This is the post print version of the article, which has been published in Acta Paediatrica. 2017, 106 (9), 1512-1518.http://dx.doi.org/10.1111/apa.13931.

Marked variability observed in inpatient management of bronchiolitis in three Finnish hospitals

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Running title: Variability in inpatient management of bronchiolitis

Word count of the abstract: 197 (≤200)

Word count of the text: 2853 (≤3250)

Tables and figures: 2 tables + 2 figures

References: 29 (≤30)

ABSTRACT

Aim: Infants hospitalized for bronchiolitis undergo examinations and treatments not supported by current research evidence guidelines. We investigated practice variations among Finnish children hospitalised for bronchiolitis.

Methods: Prospective, multi-centre cohort study was conducted in paediatric units in three University Hospitals in Finland during 2008-2010. Children under the age of two years hospitalised for bronchiolitis were enrolled. Hospital medical records were reviewed to collect data on clinical course, testing and treatments. Data were analysed separately for children meeting our strict definition of bronchiolitis, age <12 months without history of wheeze, and a loose definition, age 12-23 months or with history of wheezing episode.

Results: Among 408 enrolled children, the median age was 8.1 months. Stratifying by strict and loose bronchiolitis subgroups, clinical management varied between the three hospitals: complete blood count (ranges for strict 15-95%; loose 16-94%), chest x-ray (strict 16-91%; loose 14-72%), intravenous fluids (strict 2-47%; loose 2-41%), use of nebulised epinephrine (strict 10-84%; loose 7-50%), use of salbutamol (strict 18-21%; loose 13-84%), and use of corticosteroids (strict 6%-23%; loose 60-76%).

Conclusions: Clinical management of bronchiolitis varied considerably by institution whether using either definitions of bronchiolitis. A stronger commitment to evidence-based bronchiolitis guidelines is needed in Finland.

Keywords: bronchiolitis guidelines, bronchiolitis treatment, practice variation

Key Notes

- Many infants hospitalized for bronchiolitis undergo examinations and treatments not supported by current research evidence.
- We found that clinical management of bronchiolitis varies considerably by institution whether using the strict or loose definitions of bronchiolitis.
- A stronger commitment to evidence-based bronchiolitis guidelines is needed. As a result of our findings we recommend that further guidelines should separate these two definitions of bronchiolitis.

INTRODUCTION

Bronchiolitis is a lower respiratory tract viral infection in young children. Most European countries limit the diagnosis of bronchiolitis to infants age 12 months or younger and typically do not allow previous history of wheezing, whereas the USA uses an older age limit of less than 24 months (1). Bronchiolitis is one of the most common and costly respiratory illnesses in infants and young children (2). Approximately 100,000 bronchiolitis admissions occur annually in the USA at an estimated cost of $1.7 billion (3). In Finland, up to 3% of infants with bronchiolitis under 12 months of age are hospitalized, and up to 9% require intensive care (4). In Finland, the mean hospitalization cost for a bronchiolitis patient is €1,800 and goes up to €8,000 if paediatric intensive care is needed (4).

Several randomized controlled trials and systematic reviews have attempted to identify the optimal treatments for children with bronchiolitis (5-8). Evidence-based care remains largely supportive, including adequate oxygenation, mucus extraction, and nutrition. Despite international guidelines on bronchiolitis, the overuse of diagnostic testing, i.e. chest radiography and laboratory testing, and ineffective therapy, i.e. beta agonists, antibiotics, corticosteroids, remain common. The main reason for the overuse of testing and medications is the modest effectiveness of bronchiolitis guidelines in modifying physician behaviour (9-11).

In response to these problems, many hospitals have implemented clinical practice guidelines and recommendations based on evidence-based guidelines for bronchiolitis (12). These guidelines seldom recommend specific interventions but rather try to prevent the use of irrelevant diagnostic tests or ineffective drug treatments or other interventions. Despite the high frequency and cost of bronchiolitis care, there has been limited research on variability of care among different hospitals (9,13,14). Therefore, our aim was to investigate bronchiolitis-related practice variation in three tertiary care hospitals in Finland. Due to the expected variability in the diagnostic and management practices, we wanted to investigate practice variation in two subgroups of children less than two years of age who were hospitalized for bronchiolitis: 1) those who met our strict definition of bronchiolitis, i.e., age under 12 months of age without history of wheeze, and 2) those who did not, i.e., age 12-23 months or with history of wheeze.

METHODS

Subjects

This prospective, multicentre cohort study was conducted as part of the Multicenter Airway Research Collaboration, a programme of the Emergency Medicine Network, during two consecutive winter seasons (November through March) in years 2008 to 2010. The study was carried on in the paediatric departments of three Finnish tertiary care university hospitals in Turku, Tampere and Kuopio, Finland (15). As in its USA counterpart study (16), a standardized protocol was used to enrol a target number of consecutive patients from the inpatient ward and the intensive care unit. Inclusion criteria were an attending physician's diagnosis of bronchiolitis, age under two years, and informed consent from a guardian. Patients were enrolled within 18 hours of admission. The exclusion criteria were previous enrolment or transfer to a participating hospital over 48 hours after the original admission time. All patients were treated at the discretion of the treating physician. The institutional review board of Turku University Hospital approved the study, and this approval covered all participating hospitals in Finland.

Data collection

Investigators conducted a standardized structured interview on patients' demographic, environmental and clinical characteristics (17). Patients were evaluated daily in the ward by a physician. Hospital medical records were used to collect clinical data from the pre-admission evaluation in the emergency department as well as the child's inpatient course. These data were manually reviewed at the Emergency Medicine Network Coordinating Center and site investigators were queried about missing or discrepant data.

To evaluate bronchiolitis severity, a modified Respiratory Distress Severity Score (RDSS) was calculated based on four assessments made during the pre-admission visit: respiratory rate by age, presence of wheezing (yes or no), air entry (normal, mild difficulty, or moderate to severe difficulty), and retractions (none, mild, or moderate to severe) (15,18). Each component was assigned a score of zero, one, or two, with the exception of wheezing, which was assigned either zero (no wheezing) or two (wheezing), and then summed for a possible total score

of zero to eight per patient. When a child had one or two of the RDSS components missing (n=174), single imputation controlling for age, respiratory rate, presence of wheezing, air entry, and retractions, was used to generate the score. RDSS values were not calculated for the 15 patients missing data for more than two components of the score.

Nasopharyngeal aspirate collection and viral testing

Nasopharyngeal aspirates were collected at study entry using a standardized protocol (19). The sample was added to transport medium, immediately placed on ice, and then stored at -80^{o}C before analysis at Baylor College of Medicine. All polymerase chain reaction (PCR) assays were conducted as singleplex or duplex two-step real time PCR and used for the detection of RNA respiratory viruses; respiratory syncytial virus (RSV) types A and B, rhinovirus (RV) covering A, B and C species, parainfluenza virus types 1, 2 and 3, influenza virus types A, B and 2009 novel H1N1, human metapneumovirus, coronaviruses NL-63, HKU1, OC43 and 229E, enteroviruses and DNA pathogens for adenovirus. Details of the methods and primers and probes have been described previously (20,21).

Statistical analyses

All analyses were performed using Stata 14.1 (StataCorp LLC, Texas, USA). Data are presented as proportions and means with 95% confidence intervals (95%CIs) or medians with interquartile ranges (IQRs). For analytical purposes, we divided the cohort into two subgroups by bronchiolitis definition: children under 12.0 months of age with no history of wheeze (strict bronchiolitis) or all other children in the cohort who were 12.0-23.9 months of age or had a history of wheeze (loose bronchiolitis).

To assess variability in care by study site, bivariate associations were tested using chi-square, and Fisher's exact test, and Kruskall-Wallis test, as appropriate. To evaluate the effect of patient characteristics on practice variation between study sites, we created two multilevel mixed-effects logistic regression models for each test and treatment of interest and then calculated each model's corresponding intraclass correlation coefficient (ICC). The first model accounted for

random site effects, but did not adjust for patient-level characteristics. The second, more complete model specified random site effects while simultaneously adjusting for patient-level characteristics; i.e., age, sex, insurance provider, major relevant comorbid disorder, and RDSS. Therefore, the ICCs derived from our models that specify only random site effects represent the proportion of the total outcome variation that is attributable to site level differences without adjusting for patient-level characteristics. The ICCs from our complete models represent the total outcome variation that is attributable to site level differences after accounting for differences in patient-level characteristics.

All p values were two-tailed, with $p<0.05$ considered statistically significant.

RESULTS

Study cohort and patient characteristics

Altogether, 408 hospitalized children with bronchiolitis were enrolled (Table 1). Site A enrolled 135 patients, Site B 135 and Site C 138 patients. The median travel distances between home and hospital were13 km for Site A, 47 km for Site B, and 21 km for Site C ($p<0.001$). Among all children hospitalized for bronchiolitis, the median age was 8.1 months (IQR 3.3-14.8), they were more often male (62%), 24% had parents with asthma, and 37% had history of previous wheezing. Additionally, 13% were premature and 12% had major relevant comorbid disorder. Virology testing revealed that 43% were RSV positive and 32% were RV positive, both with and without other detected viruses.

Of all children, 206 (50%) children met our strict definition of bronchiolitis while 202 met the loose definition. Children with strict bronchiolitis were younger partly due to definition, had generally lower RDSS score although exclusively included intensive care unit patients, had RSV more often, and rhinovirus less often (all $p<0.001$) (Table 1).

Patient characteristics by site

Overall, patient characteristics did not differ by site for sex, race, prematurity or parental history of asthma. However, median age of patients and comorbidity varied between sites: at Site A the median age of patients was 6.0 months, at Site B it was 8.1 months and at Site C it was 10.4

months (p<0.001). Comorbidity was highest 17% at Site A, it was 13% at Site B and only 6% at Site C (p=0.01). Also, RDSS varied significantly by site: the mean RDSS was highest 5.3 at Site A, it was 5.1 at Site C and 4.0 at Site B (p<0.001). Taken together, Site A treated younger, more severely ill patients with highest proportion of comorbid disorders.

Testing and medical interventions by site, stratified by bronchiolitis definition

Diagnostic testing differed significantly between the hospital sites (Fig. 1). Among children with strict bronchiolitis (Fig. 1A), complete blood count (CBC) and chest x-ray were performed for nearly all patients at Site B (95% and 91%, respectively), and only few patients at Site A (15% and 18%, respectively) (both p<0.001). At Site C, CBC was performed from 61% and chest x-ray from 16% of patients with strict bronchiolitis. Intravenous fluids were given to 47% of the patients at Site B, and 8% and 2% of patients at Site A and C (p<0.001).

Among children with loose bronchiolitis (Fig. 1B), the amount of diagnostic testing remained high at Site B (CBC 94%, chest x-ray 72%), and remained low at Site A (16%, and 14%, respectively), and C (60% and 20%, respectively) (both p<0.001). Also, the difference in giving intravenous fluids between hospitals varied. Intravenous fluids were given to 41% of patients at Site B, and 2% and 7% of patients at Site A and C (p<0.001).

Medical treatments by site, stratified by bronchiolitis definition

There were also marked differences in medical treatments between the sites (Fig. 2). Among children with strict bronchiolitis (Fig. 2A), the use of nebulised epinephrine was lowest at Site A (10%), highest at Site B (84%), and intermediate at Site C (49%) (p<0.001). No difference between sites was found in the use of salbutamol (p=0.95), nor in the use of antibiotics (p=0.21). Use of corticosteroids was 6% at Site A, 8% at Site B, and 23% at Site C (p=0.03).

Among children with loose bronchiolitis (Fig. 2B), the use of bronchodilators differed between the study sites. The use of nebulised epinephrine was 8% at Site A, 50% at Site B, and 7% at Site C (p<0.001). The use of salbutamol was 84% at Site A, 78% at Site B, and 13% at Site

C (P<0.001). No difference between sites was found in the use of antibiotics (p=0.13), nor in the use of corticosteroids (p=0.26).

Inter-site variability with adjustment for patient characteristics

To evaluate the effect of patient characteristics on care variability between study sites, we calculated ICCs from mixed-effects logistic regression models (Table 2). Overall, comparing the ICCs from models that excluded patient characteristics (Model A) and the ICCs from models that adjusted for patient demographic and clinical characteristics (Model B), the site-attributable variability remained relatively consistent for each outcome after adjustment.

In the strict bronchiolitis subgroup, salbutamol and inpatient antibiotic use exhibited the lowest percentages of site-attributable variability (all ICCs <1%), while performance of CBC, chest x-ray, intravenous fluids, and use of epinephrine demonstrated the highest percentages of variability (all ICCs >40%).

In the loose bronchiolitis subgroup, use of corticosteroids and antibiotics demonstrated the lowest percentages of site-attributable variability (all ICCs <5%), while CBC performed and use of salbutamol demonstrated the highest percentages of variability (all ICCs >40%).

DISCUSSION

We found that use of diagnostic tests and treatment varied considerably between three Finnish hospitals whether a strict or loose definitions of bronchiolitis was used. Variability was not explained by the differences in patient demographics or clinical characteristics. Excessive diagnostic testing and treatments of bronchiolitis may have adverse effects and will certainly increase costs. Therefore, the latest 2014 American Academy of Pediatrics, 2015 National Institute for Health and Care Excellence and 2016 Finnish bronchiolitis guidelines recommend the supportive care of bronchiolitis with adequate oxygenation and nutrition (12,22,29). Our study was performed during 2008-2010, before publication of these latest guidelines, which may explain some of the excessive testing and treatments observed.

Considering diagnostics of bronchiolitis, we found that use of CBC and chest radiography was more common in both clinical subgroups at Site B, although the patients presented with a comparatively less severe illness. According to guidelines, clinicians should diagnose bronchiolitis and assess disease severity on the basis of history and physical examination and radiographic or laboratory studies should not be obtained routinely (12,22,29). However, clinicians should assess risk factors for severe disease, such as age less than 12 weeks, a history of prematurity, underlying cardiopulmonary disease, or immunodeficiency, when making decisions about evaluation and management of children with bronchiolitis. We speculate that the long travel distances between home and hospital at Site B might explain some of these results. If the distance between home and hospital is long, the pressure to perform diagnostic tests and give treatments before discharge might be higher.

In the treatment of bronchiolitis, the largest site differences were found in the use of epinephrine among children with strict definition of bronchiolitis, and in the use of epinephrine and salbutamol among those with loose definition of bronchiolitis. On the contrary, the variability of corticosteroid use was rather low, but it was used quite often among children with loose definition of bronchiolitis. Use of nebulized epinephrine in bronchiolitis patients less than 12 months was national practice in Finland before new randomized trials were published (23-25). This practice was also seen in the study comparing Finnish and Swedish bronchiolitis treatment practices (14). According to recent guidelines, beta agonists and corticosteroids are the most commonly overused, non-evidence-based therapies (12,22,29). Several studies and reviews have evaluated the use of bronchodilators for bronchiolitis patients under two years old, but most randomized controlled trials have failed to demonstrate a consistent benefit (6). The same is true for use of corticosteroids (8,26). The major limitation of these earlier studies was that a subgroup of high asthma risk children was not evaluated separately (20,21). However, much of the continued use of bronchodilators and corticosteroids may arise from similarities in the signs and symptoms between bronchiolitis and asthma, especially with those children close to age 2 years having risk factors for asthma or recurrent wheezing (27,28). It is not surprising that clinician choose to try beta agonists for these older children with asthma risk factors. Most likely, a 23-

month-old child with RV infection and a history of wheeze has a different kind of disease than a three-month-old infant with RSV. Since the current guidelines do not separate these two subgroups, it might be that what is true for the treatment of strict definition of bronchiolitis is not necessarily true for treatment of loose definition of bronchiolitis.

Of other treatments, use of intravenous fluids varied greatly in both bronchiolitis subgroups, with Site B preferring intravenous fluids more than the other sites. We speculate that the other sites more often used nasogastric tube for hydration, but these data were not collected in our study. Guidelines do not prefer either hydration methods, but nasogastric tube can be considered more physiological, and easier to implement, although it may trap mucus and prolong wheezing. Variability in the use for antibiotics was low.

The strengths of our study included a multiyear, multicentre cohort of severely ill bronchiolitis patients, with adjustment for demographic and clinical factors. We evaluated several clinical factors that might have influenced clinical decision-making including parent history of asthma, history of previous wheeze, RDSS, fever and comorbid conditions, but these factors did not explain the variability of practice. Our cohort represented severe bronchiolitis cases because all were admitted to hospital. Therefore, ideally there should have been less observed site variability in tests and treatments. In this paper, we show that even after adjusting for demographic and clinical factors, wide variations between hospitals persisted. Furthermore, wide variation in practice was seen between strict and loose bronchiolitis subgroups. However, this study was not designed to determine the causes for the practice variation; reasons for testing and treatment were not queried. Also, the study was performed before publication of the current guidelines, so we do not know how well the latest guidelines are followed. The follow-up studies are currently on going.

CONCLUSION

We observed marked differences in diagnostic testing and treatments for bronchiolitis both in children with strict or loose definitions of bronchiolitis. Many infants hospitalised for bronchiolitis undergo examinations and treatments not supported by current research evidence or

guidelines for bronchiolitis. These results call for stronger commitment to the evidence-based bronchiolitis guidelines (12,22,29).

ACKNOWLEDGEMENTS

We thank Ashley F Sullivan, MS, MPH (Department of Emergency Medicine, Massachusetts General Hospital, Boston, MA) for coordinating the Multicenter Airways Research Collaboration in Finland study.

FINANCE

The Academy of Finland (grant numbers 114034, 132595 and 267133), the Finnish Medical Foundation and Tuberculosis Foundation of Tampere, all in Finland, supported this work.

CONFLICT OF INTEREST DISCLOSURES: none.

Abbreviations: CBC, complete blood count; CI confidence interval; ICC, Intraclass Correlation Coefficient; IQR, interquartile range; RDSS, respiratory distress severity score; RSV, respiratory syncytial virus; RV, rhinovirus.

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FIGURE LEGENDS

Figure 1. Diagnostic tests and medical interventions by hospital study site for patient subgroups with A) strict definition of bronchiolitis (age <12 months without history of wheeze) and B) loose definition of bronchiolitis (age 12-23 months or with history of wheeze). All $p<0.001$.
Abbreviations: CBC, complete blood count; IV, intravenous fluids.

Figure 2. Medication administered during hospitalization by hospital study site for patient subgroups with A) strict definition of bronchiolitis (age <12 months without history of wheeze) and B) loose definition of bronchiolitis (age 12-23 months or with history of wheeze).

Table 1. Characteristics of hospitalized bronchiolitis patients by bronchiolitis definition (n=408)

	All subjects (n=408)		Strict bronchiolitis (n=206)		Loose bronchiolitis (n=202)		
Characteristics	**n**	**%**	**n**	**%**	**n**	**%**	**P**
Site							<0.001
A	135	33	91	44	44	22	
B	135	33	64	31	71	35	
C	138	34	51	25	87	43	
Distance between home and site, km (median, IQR)	402	19 (9-53)	205	22 (8-57)	197	17 (9-45)	0.47
Age in months (median, IQR)	408	8.1 (3.3-14.8)	206	3.7 (1.8-6.6)	202	14.8 (10.8-18.3)	<0.001
Age in months							<0.001
<1 month	23	6	23	11	0	0	
1-1.9	41	10	36	17	5	2	
2-3.9	62	15	52	25	10	5	
4-5.9	43	11	36	17	7	3	
6-11.9	95	23	59	29	36	18	
≥12	144	35	0	0	144	71	
Sex							0.12
Male	251	62	119	58	132	65	
Female	157	38	87	42	70	35	
Race							0.85
white	403	99	203	99	200	99	
black	3	1	2	1	1	0,5	
other or missing	2	0	1	0,5	1	0,5	
RDSS, quartiles							<0.001
1 (0-3.05)	99	24	65	32	34	17	
2 (3.12-5.00)	112	27	71	34	41	20	
3 (5.003-6.41)	84	21	35	17	49	24	
4 (6.44-8.0)	98	24	30	15	68	34	
missing	15	4	5	2	10	5	
Inpatient							
ICU	13	3	13	6	0	0	<0.001
Hospital LOS (days), median (IQR)	408	2 (1-3)	206	2 (1-3)	202	1.5 (1-3)	0.07
Hospital ≥3 LOS (days)	130	32	73	35	57	28	0.12
Virology							
RSV	175	43	133	65	42	21	<0.001
RV	130	32	29	14	101	50	<0.001
Number of infections							0.33
0	58	14	24	12	34	17	
1	287	70	149	72	138	68	
≥2	63	15	33	16	30	15	

Abbreviations: IQR, interquartile range; RDSS, respiratory distress severity score; ICU, intensive care unit; LOS, length of stay; RSV respiratory syncytial virus; RV, rhinovirus.

Table 2. Intraclass Correlation Coefficient assessing inter-site variability in the use of diagnostic tests and treatments for bronchiolitis, with and without adjustment for patient characteristics

Strict bronchiolitis, n=206

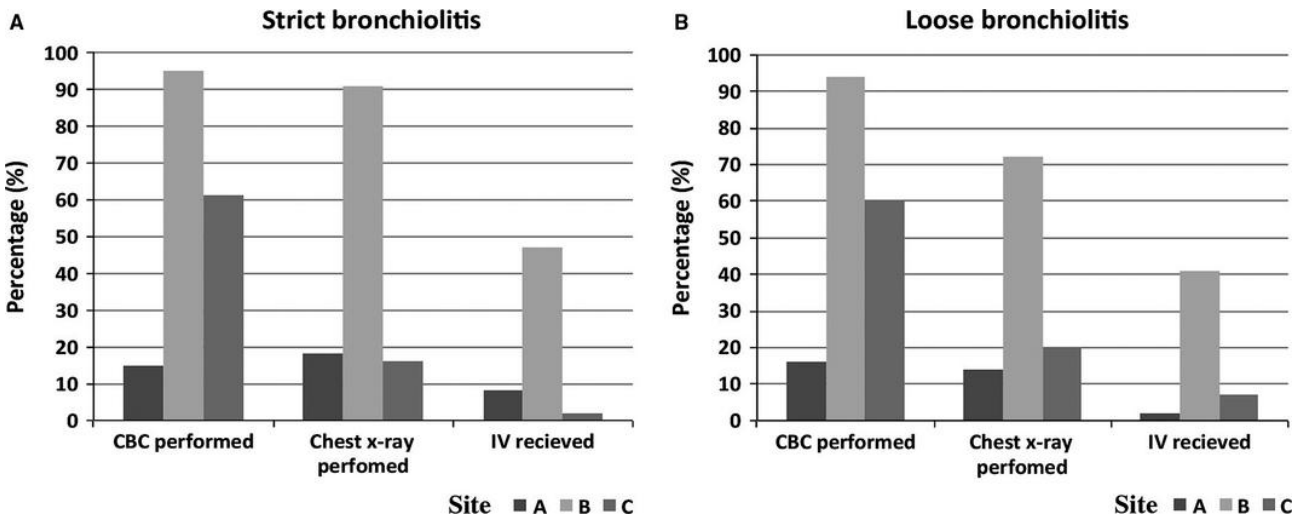
	Model A: site random effects			Model B: site random effects with adjustment for patient characteristics*		
Outcomes	**ICC (%)**	**95%CI**		**ICC (%)**	**95%CI**	
CBC performed	53%	17%	86%	56%	18%	88%
Chest x-ray performed	50%	16%	85%	52%	17%	86%
IV received	41%	9.8%	82%	56%	18%	89%
Nebulized epinephrine given	43%	12%	80%	42%	12%	81%
Nebulized salbutamol given	0%	0%	0%	0%	0%	0%
Corticosteroids	8.4%	0.6%	58%	17%	1.8%	70%
Antibiotics	0.1%	0%	100%	0.4%	0%	100%

Loose bronchiolitis, n=202

	Model A: site random effects			Model B: site random effects with adjustment for patient characteristics*		
Outcomes	**ICC (%)**	**95%CI**		**ICC (%)**	**95%CI**	
CBC performed	50%	15%	85%	53%	16%	87%
Chest x-ray performed	31%	7.4%	71%	33%	7.7%	74%
IV received	36%	7.7%	79%	33%	6.3%	79%
Nebulized epinephrine given	31%	6.7%	73%	37%	7.9%	80%
Nebulized salbutamol given	44%	13%	81%	48%	14%	84%
Corticosteroids	0%	0%	0%	4.1%	0.1%	67%
Antibiotics	1.0%	0%	73%	3.7%	0.2%	43%

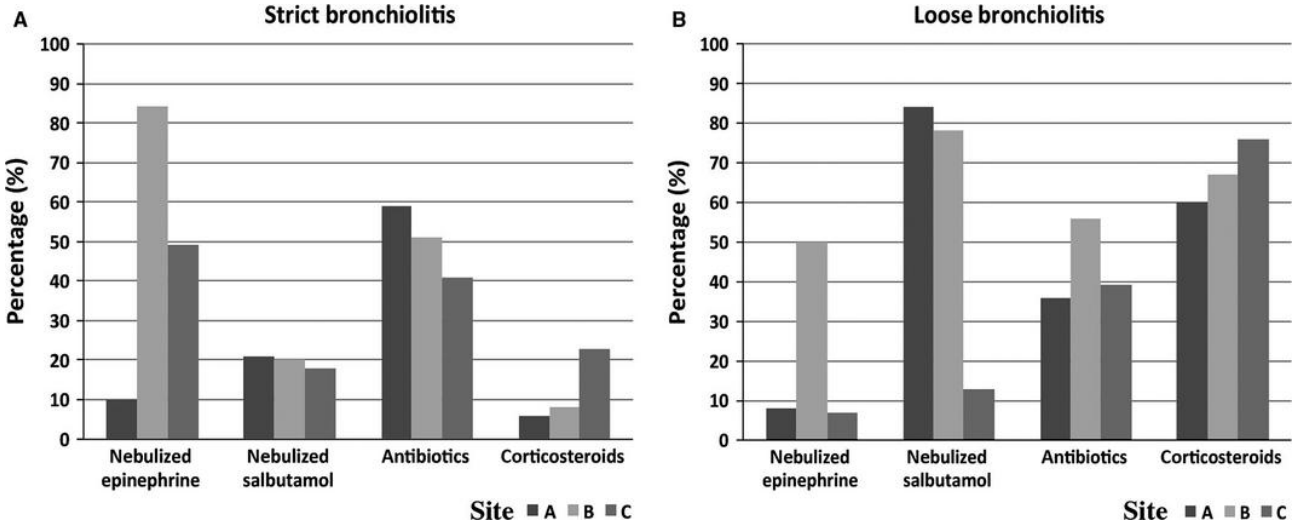
*Age, sex, insurance, major relevant comorbid disorder, respiratory distress severity score (RDSS)
Abbreviations: ICC, intraclass correlation coefficient; 95% CI, 95% confidence interval; IV, intravenous.

Figure 1



Diagnostic tests and medical interventions by hospital study site for patient subgroups with (A) strict definition of bronchiolitis (age <12 months without history of wheezing) and (B) loose definition of bronchiolitis (age 12–23 months or with history of wheezing). All $p < 0.001$. Abbreviations: CBC, complete blood count; IV, intravenous fluids.

Figure 2



Medication administered during hospitalization by hospital study site for patient subgroups with (A) strict definition of bronchiolitis (age <12 months without history of wheezing) and (B) loose definition of bronchiolitis (age 12–23 months or with history of wheezing).