropriately used a 'time-period (one week)' as the cluster so that the same ED staff who were the target of the intervention, were included in both the intervention and control arms – making the intervention effect less distinguishable. Another of the cluster controlled trials (22), included only four matched pair EDs which is an inadequate number. As well, they did not account for clustering in their analysis. This most certainly resulted in an overestimate of the effect of their study intervention. The cluster trials by Stiell were the only two which used optimal study designs, appropriate statistical analysis and included sufficient number of EDs to provide adequate power and enhance generalisability(23, 24).

Conclusion

Evidence for effective methods to translate knowledge into practice in paediatric emergency medicine is fairly limited. Studies which use optimal study designs such a cluster controlled trials and appropriate statistical analysis accounting for intracluster correlation coefficients are needed. Studies should carefully assess potential barriers to success such as attitudes and beliefs relevant to different professional groups, diseases and patient populations. Use of a theoretical model to underpin identification of barriers and mixed methods study design (qualitative and quantitative research) should also be considered. More explicit descriptions of interventions undertaken in KT studies and measurement of process, is essential to facilitate other group's implementation in their own setting. Measurement of change over longer periods is also desirable to further understand sustainability. Well designed, conducted and reported KT trials in paediatric emergency medicine are urgently needed to enhance our understanding of how best to translate knowledge into practice. Otherwise the promise of better child health outcomes from paediatric emergency research networks generating best evidence will be unfulfilled for many years to come.

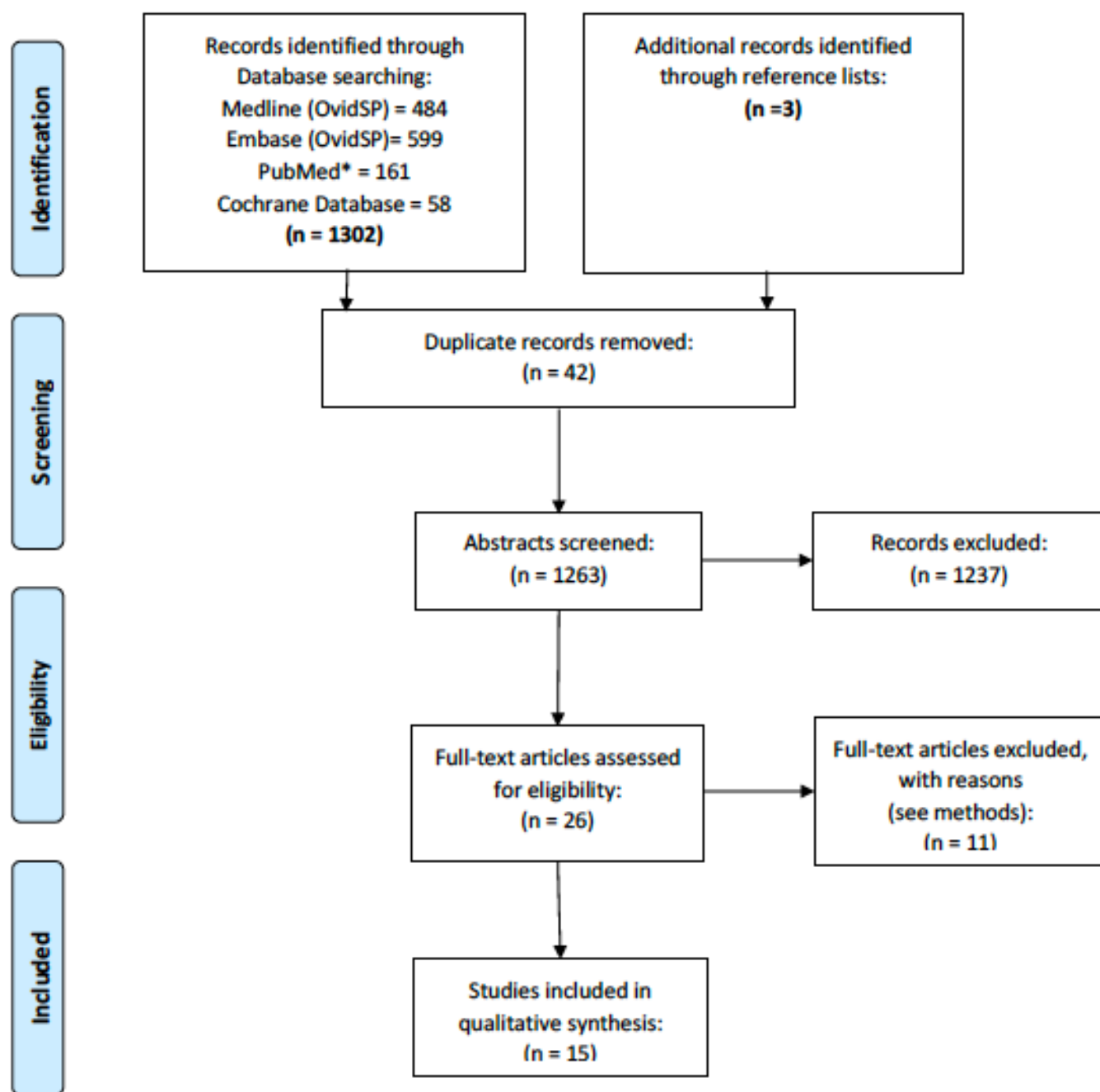
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Table 1 Search and selection strategy

Data Sources	Medline (OvidSP); EMBASE (OvidSP); PubMed; The Cochrane Database
Thesaurus terms	Broad searches were performed using the relevant thesaurus terms: (emergency care OR emergency medicine OR emergency service, hospital OR emergency ward), AND (information dissemination OR knowledge OR translational medical research OR "diffusion of innovation" OR professional knowledge OR translational research OR evidence based medicine OR evidence based emergency medicine OR randomized controlled trial OR "randomized controlled trial (topic)") AND pediatrics
Keywords	Emergency AND (knowledge translation OR dissemination OR innovation) AND (child* OR infant* OR adolesc* OR neonat* OR pediatric* OR paediatric*)
Search dates	1 January 2004 to 19 January 2015
Other information sources checked	Reference lists of included studies were searched to identify additional relevant papers (i.e. snowballing references)
Inclusion criteria	• Studies published in English language in peer reviewed journals • Studies undertaken in an emergency department setting (but not limited to the ED ie other departments could be involved) • Studies which described knowledge translation interventions adequately • The knowledge translation interventions were mostly professional interventions targeted to staff rather than patients • Studies included paediatrics but were not limited to paediatric populations
Exclusion criteria	• Studies which did not describe knowledge translation interventions sufficiently • Studies carried out in settings that did not included the emergency department

Figure 1. PRISMA information flow diagram for the systematic review



*PubMed was searched back to 2014 to capture Epubs not available in Medline.

Table 2. Studies selected for review

Author and Year	Knowledge translation aims and tools	Location and setting	Design, study period and sample	Knowledge translation Interventions	Outcome measures	Findings
Ambroggio 2013(27)	Aim: improve compliance with the community acquired pneumonia in children national antibiotic prescribing guideline Tool: Local guideline based on National antibiotic prescribing guideline for community acquired pneumonia	Cincinnati, USA: single tertiary children's hospital; ED and hospital medical (HM) department.	Single site before and after study; 6 months before data (n=67) compared with 9 months post data (n=150). Quality Improvement, plan-do-study-act methodology, with ongoing interventions. Sample: (n=217) patients aged 3 months to 19 years.	Organisational: - Multidisciplinary team designed the interventions using a process map; Professional: Interactive seminar about guidelines; Summary of guidelines emailed; reminder prescribing card; default link to guideline in electronic medical record; weekly audit of eligible patients for success or failure.	Proportion of eligible patients receiving appropriate first line antibiotic therapy; and Length of stay (LOS)	ED had an 82% absolute improvement in correct prescribing (0 vs 82%); HM department had a 60% absolute improvement (30 vs 90%). Ongoing interventions improved rates to 100% after 3 months in both locations. Pre intervention median LOS <1 day, IQR: 0-1 day, post intervention median LOS: 1 day; IQR: 0-2days <.001.
Bernstein 2009(19)	Aim to implement a high risk drug and alcohol screening intervention in emergency departments across the state i.e. "SBIRT". Screening, brief intervention and referral to treatment. Tools to assess the intervention in the ED were based on the RE-AIM theory (Reach, effectiveness, adoption, implementation and maintenance).	Massachusetts, USA: 7 hospital EDs in urban, suburban and rural community settings.	Descriptive study; 18 months data collection prospectively over implementation period with 15,383 patients screened across 7 sites. Qualitative semi-structured interviews of staff (n=24) to determine reach and success. Data from this state based study was compared with Federal data; sample age was not stated, assumed to include adolescents.	Organisational: 12 health promotion advocates (HPA) were employed in 7 EDs to do screening of at risk patients; ED and HPA staff identified at risk groups to be screened. Professional: Peer educators at each site delivered education and training to HPAs which included quarterly workshops and monthly monitoring of performance for accuracy.	RE-AIM (Reach, effectiveness, adoption, implementation and maintenance). Quantitative: total patients screened; % positive; % negative; % referred to other resources. Qualitative: identification of barriers, challenges and successes to the intervention.	SBIRT required a team focused model of delivery customised to each ED. Overcoming staff attitudes to SBIRT was best addressed by local staff champions who intervened when problems arose. The intervention relies on continued funding of the staff to implement SBIRT at each site.
Boutis 2013(31)	Aim to reduced use of radiography in management of ankle injuries in children. Tool:- Clinical decision support rule - "The Low Risk Ankle Rule" and computerised decision	Ontario, Canada: 2 urban children's hospitals, 2 urban general hospitals, 2 community based suburban hospitals; all in ED.	Multisite controlled before and after study; 18 month study period with 3 consecutive 26 week phases at the intervention sites (one 18 month period for controls); prospective data collection.	Professional: Intervention sites only: phase 1 – internal control phase i.e. clinical data collection re ankle injury management and assessment of physician satisfaction.	Proportion of eligible children who received ankle radiography; proportion of children with missed significant fractures; proportion of children who did not have radiology in ED but did so subsequently;	In comparison with control group, there was an absolute reduction of 21.9% in radiography between phase 1 to 2 and 23.9% between phase 2 – 3. No increase in clinically important fractures

Author and Year	Knowledge translation aims and tools	Location and setting	Design, study period and sample	Knowledge translation Interventions	Outcome measures	Findings
	support system (CDSS) to support the rule.		Sample: (n=2151); patients aged 3 – 16 years.	phase 2 – physician teaching sessions; pocket cards and posters of the rule; flagging of charts for ankle injuries; physician champions; use of CDSS; training of physicians in management of low risk ankle injury; phase 3 – use of CDSS only.	length of stay. Patient satisfaction and ED physician satisfaction were assessed. All were compared with the control group.	missed. Use of the rule did not affect patient or physician satisfaction or length of stay.
Cunningham 2008(21)	Aim: assess effectiveness of implementing an integrated care tool on the management of asthma Tool Local Integrated Care tool based on the United Kingdom asthma management guidelines.	Edinburgh, Scotland: single, tertiary paediatric hospital; ED and hospital respiratory department.	Cluster randomised controlled trial; 26 week trial of 7 day trial periods randomly assigned to either standard care or care delivered using the ICP in blocks of 8 weeks. Sample: (n=298); patients aged 2 - 16 years.	Organisational: Multidisciplinary team developed an Integrated care pathway (ICP) for acute asthma/wheeze which involved development of a single document for use by whole team incorporating guidelines and reducing variation. Professional: Tutorials were given in the use of these tools and underpinning knowledge.	Difference in length of hospital stay; rate of asthma improvement in physiological variables, and bronchodilator requirements; bronchodilator and prednisolone use. Discharge process: time to complete discharge criteria; provision of education to family; parent questionnaire to determine receipt and understanding of discharge information. Proportion of prescribing errors	Physiological recovery or length of stay did not improve. There was an absolute reduction of 30% in prescribing errors and an absolute increase of 39% (72% versus 33%) in prednisolone prescribing. Patient education and discharge planning improved by 48% (89% versus 41%).

Author and Year	Knowledge translation aims and tools	Location and setting	Design, study period and sample	Knowledge translation Interventions	Outcome measures	Findings
Dexheimer(3) 2014	Aim: Implement evidence based guidelines for the management of asthma: Tool: Integrated computerised asthma detection and management system in the ED.	Cincinnati, USA: single tertiary paediatric hospital; ED.	Randomised controlled trial to intervention or standard care (paper based) over a 5 month period. Sample: (n=788); patients aged 2 – 18 years.	Organisational: Multidisciplinary team refined evidence based practice guideline, care flow sheet and severity based order sheets which informed the computerised and paper based systems 2 years prior. Use of the computerised asthma management system was used to detect patients with asthma exacerbation and used computer driven work flow, tracking asthma scores at triage and onwards and delivering re-scoring reminders and relevant order sets. Professional: Physician, nurse and respiratory therapist education sessions at meetings, in two months prior; divisional email re study.	Time from ED triage to disposition decision; adherence to guidelines including asthma education ordered; asthma scoring performed; ED length of stay; hospital admissions. Survey to evaluate staff awareness of study.	The absolute difference between the two groups median time to disposition decision was 5 minutes, which was not significant, $p=0.362$. ED median length of stay was 15 minutes longer in the intervention group but this was not significant. Admission rates were also very similar. There was no difference between the two groups in any of the guideline adherence measures.

Author and Year	Knowledge translation aims and tools	Location and setting	Design, study period and sample	Knowledge translation Interventions	Outcome measures	Findings
Diaz 2004(5)	Aim: 1. Implement evidence based guideline for diagnosis and management of pharyngitis. 2. Reduce antibiotic prescription. Tool: Locally created clinical practice guideline for pharyngitis	Akron, USA: single tertiary paediatric hospital; ED.	Single site before and after study; retrospective medical record review of pre-intervention and post-intervention randomly selected cohorts, over a 4 month period, using standardized data collection. Sample: (n=443); patients aged 1.5 - 19 years.	Professional: Development of a pharyngitis pathway by ED physicians in form of a document which contains reminders re guidelines. Organisational: Triage nurse adds the pathway document to appropriate patients notes.	Compliance with guideline as indicated by appropriate diagnosis and antibiotic prescribing.	An absolute improvement in diagnosis procedure and appropriate antibiotic treatment of 47% (44% to 91%).
Doherty 2006(22)	Aim: to assess if an evidence based approach to implementation of an asthma guideline improved compliance with evidence based care Tool: Evidence based approach to implementing an established asthma guideline	New South Wales, Australia: eight rural district hospitals; EDs.	Cluster randomised controlled study; four matched pairs of rural hospitals. Retrospective medical record review of pre-intervention (n=52) and post-intervention (n=47) cohorts, over 7 month periods, using standardized data collection. Sample: (n=187); patients aged 14 + years.	At intervention sites only Organisational: Identification of practice gaps; identification of barriers to change in ED at each hospital prior to implementing the EBI tool. Professional: Guideline reformatting to useable format - incorporated in medical record; reminders with site visits twice during study period; education sessions for medical and nursing staff; audit and feedback twice per 7 months; study co-ordinator/ knowledge broker lead change.	Changes in 6 targeted areas: asthma severity; use of spirometry; use of ipratropium; use of corticosteroids; use of antibiotic; documentation of short term asthma management plan.	An absolute improvement of 26% (36% vs 62%) in the adherence to the aggregate of all six indicators.
Fong 2008(28)	Aim: improve appropriate use of Computerised Tomography (CT) scans in the management of head injury. Tool: A locally developed head injury guideline developed based on the Canadian CT Head Rule (CCTHR)	Melbourne, Australia: single tertiary hospital; mixed ED.	Single site before and after study; comparison of pre-intervention period (n=311) over 5 months, and post-intervention period (n=326) over 7 months, using standardized data collection from medical records. Retrospective pre intervention data	Professional: Development of a local guideline with a focus group; training of medical staff in prospective application of the local head injury rule.	CT head ordering rates in head injury; appropriateness of ordering CT scan. Comparison of the detection of clinically significant head injury abnormalities on CT (local rule versus CCTHR.).	An absolute increase of 27% (32% vs 59%) in the ordering of Head CT. No abnormalities were missed versus four that would have been missed using CCTHR alone.

Author and Year	Knowledge translation aims and tools	Location and setting	Design, study period and sample	Knowledge translation interventions	Outcome measures	Findings
			collection; prospective data collected post intervention. Patient follow up questionnaire used. Sample: (n=637); patients aged > 16 years.			
Johnson 2013(2)	Aim: to assess change in bronchiolitis management after publication of American Academy of Pediatrics Guideline on management of bronchiolitis Tools: non-intervention study	U.S.A: nationally representative group of EDs across the country.	Interrupted time series; retrospective review of a subset of survey data from the U.S. National Hospital ambulatory Medical Care Survey during 2001 – 2009, pre (5 years) and post (4 years) comparison of data in relation to introduction of a guideline in November 2006. Sample: (n=678); patients aged 0 - 2 years.	National: Publication of national guideline in November 2006.	Use of bronchodilators, steroids, antibiotics, and chest x-ray for bronchiolitis.	No change in use of non-recommended therapies (bronchodilators, steroids, antibiotics). Absolute reduction of 19.7% (65.3% vs 48.6%). for CXR.
Knapp(26) 2014	Aim: to compare knowledge transfer in the Emergency Department management of paediatric asthma and croup by measuring trends in corticosteroid use. Tools: national paediatric asthma guidelines versus only passive diffusion for croup.	U.S.A: nationally representative group of EDs across the country.	Interrupted time series; retrospective cross sectional study of a subset of survey data from the U.S. National Hospital ambulatory Medical Care Survey during 1995 – 2009. Comparison of trends in corticosteroid usage between the two groups over 15 year period. Asthma Sample: (n=1829); patients aged 2 – 18 years. Croup Sample: (n=1075); patients aged 6 months - 6 years.	National: Publication and dissemination of asthma guidelines in 1991 with expert panel review and update in 1997, 2001 and 2006.	Use of corticosteroids in for asthma or croup, administered in the ED.	From 1995 to 2009: absolute increase of 23% in use of corticosteroids for management of asthma. Absolute increase of 24% in use of corticosteroids for management of croup. There was no difference in the trend between the two groups, OR interaction term was 0.99.
Pannifex 2013(30)	Aim: to develop and implement standardised approach to procedural	Victoria, Australia: 10 urban hospitals and 4 regional/rural hospitals;	Multi-site uncontrolled before and after study; comparison of baseline	Organisational: Development of a clinical governance	Comparison of clinical governance; number of staff trained during	An average 33% (54 vs 87%) absolute improvement with

Author and Year	Knowledge translation aims and tools	Location and setting	Design, study period and sample	Knowledge translation interventions	Outcome measures	Findings
	sedation for children in the emergency department to improve safety. Tools: development of a training and documentation tool; and Clinical governance self-assessment checklist.	EDs..	data with 6 months post intervention qualitative data review per ED department. Convenience sample: (n=215); patients (age was not stated but conducted within paediatric patients)	checklist; review and update of training materials; development of information sheets, risk assessment and documentation forms; materials about family centred approach; development of audit tool. Professional: Workshop and training of staff.	intervention period; compliance with and documentation of risk assessment procedures; qualitative feedback from staff on their satisfaction with the intervention and perception of impacts.	compliance with all governance measures. Staff feedback very positive, increase teamwork reported.
Roukema 2008(25)	Aim: assess compliance with clinical decision support system recommendations; time spent in ED and test ordering. Tool: clinical decision support system (CDSS) developed locally for risk assessment of febrile young children.	Rotterdam, The Netherlands: single tertiary paediatric ED.	Randomised controlled trial; enrolments were over a 28 month period. Sample: (n=164); patients aged 1 - 36 months.	Organisational: Implement CDSS - based upon prediction rules to identify high risk patients - then randomised the high risk patients to immediate diagnostic tests or clinician review and ordering of tests (control group); Professional: Training for nursing staff in use of CDSS.	Compliance with the CDSS in registration of febrile children and recommendation for testing. Time at the ED; diagnostic tests in high risk group in comparison with control group.	Compliance with using CDSS 49%. Compliance with CDSS randomisation 82%. There was an absolute increase of 38% (82% vs 44%) of using CDSS to order blood tests in high risk patients. There was an absolute increase of 15 minutes (138 vs 123 min) in time in the ED.
Stiell 2009(23)	Aim: to evaluate the effectiveness of an active strategy of implementing the Canadian C-Spine Rule for appropriate ordering of cervical spine imaging; test the impact of the rule on use of imaging. Tools: the Canadian C-spine rule and active implementation strategies at intervention sites.	Canada: 12 hospitals, (6 teaching and 6 community sites); EDs.	Cluster randomised controlled study; matched pairs of 12 hospital sites. Data captured during 12 months pre intervention and 12 months post intervention. Sample: (n=11824); patients aged 16 - 100 years.	Professional: Discussion of rule with physician team and agreement on use of rule; education including pocket cards, posters; 1 hour teaching sessions; reminders of the rule when imaging requested.	Proportion of eligible patients referred for imaging of C-spine; number of clinically important injuries not identified on initial ED visit; adverse outcomes. Performance of the C spine rule at the intervention sites; accuracy of interpretation of and compliance with the rule.	An absolute reduction of 8.4% (61.7% vs 53.3%) of patients referred for imaging in the intervention group, compared with an absolute increase of 7.1% (52.8% vs 58.9%) at control sites. No fractures were missed.
Stiell 2010(24)	Aim: to evaluate the effectiveness and safety of an active implementation strategy for the Canadian	Ontario, Alberta and British Columbia, Canada: 12 hospitals (6 teaching sites & 6 community sites); EDs.	Cluster randomised controlled study; matched pairs of 12 hospital sites. Data captured during 12	Organisational: Assessed barriers prior to intervention and tailored interventions accordingly at sites;	Proportion of eligible patients referred for CT head scan; number of clinically important brain injuries not identified;	At intervention sites an absolute increase of 13.3% (62.8% vs 76.2%) in rates of CT imaging. At control sites an

Author and Year	Knowledge translation aims and tools	Location and setting	Design, study period and sample	Knowledge translation Interventions	Outcome measures	Findings
	CT Head Rule. (Aim to reduce use of CT Imaging) Tools: The Canadian CT Head Rule. An active implementation strategy.		months pre intervention (n=1049) and 12 months post intervention (n=1531). Qualitative interviews of staff; Sample: (n=2580); patients aged 16 - 99 years.	adherence to the rule was checked via the radiology department review of requests. Professional: Education sessions were held for physicians and information distributed; Use of pocket reminder cards and posters; real time reminder when requisitioning CT scans.	staff perception of using rule (and barriers and facilitators to using the rule); sensitivity and specificity of the rule (secondary outcome).	absolute increase of 6.7% (67.5% vs 74.1%). Sensitivity of the Canadian head CT rule was 100%. Unforeseen barriers to effective implementation were identified in post study feedback.
To 2010(29)	Aim: to examine whether use of a Paediatric Acute Asthma Management Guideline Reminder Card improves asthma management. Tools: A local guideline based on Canadian asthma consensus guideline. A reminder card with guideline information.	Toronto, Canada: single tertiary paediatric hospital; ED.	Single centre before and after study; retrospective chart review of ED visits over 12 months prior to the intervention were compared with 154 prospective ED visits over 12 months following the intervention. Sample: (n=432) ; patients aged < 7 years.	Professional: Development of acute asthma management guideline by local team at hospital; formatted in pocket sized reminder card; disseminated to multidisciplinary team by presentations and email, plus provision of reminder card;	Administration of systemic corticosteroids and bronchodilators during ED stay; delivery of asthma education to patient in ED; conduct of discharge planning.	An absolute increase of 23.7% in the use of corticosteroids (60.1% to 83.8%). An absolute increase of 20.7% (50.7% to 71.4%) in oxygen saturation reassessment. For discharge planning there was an absolute increase of 8.6% (72.3% vs 63.7%) in a combined measure of discharge planning.

Table 3. Summary of potentially successful knowledge translation interventions

- Identification of practice gaps locally prior to initiating change.
- Engagement of key stakeholders in development of the change initiative, ideally including the multidisciplinary team in key elements of development and implementation of the change initiative.
- Identification of potential barriers and enablers to change at the level of organisations/departments/different professional groups and individuals. Theoretical frameworks can be used in this process. Aim to address modifiable barriers and enhance enablers in the change initiative.
- Identification of staff to lead or "champion" the change initiative. These staff will have a strong knowledge of the change initiative and will be prepared to problem solve issues as they arise.
- Making new information readily accessible in a range of formats to suit different target audiences such as:
 - seminars and lecture presentations
 - small group education sessions
 - individual emails with links to new information
 - reformatting of information into a readily accessible formats such as a pocket cards, posters or incorporation into relevant medical record forms.
- Reminders and prompts that are incorporated into standard processes such as completion of medical records, test requisition forms or computerised decision support systems.
- Capacity for regular audit and feedback on the implementation and outcome of the change initiative. This is ideally undertaken internally and feedback given by a supervisors.

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CONCLUSIONS AND OUTLOOK

Bronchiolitis is an important disease for paediatric emergency and inpatient paediatric staff to understand and manage effectively, as it is the most common reason for infants under one year of age to be admitted to hospital, and the most common reason for non-elective admission in this age to the intensive care unit. My contribution as outlined in this thesis has shown that clinical care of bronchiolitis in Australia and New Zealand is variable and includes many interventions that have been shown to be of no benefit; that nasogastric hydration is safe and effective and should be considered the first option in non-oral hydration; that new forms of non-invasive ventilation were being introduced without adequate evidence; and then provided the evidence to guide clinical use of high flow nasal canula. Finally my contribution has demonstrated that there is inadequate evidence to understand how to effectively implement new evidence into clinical practice in the emergency department, and that high quality studies are needed to ensure we understand how to influence clinician decision making, and has outlined a way forward for this in our region. My contribution has influenced clinical practice throughout Australia and New Zealand with all state and regional clinical practice guidelines recommending initial nasogastric hydration, and the use of high flow nasal cannula as rescue, rather than initial, therapy.

The initial work on bronchiolitis identifying the need for a regional, collaborative and evidence based guideline, and identifying the need for evidence for implementation methods has led to the commencement of two PhDs by co-investigators. Ms Sharon O'Brien RN (**Paper 6-1** and **Appendix 2, 3 and 4**), and Ms Libby Haskell RN (**Appendix 3 and 4**) The PhD by Ms O'Brien included the development of the Australasia Bronchiolitis Guideline, and will include the update in 2020, ensuring the guideline remains current. The PhD by Ms Haskell has developed and implemented the cluster randomised trial on implementation of the Australasian Bronchiolitis guideline aiming to fill the evidence gap identified in **Paper 7-1** with locally applicable information.

The research included in this thesis has included randomised controlled trials, retrospective reviews of clinical care, clinician surveys and systematic reviews of the literature. The research has required the involvement of multiple sites to ensure adequate numbers of infants with bronchiolitis were available in an appropriate time frame. This highlights the need for robust means to identify and engage research sites and clinicians to ensure multicentre research is possible. The research outlined has

used the Paediatric Research in Emergency Departments International Collaborative (PREDICT) as the vehicle to engage these sites. The randomised controlled trial comparing nasogastric and intravenous hydration in bronchiolitis was the first interventional trial undertaken by the PREDICT network and my interaction with the network has contributed to its growth into a successful clinical trials network. The trials outlined in this thesis were large and required significant funding to complete. As part of this research I led successful National Health and Medical Research Council Project and Centre of Research Excellence grant applications.

The research in this thesis is ongoing: the cluster randomised controlled trial of implementation of the Australasian bronchiolitis guideline will soon be published and the Australasian bronchiolitis guideline will be updated with new evidence within the next year. Plans are being developed to measure the sustainability of change in practice from the cluster randomised trial, and for audit of the use of high flow nasal cannula use in bronchiolitis to determine whether an evidence implementation plan needs to be developed to ensure high flow use becomes evidence based.

Ongoing research and knowledge translation efforts in bronchiolitis are important to ensure the many infants in Australia and New Zealand that present to the many emergency departments that see children in our countries receive the best, most appropriate treatment wherever they present.

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APPENDICES

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