Infant Pneumonia and Subsequent Risk of Chronic Respiratory Disorders

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BACKGROUND

- Studies of sequelae of community-acquired pneumonia (CAP) in otherwise healthy infants are needed to identify if early CAP adversely affects lung growth/function leading to chronic lung disease[1-9]
- It has been hypothesized that early lung infection may lead to disruption of alveoli volume/lung growth or chronic inflammation resulting in recurrent or persistent symptoms
- Current evidence linking CAP in infancy (i.e., among children aged <2 years) with long-term consequences for the rapidly developing lung is primarily anecdotal and limited

OBJECTIVE

- The objective of our study was to examine the impact of CAP in infancy on subsequent respiratory health

METHODS

Study Design and Data Source

- Retrospective matched-cohort design and data from the Optum® de-identified Electronic Health Record Dataset (2009-2018), a fully integrated US electronic health records repository, were employed

Study Population

- Study population comprised children aged <2 years who were hospitalized for CAP ("CAP patients") and matched counterparts without evidence of pneumonia before age 2 years ("comparison patients"):
  - CAP hospitalizations were identified based on acute-care inpatient facility records with:
    - 1° diagnosis of pneumonia (irrespective of 2° diagnoses); or
    - 1° diagnosis of bacteremia or respiratory failure and a 2° diagnosis of pneumonia; and
    - Evidence of chest x-ray on day of, day after, or during the 3-day period before hospital admission
- CAP patients and comparison patients were matched (fixed 1:5 ratio, without replacement) using estimated propensity scores and nearest-neighbor approach:
  - Propensity scores for CAP (vs. comparison) were estimated using multivariable logistic regression; independent variables included month and year of birth, sex, birth status, and vaccination history
- Patients with conditions that increase risk of CAP or complications (eg, extreme prematurity, immunodeficiency, congenital abnormality, respiratory disease [eg, bronchopulmonary dysplasia]) before age 2 years were excluded

Study Outcomes

- Study outcomes were assessed from age 2 years to age 5 years, date of last healthcare activity, or end of study period, whichever occurred first:
  - Chronic respiratory disorders (asthma, bronchitis, hyperactive airway disease, recurrent pneumonia, recurrent otitis media, recurrent sinusitis, recurrent wheezing)
  - Recurrent pneumonia
  - Recurrent otitis media
  - Asthma, recurrent wheezing, or hyperactive airway disease

Statistical Analyses

- Annual rates of study outcomes–and relative rates for CAP vs. comparison patients–were evaluated over 3-year follow-up period from age 2 to age 5 years
- Time to first evidence of study outcomes was evaluated using Cox proportional hazards models
- Analyses were conducted considering all patients as well as patients stratified by CAP etiology (bacterial, viral, unspecified) and age at initial CAP hospitalization (0 - <6, ≥6 - <12, ≥12 - <24 months)

LIMITATIONS

- Algorithm for identifying CAP has not been formally evaluated against a "gold standard" and thus its accuracy is unknown
- Operational algorithms used to characterize comorbidity profiles undoubtedly resulted in misclassification of some patients
- CAP and comparison patients may be systematically different in terms of unobserved characteristics, which could bias study results
- Comparisons within patient subgroups may be underpowered in certain instances and should be interpreted with caution

CONCLUSIONS

- Infant CAP foreshadows an increase in subsequent risk of chronic respiratory disorders
- Studies are needed to determine whether increased rate of chronic respiratory disorders reflects damage resulting from early CAP, or if early CAP is a marker for children who are at increased risk for respiratory disorders, or both

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RESULTS

Baseline Characteristics

- Among CAP patients (N=1,343):
  - % with only 1 CAP hospitalization before age 2 years: 97%
  - Mean age at first CAP hospitalization: 8.9 months
  - Etiology during first CAP hospitalization: bacterial, 20%; viral, 27%; unspecified 53%
- CAP patients and matched comparison patients (N=6,715) were well-balanced on baseline characteristics and follow-up duration (Table 1)

Study Outcomes

- Rates of chronic respiratory disorders from age 2-5 years were significantly higher among CAP (vs comparison) patients (Tables 2-3)
- Analyses across subgroups defined on CAP etiology demonstrated higher rates of outcomes among CAP patients across all strata
- Results within subgroups defined on age at first CAP hospitalization were comparable to those from base-case analyses:
  - Findings support hypothesis that damaged or persistent inflammation from CAP in infancy increases risk of chronic respiratory disorders after age 2 years

Table 1. Characteristics of CAP patients and matched counterparts at age 2 years

	CAP Patients All (N=1,343)	Bacterial (N=265)	Viral (N=360)	Unspecified (N=718)	Comparison Patients (N=6,715)	Standarized Difference*
Age, Months (@ first CAP admission)						
Mean (SD)	8.9 (7.0)	9.8 (7.6)	7.2 (6.4)	9.3 (6.9)	--	--
Male, %	55.2	55.5	55.6	55.0	55.0	0.005
Birth Status, %						
Premature/Low Birth Weight	6.0	4.9	8.6	5.2	6.4	0.016
Full Term	92.9	93.2	90.6	93.9	92.7	0.007
Unspecified	1.1	1.9	0.8	1.0	0.9	0.019
No. of CAP Hospitalizations (before age 2 years), %						
1	96.6	98.1	95.6	96.5	--	--
2	3.4	1.9	4.4	3.3	--	--
≥3	0.1	0.0	0.0	0.1	--	--
Duration of Follow-Up, Mean (SD)	757 (356)	674 (356)	773 (348)	780 (355)	729 (362)	0.078

SD: standard deviation
*Standarized difference corresponds to comparison of CAP patients vs. all matched comparison patients

Table 2. Rates and relative rates of chronic respiratory disorders after age 2 years among CAP patients versus comparison patients

	No. of Patients	All Chronic Respiratory Disorders Rate per 100 PYs	Relative Rate (95% CI)	Recurrent Pneumonia Rate per 100 PYs	Relative Rate (95% CI)	Recurrent Otitis Media Rate per 100 PYs	Relative Rate (95% CI)	Recurrent Wheezing, Asthma, or Hyperactive Airway Disease Rate per 100 PYs	Relative Rate (95% CI)
All Patients									
CAP Patients	1,343	11.6	2.4 (2.2 - 2.7)	1.8	6.5 (4.2 - 10.1)	2.4	1.5 (1.2 - 1.9)	6.1	3.5 (2.9 - 4.3)
Bacterial	265	11.7	2.4 (1.9 - 3.0)	1.8	6.5 (2.6 - 11.8)	2.7	1.7 (0.8 - 2.6)	5.7	3.3 (2.2 - 4.6)
Viral	360	11.7	2.4 (2.0 - 2.9)	1.4	5.1 (2.4 - 9.6)	2.9	1.8 (1.1 - 2.6)	6.6	3.8 (2.7 - 5.0)
Unspecified	718	11.6	2.4 (2.1 - 2.8)	2.0	7.1 (4.4 - 11.6)	2.2	1.3 (0.9 - 1.8)	6.0	3.5 (2.8 - 4.3)
Comp. Patients	6,715	4.8	---	0.3	---	1.6	---	1.7	---
Age at Initial CAP Hospitalization									
0 to <6 Months									
CAP Patients	552	8.9	1.8 (1.4 - 2.1)	1.0	4.6 (1.9 - 10.7)	3.1	1.8 (1.2 - 2.6)	3.9	2.4 (1.7 - 3.4)
Bacterial	101	9.2	1.8 (1.1 - 2.7)	0.5	2.5 (0.0 - 9.7)	4.3	2.5 (1.0 - 4.5)	2.7	1.6 (0.4 - 3.3)
Viral	180	9.2	1.8 (1.3 - 2.5)	0.5	2.5 (0.0 - 8.3)	3.5	2.0 (1.0 - 3.3)	4.9	3.0 (1.6 - 4.8)
Unspecified	271	8.5	1.7 (1.3 - 2.2)	1.4	6.6 (2.3 - 16.2)	2.5	1.4 (0.7 - 2.3)	3.7	2.3 (1.4 - 3.4)
Comp. Patients	2,760	5.1	---	0.2	---	1.7	---	1.6	---
≥6 to <12 Months									
CAP Patients	308	11.7	2.6 (2.0 - 3.3)	1.6	5.8 (2.1 - 17.0)	1.7	1.1 (0.5 - 2.1)	5.5	2.9 (1.9 - 4.2)
Bacterial	46	8.0	1.8 (0.6 - 3.1)	0.0	0.0 (0.0 - 0.0)	1.1	0.7 (0.0 - 2.4)	2.3	1.2 (0.0 - 3.3)
Viral	87	12.9	2.8 (1.9 - 3.9)	3.1	11.4 (3.0 - 36.4)	1.6	1.0 (0.0 - 2.5)	6.7	3.5 (1.8 - 5.8)
Unspecified	175	12.0	2.6 (1.9 - 3.5)	1.1	4.2 (0.7 - 13.7)	2.0	1.3 (0.5 - 2.7)	5.7	3.0 (1.7 - 4.7)
Comp. Patients	1,540	4.5	---	0.3	---	1.5	---	1.9	---
≥12 to <24 Months									
CAP Patients	483	14.6	3.2 (2.7 - 3.7)	2.9	7.9 (4.5 - 14.3)	2.1	1.4 (0.8 - 2.1)	8.8	5.2 (4.0 - 6.8)
Bacterial	118	15.3	3.3 (2.4 - 4.4)	3.7	10.1 (3.3 - 22.1)	1.9	1.2 (0.2 - 2.7)	9.8	5.7 (3.5 - 8.4)
Viral	93	15.1	3.3 (2.2 - 4.2)	1.5	4.1 (0.0 - 10.4)	3.0	2.0 (0.6 - 3.8)	9.6	5.6 (3.2 - 8.6)
Unspecified	272	14.2	3.1 (2.5 - 3.7)	3.1	8.3 (4.3 - 16.0)	1.9	1.3 (0.6 - 2.2)	8.2	4.8 (3.5 - 6.7)
Comp. Patients	2,415	4.6	---	0.4	---	1.5	---	1.7	---

PY: person-year

Table 3. Adjusted hazard ratios for time to first evidence of chronic respiratory disorders after age 2 years among CAP patients versus comparison patients

	No. of Patients	All Chronic Respiratory Disorders HR	95% CI	Recurrent Pneumonia HR	95% CI	Recurrent Otitis Media HR	95% CI	Recurrent Wheezing, Asthma, or Hyperactive Airway Disease HR	95% CI
All Patients									
CAP Patients	1,343	2.8	2.4 - 3.2	6.7	4.4 - 10.3	1.6	1.2 - 2.1	3.8	3.1 - 4.6
Comp. Patients	6,715	--	--	--	--	--	--	--	--
CAP Patients									
Bacterial	265	2.5	1.9 - 3.3	7.1	3.4 - 14.7	1.5	0.9 - 2.7	3.5	2.3 - 5.1
Viral	360	2.7	2.2 - 3.4	5.2	2.7 - 10.3	1.8	1.2 - 2.8	4.2	3.1 - 5.7
Unspecified	718	2.9	2.4 - 3.4	7.4	4.6 - 11.9	1.5	1.0 - 2.2	3.7	2.9 - 4.7
Comp. Patients	6,715	--	--	--	--	--	--	--	--
Age at initial CAP hospitalization									
0 to <6 months									
CAP Patients	552	1.9	1.5 - 2.4	5.1	2.2 - 11.6	1.9	1.3 - 2.8	2.4	1.7 - 3.5
Comp. Patients	2,760	--	--	--	--	--	--	--	--
CAP Patients									
Bacterial	101	1.9	1.1 - 3.0	2.9	0.4 - 22.7	2.3	1.1 - 4.7	1.7	0.7 - 4.2
Viral	180	2.0	1.4 - 2.9	2.9	0.6 - 13.0	2.1	1.2 - 3.7	3.1	1.8 - 5.1
Unspecified	271	1.9	1.4 - 2.5	7.1	2.8 - 17.7	1.6	0.9 - 2.7	2.3	1.4 - 3.7
Comp. Patients	2,760	--	--	--	--	--	--	--	--
≥6 to <12 months									
CAP Patients	308	2.9	2.2 - 3.9	6.9	2.7 - 17.9	1.1	0.6 - 2.2	2.9	1.9 - 4.5
Comp. Patients	1,540	--	--	--	--	--	--	--	--
CAP Patients									
Bacterial	46	1.8	0.9 - 4.0	0.0	0.0 - 0.0	0.7	0.1 - 5.2	1.3	0.3 - 5.3
Viral	87	3.2	2.0 - 4.9	15.8	5.3 - 47.4	0.9	0.3 - 3.0	3.6	1.9 - 6.7
Unspecified	175	3.0	2.1 - 4.3	4.4	1.3 - 15.2	1.4	0.6 - 3.1	3.0	1.8 - 5.0
Comp. Patients	1,540	--	--	--	--	--	--	--	--
≥12 to <24 months									
CAP Patients	483	3.9	3.1 - 4.7	9.0	5.0 - 16.3	1.5	0.9 - 2.4	6.0	4.4 - 8.1
Comp. Patients	2,415	--	--	--	--	--	--	--	--
CAP Patients									
Bacterial	118	3.6	2.5 - 5.2	11.2	4.8 - 26.4	1.1	0.4 - 3.0	6.7	4.1 - 10.8
Viral	93	4.0	2.7 - 5.8	4.9	1.4 - 16.9	1.8	0.8 - 4.1	6.6	4.0 - 10.9
Unspecified	272	3.9	3.1 - 5.0	9.5	5.0 - 18.3	1.5	0.8 - 2.8	5.6	3.9 - 7.9
Comp. Patients	2,415	--	--	--	--	--	--	--	--

CI: confidence interval; HR: hazard ratio; PY: patient-year