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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 **(Tale 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 Zealand[38]. 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 shoud 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

Stuart Dlaziel and Franz babl are Section Editors, Paediatric Emergency Medicine, for Emergency Meedicine Australasia.

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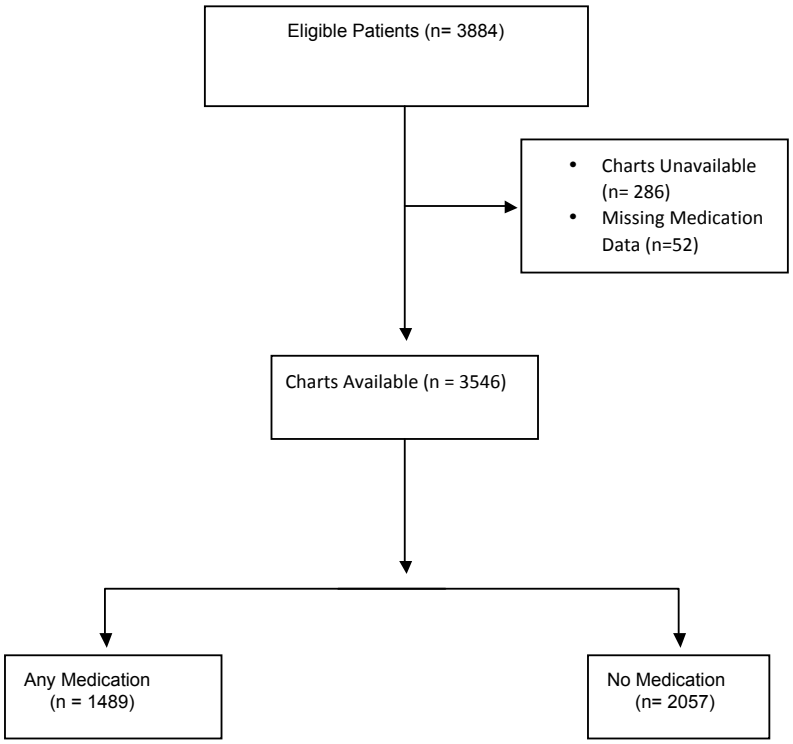
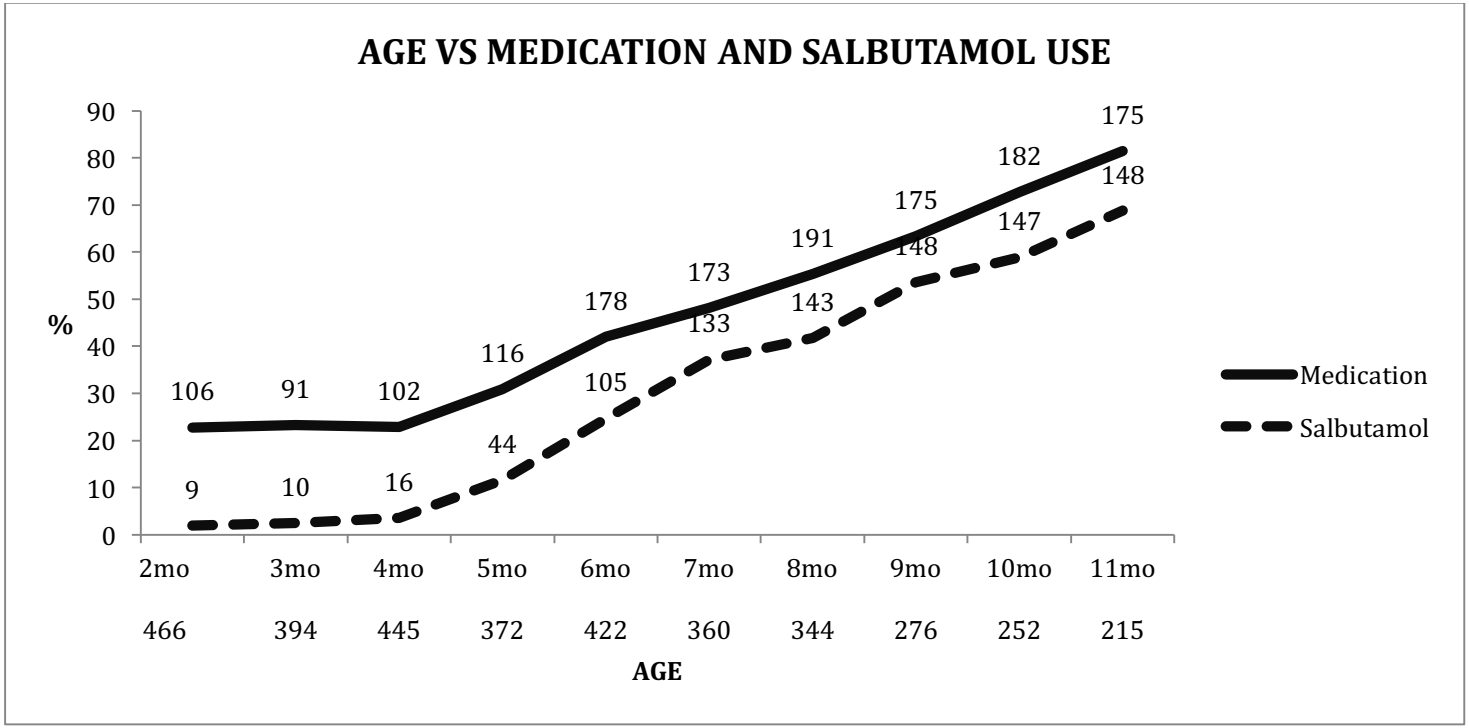


Figure 1. Flow chart of patient recruitment and medications used in bronchiolitis



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	%

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

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

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

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

ICU=Intensive Care Unit n=number of patients

Table 4. Antibiotic use in management of infants with bronchiolitis in patients with investigations compared to patients without investigations

		Antibiotics		No Antibiotics		Odds Ratio	P Value
		n	%	n	%		
Investigations	YES	627	24.0	1,986	76.0	9.8	P <0.001
	NO	29	3.0	900	97.0	(6.7 -14.3)	
CXR	YES	510	42.0	702	58.0	10.9	p<0.001
	NO	145	6.0	2,176	94.0	(8.9 - 13.3)	
NPA	YES	525	23.0	1,795	77.0	2.5	P<0.001
	NO	130	11.0	1,091	89.0	(2 - 3)	
NPA pos	YES	424	24.0	1,364	76.0	1.3	P=0.02
	NO	101	19.0	431	81.0	(1 - 1.7)	
NPA pos	RSV	247	23.0	834	77.0	0.9	P=0.29
	OTHER	177	25.0	530	75.0	(0.7 - 1.1)	

n=number of patients NPA=Nasopharyngeal Aspirate CXR=Chest X-Ray