**International Practice Patterns of Antibiotic Therapy and Laboratory Testing in Bronchiolitis**

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**Abbreviations:**

ED Emergency Department

OR Odds Ratio

CI Confidence Interval

U.S. United States

U.K. United Kingdom

ICU Intensive Care Unit/s

PERN Pediatric Emergency Research Networks

PERC Pediatric Emergency Research Canada

PEM-CRC Pediatric Emergency Medicine Collaborative Research Committee

PECARN Pediatric Emergency Care Applied Research Network

PREDICT Pediatric Research in Emergency Departments International Collaborative

PERUKI Pediatric Emergency Research United Kingdom and Ireland

REPEM Research in European Pediatric Emergency Medicine

SAS Statistical Analysis System

**Table of Contents Summary**

This global bronchiolitis Emergency Department study illustrates that while the use of antibiotics in infants with bronchiolitis in pediatric emergency departments is uncommon, laboratory testing is frequently performed, particularly outside of the U.K./Ireland, irrespective of patient-level characteristics.

**What is Known on This Subject:** There is an important knowledge gap regarding the international patterns of antibiotic use and laboratory testing in infants diagnosed with bronchiolitis in Emergency Departments. This information may help future international efforts on averting non-indicated management strategies for this common disease.

**What This Study Adds:** The use of antibiotics in bronchiolitis is uncommon. However, the rate of antibiotic therapy in infants with versus without chest radiography is variable across networks and sites, independent of bronchiolitis severity. Laboratory testing is frequently performed outside of the U.K./Ireland.

**Contributors’ Statement Page**

Dr. Zipursky conceived the study, co-wrote the study protocol and wrote the manuscript.

Dr. Kuppermann designed the study, provided major input into the concept and analysis of the study and drafting and revision of the manuscript.

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Dr. Benito designed the study, drafted the manuscript and revised it for intellectual content.

Dr. Schuh conceived the study, co-wrote the study protocol, wrote the manuscript and revised it critically for intellectual content.

**International Practice Patterns of Antibiotic Therapy and Laboratory Testing in Bronchiolitis**

**Introduction**

Bronchiolitis is a viral lower respiratory infection, with small airways inflammation and edema[1](#_ENREF_1), [2](#_ENREF_2). It is the most common reason for hospitalization in infants in the United States and other Western countries[3-5](#_ENREF_3). Contrary to the recommendations of bronchiolitis guidelines[1](#_ENREF_1), [6-14](#_ENREF_6) , many infants diagnosed with bronchiolitis in the emergency department (ED) receive ineffective medications such as bronchodilators and systemic corticosteroids and are exposed to radiation from unnecessary chest radiography and the use of these varies considerably between countries and institutions[15-18](#_ENREF_15).

Infants with bronchiolitis are at low risk of serious bacterial infections[19-21](#_ENREF_19), and experts discourage routine laboratory testing and antibiotic use, unless bacterial infections are suspected[1](#_ENREF_1), [6-14](#_ENREF_6). Although use of these interventions remains common,[22](#_ENREF_22), [23](#_ENREF_23) our knowledge about their use has been derived primarily from studies of hospitalized patients[24-31](#_ENREF_24). Studies that have included ED patients are sparse and preceded publication of recent bronchiolitis guidelines[32](#_ENREF_32), [33](#_ENREF_33), were single-centre[34](#_ENREF_34), [35](#_ENREF_35) , were restricted geographically to a single region or country[16](#_ENREF_16), [22](#_ENREF_22), [25](#_ENREF_25), [36](#_ENREF_36) and have not explored their association with patient-level factors.

As initiatives to minimize unnecessary interventions are increasing,[37](#_ENREF_37), [38](#_ENREF_38) a better understanding of the international patterns of antibiotic use and laboratory testing in infants with bronchiolitis is required. A global evaluation of testing and interventions employed is needed to assist with benchmarking which can be employed to guide future quality improvement initiatives designed to minimize unnecessary testing and treatment.

To address this knowledge gap, we conducted a planned secondary analysis of a retrospective cohort study of previously healthy infants with bronchiolitis who presented to the EDs associated with pediatric emergency research networks (PERN) in Canada, the United States, Spain/Portugal, United Kingdom/Ireland and Australia/New Zealand in order to evaluate variation in antibiotic use and laboratory testing across research networks, after adjustment for patient-level characteristics. We hypothesized there would be significant variation between networks.

**Methods**

**Study Design and Population**

We conducted a retrospective cohort study at 38 pediatric PERN-related EDs in eight countries. The PERN is a global collaborative research network comprised of several national/regional networks[39](#_ENREF_39). Participating networks at the time included: 1) Pediatric Emergency Research Canada (PERC); 2) Pediatric Emergency Medicine Collaborative Research Committee (PEM-CRC) and Pediatric Emergency Care Applied Research Network (PECARN) in the United States; 3) Paediatric Research in Emergency Departments International Collaborative (PREDICT) in Australia & New Zealand; 4) Paediatric Emergency Research United Kingdom & Ireland (PERUKI), and 5) Research in European Paediatric Emergency Medicine (REPEM) in Europe, including Spain & Portugal.

The original study population included infants younger than 12 months of age, diagnosed with bronchiolitis in the participating EDs between January 1, 2013 and December 31, 2013. We defined bronchiolitis as the first presentation of acute respiratory distress with lower respiratory symptoms.[1](#_ENREF_1), [12](#_ENREF_12) As bronchiolitis symptoms may last up to one month, we excluded infants with previous visits to a health care provider for bronchiolitis symptoms 1 month or more prior to the index ED visit. We also excluded those with co-existent lung disease, congenital heart disease, immunodeficiency, neuromuscular/neurologic/bone disease, metabolic/genetic, kidney or liver disease, and those previously enrolled in the study. Because febrile infants with documented viral infections younger than 2 months of age remain at a non-negligible risk for serious bacterial infections[40](#_ENREF_40), we have limited this study to infants 2-12 months of age.

**Patient Identification and Study Execution**

At each hospital, we identified the medical records of all infants who presented to the ED within the study period and had an International Classification of Disease 9 or 10 discharge diagnosis of bronchiolitis (codes J 21·0, 21·8, 21·9/466·1). Using a random number generator, each site identified a random sample of medical records for review. We collected patient study data according to standard methods for medical record reviews[41](#_ENREF_41), with all study variables defined *a priori.* We itemized these variables in a manual of operations with data source hierarchy, which was employed by all site investigators and data abstractors. To standardize research procedures, site investigators were educated in data extraction procedures on site-and study-specific terms (e.g. dehydration); site investigators reviewed the case report forms to ensure information clarity. Trained abstractors assessed eligibility and recorded data into a web-based database until at least 50 medical records were included in the parent study from each site.

Abstracted data included patient demographics, presenting symptoms and physical examination findings in the ED, vital signs including temperature and oxygen saturation measured on room air at triage, and medications administered in the ED and prescribed at ED discharge. We collected information on suspected bacterial infections, blood, urine and nasopharyngeal microbiology tests, chest radiography, and patient disposition location [i.e. home, inpatient ward, intensive care unit (ICU)].

**Outcome Measures**

The primary outcome measure was systemic administration of at least one antibiotic in the ED or a prescription for an antibiotic at ED discharge. The secondary outcome was performance of at least one non-recommended laboratory test [1](#_ENREF_1), [21](#_ENREF_21) in the ED. The bronchiolitis guidelines advise against routine chest radiography, with the exception of infants considered for admission to ICU[42](#_ENREF_42). Bacteremia is very uncommon in febrile infants with viral infections 2 months and older[40](#_ENREF_40). However, febrile infants with bronchiolitis 2 months of age and older remain at risk of urinary tract infections[43](#_ENREF_43), and this risk is of main concern in those younger than 3 months of age[44](#_ENREF_44). Some institutions use viral testing for cohorting of hospitalized patients with bronchiolitis[10](#_ENREF_10), [11](#_ENREF_11), [14](#_ENREF_14). Therefore, we defined non-recommended laboratory tests as any of the following: chest radiography in infants not admitted to ICU, nasopharyngeal viral testing in infants discharged home from the ED, complete blood count or blood culture, urinalysis in afebrile infants (i.e. temperature in triage <38.0°C) or urine culture in afebrile infants and in febrile infants ≥ 3 months of age.

**Analyses**

To ensure our study cohort would have adequate power to evaluate the association between study network and antibiotic use, we calculated the sample size required to provide 80% power using a 5% two-sided significance level, with adjustment for 12 patient-level characteristics, assuming an average of 25% of infants received antibiotics[22](#_ENREF_22). Using these assumptions and allowing for 15 patients with the outcome for each variable examined , we determined a sample of at least 180 infants with and 540 infants without antibiotics, respectively, would suffice for this study[45](#_ENREF_45).

We used proportions and 95% confidence intervals to describe categorical data and means with standard deviations or medians with interquartile ranges for continuous data. Relevant 95% confidence intervals were calculated around proportions. The PEM-CRC and PECARN networks were treated as a single network, as both are based in the U.S.

Bivariable logistic regression analysis was used to examine the association between each variable and antibiotic administration. Thereafter, multivariable logistic regression was performed to determine the association between administration of antibiotics as a binary dependent variable and potential predictors. Because the ED physicians may be more inclined to offer antibiotics to febrile infants with more severe disease and those with suspected bacterial infections, we sought to reduce confounding by indication by including the following *a priori* defined variables: age 2 months[46](#_ENREF_46), poor feeding, dehydration, nasal flaring/grunting, chest retractions, reported or observed apnea, oxygen saturation, respiratory rate, temperature ≥ 38.0°C in triage, suspected bacterial infection (i.e. documented secondary diagnosis of otitis media, pneumonia, urinary tract infection or sepsis), chest radiograph in the ED, and the network. Predictor variables with bivariable p-values <0.2 were included in the multivariable analysis. Because there is known variation across networks in obtaining chest radiographs[17](#_ENREF_17), we tested for the interaction between chest radiography and network and, if significant, included this interaction term in the multivariable analysis. We have also tested for collinearity between chest radiography and suspected bacterial infection as chest radiography frequently leads to incorrect diagnosis of bacterial pneumonia and antibiotic use[47](#_ENREF_47).

We assumed data were missing at random. We used fully conditional specification to impute missing data. As a sensitivity analysis, we independently analyzed 5 copies of the continuous and categorical data, each with missing values suitably imputed.[48](#_ENREF_48) Given that management was likely similar within sites, we incorporated the ED as a random effect.

We used multiple logistic regression analyses to examine the associations between a) non-recommended laboratory testing and network, b) hospitalization from the ED and antibiotic use and c) hospitalization and use of at least one non-recommended test, after adjustment for the patient-level characteristics. The analyses were performed using SAS version 9·4 and PROC GLIMMIX (SAS Institute Inc.).

**Results**

*Study Population*

A total of 5,305 potentially eligible infants were identified at the 38 participating EDs. Of these, 2,183 met exclusion criteria, leaving 3,022 eligible participants. Of these, 2359 infants had complete data for all study variables: 476 at eight Canadian pediatric EDs [PERC], 718 at ten EDs in the U.S. [PEM-CRC and PECARN], 497 children at eight EDs in Australia & New Zealand [PREDICT], 592 at nine EDs in U.K. & Ireland [PERUKI] and 76 infants at three EDs in Spain & Portugal [REPEM]. Of the 2359 study infants, 1553(65.8%) were discharged home, 769 (32.6 %) were admitted to an inpatient unit and 37 (1.6 %) required ICU care. The characteristics of the infants are described in Table 1.

*Antibiotic Use*

A total of 180/2359 (7.6 %) infants were administered antibiotics. Of the 180 infants given antibiotics, 120 (66.7%) had documented suspected bacterial infections: 72 with otitis media, three with urinary tract infection, four with suspected sepsis and 45 with pneumonia (four infants had more than one bacterial diagnosis).

The rates of antibiotic therapy were 80/718 (11.1%) in the U.S., 39/476 (8.2%) in Canada, 34/497 (6.4%) in Australia/New Zealand, 21/592 (3.5%) in the U.K./Ireland and 6/76 (7.9%) in Spain/Portugal. The proportional use of antibiotics at individual EDs ranged from 0% to 21.0%.

Infants treated with antibiotics were more likely to have more severe respiratory distress, lower oxygen saturation, and fever compared to those not treated with antibiotics (Table 2).

*Variation in Antibiotic Therapy*

In the multivariable analysis, the interaction between network and chest radiography was not significant (p=0.11) and thus not included. As chest radiography and suspected bacterial infection were highly related (p<0.0001), only one of these variables could be used in the multivariable analysis. Because most physicians would have a low threshold for using antibiotics for suspected bacterial infections, we were interested in the association between antibiotic use and chest radiography and therefore included this variable in the multivariable analysis. After adjustment for patient-level characteristics, we found that the antibiotic therapy was associated with chest radiography (OR 2.29; 1.62-3.24), apnea (OR 2.20; 1.14-3.52) and fever (OR 2.40; 1.74-3.43). However, antibiotic use did not vary across networks (p=0.15). Compared to the U.K./Ireland (with the lowest rate of use), the respective adjusted odds of antibiotic use were: 1.60 (95% CI 0.83-3.26) in Canada, 2.25 (1.20-4.20) in the U.S., 1.80 (0.91-3.57) in Australia/New Zealand and 1.50 (0.46-4.86) in Spain/Portugal. The multiple imputation procedure did not change these results.

*Antibiotic Therapy and Patient Disposition*

The rates of antibiotic therapy were 64/769 (8.3 %) for infants admitted to inpatient wards, 8/37 (21.6 %) for those managed in the ICU and 108/1553 (7.0%) for infants discharged home (adjusted OR for the difference in hospitalized versus discharged infants 1.31; 95% CI 0.95-1.78; p=0.09).

*Laboratory Testing*

Of the 2359 study infants,768 (32.6%) had at least one non-recommended test: 591 had nasopharyngeal viral testing without admission to hospital, 507 had chest radiographs without ICU admission, 222 had complete blood counts, 129 had blood cultures, 86 afebrile infants had urinalyses and 49 febrile infants ≥3 months of age had urine cultures (some infants had more than one test). The rate of performance of at least one of these tests per ED varied between 5.6 % and 73.7%.

The rate of performance of at least one non-indicated test was 38/76 (50.0%) in Spain/Portugal, 210/476 (44.1%) in Canada, 286/718 (39.8%) in the U.S, 146/497 (29.4%) in Australia/New Zealand and 88/592 (14.9%) in the U.K./Ireland. In multivariable analysis, laboratory testing was associated with the network, indicators of respiratory distress, fever and suspected bacterial infection (Table 3). After adjusting for patient-level variables, the use of laboratory testing varied widely (Figure 1) and was significantly higher in North America compared to the U.K./Ireland (Table 3). The multiple imputation procedure did not change these results. The ED also represented a significant source of variation of laboratory testing (p<0.0001).

The rate of testing was 405/1553 (26.1%) in discharged infants, 334/769 (43.4%) in those admitted to the ward and 27/37 (72.9%) in infants admitted to the ICU. The adjusted OR for laboratory testing in admitted versus discharged infants was 1.84 (95% CI 1.46-2.37), p<0.0001.

**Discussion**

In this large international study of infants evaluated in the ED for bronchiolitis, the overall rate of antibiotic therapy was consistently low across networks. When a chest radiograph was obtained, antibiotics were more likely to be given, independent of bronchiolitis severity and fever. On the other hand, use of laboratory testing was substantial, particularly outside of the U.K./Ireland and varied widely across networks, independent of patient-level characteristics. The use of non-indicated laboratory testing was also positively associated with hospitalization.

Previous ED-focused studies of antibiotics in bronchiolitis have yielded wide-ranging results, from 6%[36](#_ENREF_36) to 33%[23](#_ENREF_23). The factors which may have contributed to this wide-range include one U.S. study published prior to the U.S. guidelines[32](#_ENREF_32) and two studies from general EDs, where the rate of bronchiolitis interventions is higher[16](#_ENREF_16), [22](#_ENREF_22). Other publications represented collaborative efforts with focused resource-reducing interventions implemented by physicians trained in pediatric emergency medicine, which yielded low antibiotic use[36](#_ENREF_36). Our results show that the international rate of antibiotic administration is low, and close to the published achievable benchmarks of care[49](#_ENREF_49).

Although chest radiography in children with typical bronchiolitis infrequently identifies other pathology and frequently leads to unnecessary use of antibiotics, radiography use in bronchiolitis is common and often high in many countries[17](#_ENREF_17), [22](#_ENREF_22), [47](#_ENREF_47), [50](#_ENREF_50), [51](#_ENREF_51). Our study highlights that the use of chest radiography in bronchiolitis is substantial (23%) and associated with antibiotic use, irrespective of disease severity. Limiting its use to infants with atypical presentations and infants with airway compromise and severe disease may further decrease the use of antibiotics and hospital costs[47](#_ENREF_47).

Despite the evidence that laboratory testing rarely impacts bronchiolitis management and that bacterial infections in bronchiolitis are uncommon[34](#_ENREF_34), [52](#_ENREF_52), [53](#_ENREF_53), our study shows that these tests continue to be performed frequently in many parts of the world. Plausible reasons may include “automatic” blood draws with intravenous placement, uncertainty about institutional policies, perceived need for reassurance about the diagnosis, perception of “doing something” and parental desire for a viral label[52](#_ENREF_52), [54](#_ENREF_54). There is also concern about urinary tract infections in febrile infants with bronchiolitis younger than 3 months of age[43](#_ENREF_43). While a recent meta-analysis suggests that the urinary tract infection rate in febrile infants with bronchiolitis may be less common than previously reported[55](#_ENREF_55), a large definitive study addressing this question would help inform practice about this common dilemma.

Virology testing in discharged infants constituted the most frequently performed non-indicated test in this study. Virology testing does not assist with bronchiolitis management and does not predict outcomes[34](#_ENREF_34), [56](#_ENREF_56). Because the viruses causing bronchiolitis are transmitted in a similar way, careful attention to infection-control practices is likely more prudent than identification of specific viruses[42](#_ENREF_42), [57](#_ENREF_57).

Pediatric emergency providers in the U.K/Ireland perform these tests much less frequently, irrespective of disease severity. This finding complements previous reports which concluded that the practice of paediatric emergency medicine in the U.K./Ireland appears to be less intervention-intensive compared to other regions. Specifically, infants evaluated in the ED with bronchiolitis in the U.K./Ireland have lower rates of chest radiography and ED discharge pharmacotherapy than elsewhere[17](#_ENREF_17), [18](#_ENREF_18). Based on a survey of physician practice patterns of U.K./Ireland and Canada, febrile neonates with bronchiolitis may also undergo fewer lumbar punctures than in Canada[17](#_ENREF_17), [18](#_ENREF_18), [58](#_ENREF_58).

Quality improvement strategies can reduce use of unnecessary interventions in bronchiolitis[3](#_ENREF_3), [36](#_ENREF_36), [59](#_ENREF_59), [60](#_ENREF_60). A recent project targeting inpatients using a multi-faceted approach demonstrated significant reduction in chest radiography and viral testing[35](#_ENREF_35) without an increase in balancing measures. Implementation of similar strategies has also positively influenced physician behavior in other similar disease processes[61-63](#_ENREF_61). Similar quality-improvement initiatives are needed in the ED setting. As parental pressure to provide interventions may be a driver of care in infants with bronchiolitis in some countries[64](#_ENREF_64), ED clinicians need to have higher confidence in the evidence-based bronchiolitis care and convey this trust to families[24](#_ENREF_24).

Our retrospective design carries inherent limitations. Given this design, causality cannot be ascertained. Furthermore, because we do not have results of either chest radiographs or laboratory tests, we cannot comment on their contribution to care. While we have focused on testing in the ED, some admitted infants may have had additional testing performed on the ward. Nonetheless, the EDs represent the main location of these interventions[65](#_ENREF_65), [66](#_ENREF_66). Additionally, bacterial infections may not have been completely documented. Because the majority of infants given antibiotics had suspected bacterial co-infections, we could not analyze factors impacting antibiotic treatment in those without these co-infections. A modest sample of pediatric EDs within each country participated; hence our results may not be fully representative of the management of all infants with bronchiolitis within a given country/region. Also, there was a limited number of participants at some EDs, and some EDs may thus have been under-represented. This was particularly true of Spain and Portugal. Because infants younger than 2 months of age were excluded, the results do not apply to this sub-population.

In conclusion, in this multicenter, multi-national study, we found that while the use of antibiotics in infants with bronchiolitis in pediatric EDs is uncommon, laboratory testing is frequently performed, particularly outside of the U.K./Ireland, irrespective of patient-level characteristics. The rate of antibiotic therapy in infants with versus without chest radiography is highly variable across networks and sites, independent of bronchiolitis severity. In view of the high global prevalence of bronchiolitis and the cost of bronchiolitis care, our results highlight the need for development of international bronchiolitis benchmarks, guidelines, and quality initiatives to optimize the global management of bronchiolitis.

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