Antibiotic use in infants hospitalized with bronchiolitis.

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Abbreviations: RSV – Respiratory syncytialvirus; LOS – Length of stay; AAP – American Academy of Pediatrics;

Abstract

Background and Objectives
Acute viral bronchiolitis is the leading cause of hospitalization in infants. Despite no evidence of its effect, the use of antibiotics in the treatment of bronchiolitis is still widespread. The aims of the present study were to identify the rate and type of antibiotic use in infants hospitalized with acute bronchiolitis in Southeast Norway, to compare this use to other countries, and to explore the association between antibiotic use and disease severity.

Methods
404 infants hospitalized with moderate to severe acute bronchiolitis in eight hospitals in Southeast Norway completed a clinical trial of inhaled racemic adrenaline. The mean length of stay was 3.3 days, 44% received oxygen support, 29% nasogastric tube feeding and 7% ventilatory support. Data on the use of antibiotics has been obtained from individual patient records from all patients. Studies for comparison of antibiotic use were chosen after searching the following electronic search bases: Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, and Medline/Pub Med.

Results
8.4 % (n=34) of the patients received systemic antibiotics, (4,2% intravenous and 4,2% oral), most commonly penicillin (41%), ampicillin (26%) and gentamicin (24%). Patients treated with antibiotics stayed longer in hospital than those untreated (135.5 vs. 65.9 hours, $p<0.001$). Patients that received supportive therapy also received more antibiotics: oxygen (17.4% vs. 1.4%, $p<0.001$), feeding (15.5% vs. 5.7%, $p=0.03$) and ventilatory (48.3% vs. 5.3%, $p<0.001$) support. Use of antibiotics for bronchiolis in other studies ranged from 18 -99 %.

Conclusion
The use of antibiotics is substantially lower than previously reported in any geographical region. With length of stay and use of supportive care comparable to other countries, we believe the findings support a restrictive approach in bronchiolitis management

Introduction

Acute bronchiolitis is a leading cause of hospitalization in the first six months of life (1, 2). The aetiology is airway viruses, most commonly respiratory syncytial virus (RSV) accounting for 50 – 80 % of the cases, however other viruses are also associated with the disease (3). There is a consensus that antibiotics are not recommended as standard treatment (1, 2, 4), and the risk of bacteraemia, meningitis or other serious bacterial infections is very low (1, 2, 4-6).

Regardless of the restrictive recommendations, the use of antibiotics in the treatment of bronchiolitis is widespread (2, 7-16) Although higher rates of bacterial co-infection have been reported in children requiring intensive care treatment, antibiotic use remains excessive also in this patient group (17-19). Antibiotics come with costs and common adverse reactions such as diarrhoea, vomiting, rash and abdominal pain (1). Furthermore it is well recognized that excessive antibiotic use has a causal effect on bacterial resistance, which is an increasing problem worldwide (20-24). About 60 % of all antibiotics are used for respiratory infections (25), and no age group consumes more than children < five years (26).

The decision to start antibiotic treatment is usually based on the infant's clinical condition, results from laboratory testing and chest radiography (8). The excessive use has been attributed to young age, fever, radiological testing, and fear of bacterial co-infection, as well as parental pressure and anxiety in the clinician (2, 8, 15). Implementation of evidence-based guidelines and rapid viral diagnostics has both been attempts to increase treatment compliance and reduce antibiotics overuse (8, 9, 27, 28).

The primary aim of the present study was to identify the rate and type of antibiotic use in infants with acute bronchiolitis in Southeast Norway. Secondary aims were to compare the antibiotic use in our study population with that in other countries, and to explore the association between antibiotic use and disease severity in terms of length of hospital stay and the use of supportive care.

Subjects and Methods

Study design

The Bronchiolitis ALL-study is a multicenter, randomized, factorial designed clinical trial comparing the effect of inhaled racemic adrenaline versus saline and two inhalation strategies (on demand versus fixed schedule) in infants in Norway during two consecutive winter seasons from January 2010 through May 2011. (29) Inclusion criteria were age <12months and clinical signs of moderate to severe bronchiolitis. (30) A clinical score of ≥4 on a scale from 1 to 10 (10 worst, see online supplement, Table S1) were used to indicate moderate to severe illness. Exclusion criteria were severe underlying disease, >1 episode of previous wheeze, >4 weeks continuous lower airway symptoms (e.g. cough) and use of inhaled or systemic steroids for the previous 4 weeks. The use of supportive care was recorded daily, results of chest radiography and laboratory data were documented, and the use of antibiotics was registered on discharge.

Subjects

All 404 infants from the original RCT were included in the present study, (59.4% boys, mean age 4.2 months) were admitted for hospitalization with moderate to severe bronchiolitis in one of the eight participating hospitals in South East Norway. The mean (±SD) length of stay (LOS) was 80±67 hours. Baseline data were obtained on admission (table 1). Supportive therapy was administered as oxygen in 43.7%, nasogastric tube feeding in 29.1% and non-invasive ventilatory support (CPAP) in 7.4% (figure 3).

Methods

To ensure the correct rate of antibiotic use, all individual patient records were reviewed. Indications for antibiotic use, length of treatment, type of antibiotics and whether treatment

was changed or shortened, were recorded from the patient journals. Patients treated with local antibiotics only were categorized as not receiving antibiotics.

The studies used for comparison were chosen after searching the following electronic search bases: Cochrane Database of Systematic Reviews (1996- November 2014), Cochrane Central Register of Controlled Trials (1898- November 2014), and Medline/Pub Med (1946-February 2015) The search terms used were "bronchiolitis", "acute bronchiolitis, "bronchiolitis AND antibiotics", "bronchiolitis AND management", and "bronchiolitis AND treatment". Articles in English, Spanish, French, Norwegian, Swedish and Danish were considered. The five first search-pages for each search term were reviewed, resulting in more than 1000 articles being considered for inclusion. Most studies were excluded based on title and/or abstract, and around 200 articles were reviewed full text. 12 studies were carefully selected based on similarity to our study population, and availability of information about antibiotic use. Only studies of infants < 1 year of age hospitalized for bronchiolitis were originally included, but we expanded with three studies including children < 2 years, and one including children up to 18 months, as the mean age was still between 3-6 months. Larger review articles or randomized controlled trials were preferred. We aimed to include studies from different parts of the world with emphasize on western countries, where similarity in management and degree of illness was assumed to be comparable.

Statistical analysis

Continuous data are presented as means (+/-SD), and categorical data are presented as numbers and percentages. Categorical data were analyzed with the use of the Pearson chi-square or Fischers exact test, while independent samples t-test was used to analyze parametric continuous variables. In continuous variables with a non-normal distribution (including length

of stay), comparisons between groups were analyzed with the use of a robust, two-sample t-test and Huber's M-estimator, with 95% confidence intervals.
The two groups (antibiotics vs. no antibiotics) were compared in terms of baseline characteristics and use of supportive care.

The study was approved by the Regional Committees for Medical and Health Research Ethics and by the Norwegian Medicines Agency and is registered in the Norwegian Biobank Registry. Written informed consent was obtained from a parent of each child before the start of therapy. The study was audited by the Norwegian Medicines Agency in 2011. The trial was registered in ClincialTrials.gov (NCT00817466) and EudraCT (2009-012667-34). Details on randomization and study medication are described in the original study article (29).

Results

8,4 % (34/404) of the infants received systemic antibiotics, (4,2 % IV and 4,2 % orally), (see Online Supplement, Table S2 for individual data on specific indications, treatment, chest x-ray, microbial diagnostics and blood chemistry). Indications for use were recorded as lower respiratory tract infection in 26 patients, including sepsis in five and pertussis in three individuals (two confirmed). Six patients were treated for otitis media while urinary tract infection and tonsillitis were diagnosed in one patient each. In four patients, treatment was initiated before admission to hospital (see Online Supplement for characteristics, Table S3). Most commonly administered antibiotics were penicillin (n=15, 44%), ampicillin (n=9, 26%), gentamicin (n=8, 24%), erythromycin (n=4, 12%) and amoxicillin (n=4, 12%). 10 (29%) received more than one type of antibiotics, 7 (21%) the combination of ampicillin and gentamicin. Mean length of treatment in hospital was 4,7 days (data available for 29 /34) and 11 infants continued treatment after discharge.

12 studies were selected for comparison based on similarity to our study population, and availability of information about antibiotic use (Table 2). Due to the variability in the data that are reported, statistical analyses to compare the study populations have not been performed. However, mean age was between 3-6 months in all studies included, and the majority of all study populations were male. The range of antibiotic use varied from 18,2 % to 90 %, and only one study had rates below 30 % (31) (Figure 1). Two of the studies stated which type of antibiotics was most commonly used (9, 13). Length of stay was shorter in our study than in six of the eight other studies that reported this information. Few studies reported baseline characteristics and use of supportive care.

In the present study, the baseline characteristics of the patients that received antibiotics versus no antibiotics were similar, except for measurements of oxygen saturation (93.8% versus 96.2%, $p<0.001$) C-reactive protein (mean 26.8 vs.13.9, $p=0.006$) and neutrophils (5.8 vs.3.5, $p=0.002$) (table 1). The use of chest radiography in the antibiotic group was higher (88.2% vs.39.5, $p<0.001$). Use of antibiotics was significantly associated with longer hospital stay (mean 135.5 hours (95% CI 117.0-154.1) vs. 65.9 hours (95% CI 47.2-85.1), $p<0.001$) (Figure 2), and use of supportive therapy (all $p<0.03$). Antibiotics use was highest in patients who were treated with CPAP (48.3% vs. 5.3%, $p<0.001$). Patients who received oxygen (17.4% vs. 1.4%, $p<0.001$) and nasogastric tube feeding (15.5% vs. 5.7%, $p=0.03$) were also more frequently treated with antibiotics (Figure 3). All analyses are unadjusted.

Discussion

In hospitalized infants with moderate to severe acute bronchiolitis in Southeast Norway, we found that the rate of systemic antibiotic use was substantially lower than what has previously been reported in any other geographical region, while the mean length of stay (3.3 days) was similar or lower to that reported in other studies. The most commonly used antibiotics were of the narrow spectrum type (penicillin and ampicillin).

Our findings may indicate that low rates of antibiotics for bronchiolitis is not associated with increased disease severity in terms of prolonged LOS. Few of the studies reported use of supportive care, making this more difficult to discuss. However, the number of patients treated with supplemental oxygen was lower in our study compared to four of the five studies reporting such use and there is no evidence of antibiotics reducing need for oxygen therapy(6). The use of CPAP in the present study was similar as in other studies (32).

The three largest studies included in table 4 are all cross-sectional American studies, where mean antibiotic rate was reported to be respectively 45 %, 39 % and 32,9 % (12, 15, 33). The infants in these studies are comparable to ours in terms of mean age and gender, while LOS appears to be somewhat shorter. However, only two of the studies reported LOS, of which one excluded (33) all patients with LOS > 7 days. Use of chest radiography was higher and found to be a significant predictor of antibiotic use in one of the studies (15). All studies demonstrated a substantial variation in bronchiolitis management across hospitals, however Florin et al (33) found that use of antibiotics had the narrowest range of variation compared to use of albuterol, racemic epinephrine, corticosteroids and chest radiography.

Several recently published articles report a lack of reduction in antibiotic use despite the publication of new guidelines (11, 12, 33, 34). As these studies demonstrate, changing practice is difficult to achieve, especially in larger and less integrated health care systems like that in the United States (34). Local hospitals or countries with smaller populations of patients and practitioners may be more responsive to change as demonstrated by other authors (27, 35, 36). This might be part of the explanation for the low rate found in Norway, but does not fully explain the excessive use persisting in most other countries.

The present study was not designed to report effects of antibiotic treatment for bronchiolitis, and we have not adjusted for confounding factors. We have therefore not attempted to address the casual relationship between antibiotic effect and LOS, and the results must be regarded as descriptive. Moreover, despite similar inclusion criteria, it is difficult to compare study populations across studies and countries as long as the inclusion criteria are not identical.

In the present study we found that the prevalence of antibiotic treatment due to concomitant infection was low (10/404). This is in compliance with Norwegian national guidelines for treatment of respiratory tract infections (25, 37, 38), which constituted the majority of the cases (9/10). Antibiotic consumption in general and the use of broad-spectrum antibiotics are substantially lower in Norway than in the USA and most of Europe(23, 39-41). Pneumococcus are generally sensitive to penicillin, which is the antibiotic of choice for bacterial airway infections. (42, 43).

Still there is great potential for reducing unnecessary antibiotic use even in Norway, including in the treatment of bronchiolitis (25, 39, 41). Unfortunately we were not able to find any relevant studies for comparison from the other Scandinavian countries, were antibiotic use has been shown to be similar to Norwegian practice (40).

We found that use of antibiotics was highly associated with the length of hospital stay and patients receiving supportive care were much more likely to receive antibiotics. There are several possible confounders that we have not adjusted for, and hence we do not aim to report any effects. Nonetheless the association between antibiotic treatment and increased LOS has been documented previously (15, 33, 44).

Except for oxygen saturation, which was significantly lower in the antibiotic group, the children were similar in baseline characteristics, including total severity score. Infectious parameters were higher on inclusion in the group that later received antibiotics, and results from laboratory testing were used in the decision to start antibiotic treatment in more than 1/3 of the patients (table S2). Use of chest radiography was also higher, and has been associated with increased use of antibiotics in other studies.

An interesting aspect is the distinction between bronchiolitis, other obstructive airway diseases, and pneumonia. Lower airway infections have been found to be the most common cause of mortality in children less than five years of age in any region of the world (45). In order to prevent this, WHO promoted a clinically based management algorithm (Integrated Management of Childhood Illness – IMCI) in 1991, stating that any child with a cough and fast breathing should be classified as pneumonia, and therefore should be treated with antibiotics. This guideline does not take into account that episodes of obstructive airways are mainly of viral origin, or even non-infectious and therefore might lead to an over-diagnosis of bacterial pneumonia and excessive antibiotic use (46, 47). Moreover this could potentially delay the patients from receiving correct treatment such as inhalations or oxygen therapy, which again may cause prolonged or even more serious illness. (46, 47)

Conclusion

Antibiotic use in infants with bronchiolitis in South East Norway is 8,4 %, which is substantially lower than previously reported in any other geographical region,where use of antibiotics range from 18-99 %. Length of stay and use of supportive care is still comparable to other countries. The infants who were treated with antibiotics had significantly lower saturation and higher levels of CRP and neutrophils on inclusion. Use of radiography and supportive care was more frequent and LOS was longer compared to those not treated with antibiotics.

There is a significant variation in bronchiolitis management,(33, 48) and antibiotics along with other interventions continue to be overused(49). Current efforts should therefore focus on strategies to decrease unnecessary and ineffective testing and treatment.(49) With antibiotic resistance becoming an increasing problem worldwide, it is of high importance to reduce the use of antibiotics when possible, in line with the current recommendations.(2) We believe the present study support a restrictive approach to antibiotic use in the treatment of bronchiolitis.

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Tables

Table 1 – Baseline characteristics

Characteristics	Systemic Antibiotics (n=34)	None or local antibiotics (n=370)
Male sex - no (%)	20/34 (58.8)	220/369 (59.5)
Age, months (95 % CI)	3.8 (2.6-4.9)	4.2 (3.9-4.5)
Atopic eczema	1/32 (3.1)	39/341 (11.4)
Reported allergies	0/32	7/340 (2.1)
1 previous obstructive episode (%)	8/31 (25.8)	90/330 (27.3)
>1 week of persistent respiratory symptoms (%)	2/28 (7.1)	43/320 (13.4)
Parental asthma (%)	6/31 (19.4)	77/294 (26.2)
Parental rhino conjunctivitis (%)	15/32 (46.9)	98/324 (30.3)
Clinical score (95 % CI)	5.1 (4.7-5.5)	4.9 (4.8-5.0)
SpO2 (95 % CI)	93.8 (92.3-95.1)*	96.2 (95.9-96.5)
Respiratory rate (95 % CI)	53.6 (49.7-57.5)	53.5 (52.3-54.7)
Heart rate (95 % CI)	152.5 (144.9-160.0)	153.7 (151.8-155.7)
RSV positive (%)	27/29 (93.1)	273/333 (82.0)
Chest x-ray obtained (%)	30/34 (88.2)*	146/370 (39.5)
Chest x-ray opacities		
Consolidated (%)	9 (30)	18 (12,3)
Perihilar (%)	14 (46.7)	73 (50.7)
Atelectasis (%) §	7 (23)	16 (11)
Haemoglobin (95 % CI)	11.8 (11.1-12.5)	11.8 (11.7-12.0)
Leukocytes (95 % CI)	13.0 (10.5-15.6)	10.9 (10.5-11.3)
Neutrophils (95 % CI)	5.8 (4.4-7.1)**	3.5 (3.3-3.8)
Lymphocytes (95 % CI)	5.5 (3.8-7.2)	5.7 (5.5-5.9)
Platelets (95 % CI)	432.9 (386.4-479.4)	414.4 (401.9-426.9)
CRP (95 % CI)	26.8 (18.1-35.5)***	13.9 (11.7-16.1)+
PH (95 % CI)	7.36 (7.35-7.7.37)	7.36(7.35-7.36)
PCO2 (95 % CI)	6.1 (5.6-6.7)	5.7 (5.6-5.8)
Sodium (95 % CI)	137.4 (136.7-138.1)+	138.0 (137.8-138.2)
Potassium (95 % CI)	4.9 (4.6-5.1)§	4.8 (4.8-4.9)
Creatinine (95 % CI)	19.9 (17.3-22.6)+	18.3 (17.7-18.9)+

Baseline characteristics in infants treated with systemic antibiotics vs. infants treated with none or only local antibiotics.
*P<0.001, ** p<0.002, ***p<0.006.
+Data available from >85 % of the population, except for cases marked with + where data was available from 70-85% of the population.
§ Atelectasis was described as either segmental (linear) (3/7, 7/16) or consolidated (4/7, 9/16) in the chest x-ray descriptions.