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Research paper

Restrictive antibiotic use in children hospitalized for pneumonia: A retrospective inpatient study

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ABSTRACT

Introduction: Reducing antibiotic use is a global priority, but the extent to which antibiotic prescriptions can be reduced in children hospitalized for community-acquired pneumonia is unknown. This study aimed to analyse the prescribing experience from a facility with a long-standing practice of restrictive antibiotic use.

Methods: We conducted a retrospective analysis of children from birth to 18 years, hospitalized for pneumonia at an integrative medicine hospital in Germany. Antibiotic prescription rate and clinical outcomes were analyzed. The Moreno Bacterial Pneumonia Score, a composite laboratory, clinical and radiologic score, was applied to estimate the proportion of viral and bacterial pneumonia.

Results: 252 pneumonia episodes were included, with 172 categorized as probably viral and 80 as bacterial pneumonia. Antibiotic prescription rate was 32 % overall, 26 % for presumed viral and 51 % for presumed bacterial pneumonia. Children with probable bacterial pneumonia who were managed with antibiotics had higher CRP values than those managed without antibiotics ($p < 0.001$). 13 % of bacterial pneumonia episodes initially managed without antibiotics received antibiotics after hospital day 2. Hospitalization duration was longer for bacterial pneumonia episodes managed with antibiotics than those managed without (7.0 versus 4.9 days, $p = 0.003$).

Conclusions: The observed antibiotic prescription rate of 32 % was much lower than rates reported in the literature - 88–98 %. Children were safely managed with a restrictive antibiotic prescription strategy when physicians judged this to be appropriate. Our findings suggest that a delayed prescription strategy for childhood pneumonia deserves further study.

Trial registration: the study was registered at clinicaltrials.org, NCT03256474.

1. Introduction

Reduction of antibiotic use has become an international priority in the context of rising antimicrobial resistance. [1] Additional support for the importance of reducing antibiotic use in childhood derives from epidemiological investigations revealing a strong association between antibiotic induced gut dysbiosis in children and subsequent disease in adulthood. [2] Recent efforts for judicious antibiotic use in childhood pneumonia have focused on reducing broad-spectrum antibiotics [3], but limited attention has been devoted to ways to avoid unnecessary antibiotic use in pneumonia in inpatients. Delayed antibiotic prescription is a well-accepted approach for otitis media and has been found useful in adults with upper respiratory infection as well [4,5].

Targeting antibiotics to bacterial pneumonia, an obvious step to reduce antibiotic use, is hampered by the lack of a single clinical, laboratory or radiographic parameter to reliably distinguish between viral and bacterial pneumonia. [6,7] Viruses are a common cause of pneumonia and were the only identifiable pathogen in 66 % of children

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hospitalized in the U.S. for pneumonia [8]. U.S. guidelines, based on high quality evidence, have concluded that antibiotics are not routinely required in the outpatient setting for pre-school children with community acquired pneumonia [9].

We performed an exploratory evaluation of the outcomes of children hospitalized for pneumonia in a hospital in Germany that has for many years practiced a highly restrictive antibiotic prescription strategy.

2. Methods

2.1. Study design and participants

A retrospective analysis was conducted among children from birth to 18 years who were hospitalized with pneumonia at the Filderklinik (Filderstadt, Germany). Primary outcomes were the antibiotic prescription rate, duration of hospitalization and rate of complications and relapses.

Once pneumonia is diagnosed, the hospital's longstanding routine calls for the attending pediatrician to assess the clinical severity of disease and determine the likely viral or bacterial origin, and - upon a discussion with the parents - to decide whether to initiate antibiotics or not. Antibiotics may still be started at a later date if deemed necessary. In addition to conventional care, all children receive supportive treatment from Anthroposophic Medicine, a complementary whole medical system (details of typical treatments have been published previously). [10] [11] Antipyretics are used only when children are very uncomfortable or unable to hydrate themselves and not for the purpose of lowering temperature [12,13].

2.2. Data source and procedures

Electronic medical records were searched for children hospitalized with a primary ICD-10 diagnosis of pneumonia between December 2006 and the end of November 2010. We then reviewed all identified clinical records and extracted clinical findings, laboratory results, treatments and diagnoses.

We retroactively applied the Moreno Bacterial Pneumonia Score (BPS) to differentiate between probable viral and bacterial pneumonia. To calculate the BPS, 1 point is assigned for a peripheral band count > 5%; 2 points for age > 9 months; 2 points for peripheral absolute neutrophil count > 8,000 cells/mm3; 3 points for axillary temperature > 39.0 ˚C, and -3 to 7 points for chest x-ray findings (based on the Khamapirad and Glezen method [16]). The BPS can range between -3 to 13; a BPS > 4 is considered indicative of bacterial pneumonia (sensitivity 100 %, specificity 93.8 %, positive predictive value 75.8 %, negative predictive value 100 %). [14]. As our hospital laboratory only provides fully automated blood counts without neutrophil band counts we calculated the BPS without a band count; we nevertheless retained the BPS > 4 for bacterial pneumonia to prioritize a stringent threshold. A radiologist assigned the X-ray scores based on the Khamapirad and Glezen method [16] and was blinded to patient identity and clinical information. Children without a chest radiograph or any missing laboratory item other than band count were excluded. The BPS was shown to have a high area under the curve in the initial validation study (AUC = 0.996) [14], and children classified as viral pneumonia on the basis of this score were safely managed without antibiotics in a prospective outpatient observational study [15]. To our knowledge, this is the only validated measure to attempt differentiation between viral and bacterial pneumonia.

Parents of children classified as bacterial pneumonia were contacted by telephone in 2017 to inquire about relapse within 30 days of the initial pneumonia discharge as well as later pneumonia incidences. Hospital charts were also searched for possible pneumonia readmissions (patient files from primary care providers could not be reviewed as in Germany these are not available to other parties).

2.3. Statistical analysis

All statistical analyses were performed using the Statistical Package for Social Sciences (IBM SPSS Statistics, version 22). Depending on the properties of the respective measures, *t*-tests for independent means and Chi-square tests were calculated for comparing children with bacterial and viral pneumonia. The *p*-value for significance was set at .05 for each test. However, to reduce the error of multiple testing, the Bonferroni-Holm method was applied to all analyses with valid entries for > 65 % of children in each group/subgroup. The same statistical methods were applied to compare the subgroups of children with bacterial pneumonia, treated with or without antibiotics. Cohen's *d* effect sizes were calculated when clinical measures were found to be significant in order to assess the clinical magnitude of findings (effect sizes were not calculated for any demographic measures).

The study was approved by the ethics committee of Tübingen University and registered at clinicaltrials.org, NCT03256474.

3. Results

A total of 350 patients aged 2 weeks to 18 years were hospitalized with a diagnosis of pneumonia during the study period. 252 pneumonia episodes had sufficient data for calculating BPS values, and thus were included in the study. 80 patients (32 %) were categorized as probable bacterial pneumonia (BPS > 4) and 172 (68 %) as probable viral pneumonia (see Fig. 1). The overall antibiotic prescription rate was 32 %.

Comparisons between presumed viral and bacterial pneumonia cases are reported in Table 1. Children classified as viral pneumonia had a lower mean age, lower admission temperatures, and lower C-reactive protein (CRP) and venous pH values. Leucocyte counts differed as expected from the BPS categorization. Respiratory rate on admission was insufficiently documented and could not be included. 26 % of viral pneumonia episodes were treated with antibiotics, compared to 51 % of bacterial pneumonia. Length of hospitalization did not differ significantly between viral and bacterial pneumonia for the overall sample.

3.1. Presumed viral pneumonia episodes with borderline bacterial pneumonia scores

We analyzed presumed viral pneumonia episodes further that had a BPS = 3; i.e., those that potentially could have been classified as bacterial pneumonia if band counts were available. 25 % (44 of 172) of viral pneumonia episodes had a BPS = 3. Of these, 34 (77 %) were successfully managed without antibiotics.

3.2. Presumed bacterial pneumonia episodes, managed with and without antibiotics

We compared the 80 episodes classified as bacterial pneumonia: 39 (49 %) were managed without antibiotics and 41 (51 %) with antibiotics (Table 2). Anamnestic characteristics and clinical findings on admission were similar between these two sub-groups except for higher CRP values in the subgroup managed with antibiotics. Other differences (longer fever duration before hospitalization, higher leukocyte and neutrophil counts and longer hospitalization in the antibiotic group) were no longer significant after adjustments were made with the Bonferroni-Holm method.

Use of complementary medicine was equally high in both subgroups: 100 % received anthroposophic medications and 87.5 % (87.2 and 87.8 % respectively) received external chest compresses.

One child with pervasive neurologic disabilities (Lennox Gastaut Syndrome, tetraplegia) and recurrent bronchopulmonary infections died from aspiration pneumonia in spite of antibiotic treatment started before admission and intensive care management. No other

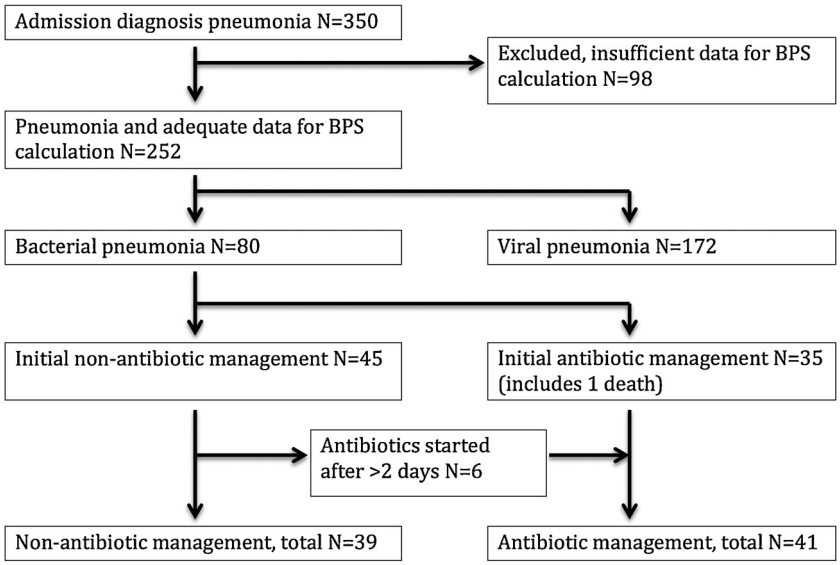

Fig. 1. Selection process flowchart: from initial chart review to patient management.

complications were observed.

3.3. Delayed antibiotic prescription

6 of the 45 children (13 %) categorized as having bacterial pneumonia, but not initially treated with antibiotics, were subsequently judged to be in need of this treatment and were begun on antibiotics > 2 days after admission. Chart reviews revealed that all 6 of these children were started on antibiotics because of lack of improvement and/or clinical/laboratory deterioration, with all improving rapidly once on antibiotics (see Table 3a), with none experiencing complications.

3.4. Follow-up interviews

Telephone follow-up calls were made in 2017 with all patients classified as having had bacterial pneumonia: 42 interviews (53 %) were conducted, 35 patients (44 %) could not be reached, parents of 2 children (3%) refused; and 1 child (1%) had two bacterial pneumonia episodes during the analysis period. Relapses within 4 weeks of hospital admission and later, along with new pneumonia cases were low in children who received antibiotics as well as those who did not (Table 3b).

3.5. Microbiological testing and antibiotics used

30 tests for Respiratory Syncytial Virus were performed with 13

Table 1
Comparisons between viral and bacterial pneumonia episodes.

	Total pneumonia,N = 350	Viral pneumonia,N = 172	Bacterial pneumonia,N = 80	*p*-values	Cohen's *d*
Mean age, years (SD)	3.66 (3.5)	2.96 (2.7)	4.85 (4.0)	< 0.001 *	
Female gender (%)	151(43)	72 (42)	31 (39)	0.640	
Temperature on admission, C° (SD)	38.7 (1.1)	38.5 (1.0)	39.3 (0.9)	< 0.001 *	−0.82 (large)
	N = 348	N = 171	N = 80		
Reduced general appearance, (%)	266 (83)	130 (82)	67 (92)	0.159	
	N= 319	N = 158	N = 73		
Oxygen saturation, minimum during stay, %	88.8 (7.5)	88.03 (7.1)	90.4 (6.9)	0.035	
	N = 254	N = 126	N = 57		
CRP mg/L, maximum (SD)	6.61 (7.4)	4.97 (5.8)	11.65 (8.8)	< 0.001 *	−0.92 (large)
	N = 340	N = 172	N = 80		
Leucocytes 10^9/L, maximum	15.5 (9.0)	13.8 (9.1)	20.4 (8.8)	< 0.001 *	−0.74 (large)
	N = 338	N = 172	N = 80		
Neutrophils 10^9/L, maximum	10.3 (7.9)	8.7 (7.9)	15.5 (7.5)	0.005	−0.88 (large)
	N = 335	N = 172	N = 80		
pH venous minimum (SD)	7.4 (0.1)	7.39 (0.0)	7.42 (0.1)	0.001 *	−0.47 (small)
	N = 294	N = 154	N = 66		
pCO2 venous, maximum (SD)	38.9 (8.9)	39.8 (7.8)	37.1 (7.0)	0.078	
	N = 294	N = 154	N = 66		
Base excess	−0.43	−0.59 (3.3)	0.53 (3.5)	0.025	−0.33 (small)
	N = 294	N = 154	N = 66		
Antibiotic therapy, n (%)	111 (32)	45 (26)	41 (51)	< 0.001 *	
	N = 348	N = 171	N = 80		
Complementary medicine : medications, (%)	348 (99)	171 (99)	80 (100)	0.494	
	N = 350	N = 172	N = 80		
Mean hospital duration, days	5.2 (3.2)	5.3 (3.2)	6.0 (3.2)	0.094	
	N = 350	N = 172	N = 80		

Selected parameters shown. Strength of effect for Cohen's d: small = 0.2, medium = 0.5, and large = 0.8. Asterisks: significant after adjustment with the Bonferroni-Holm method.

Table 2
Comparisons between bacterial pneumonia episodes, managed with and without antibiotics.

	Bacterial pneumonia, all, N = 80	Bacterial pneumonia without antibiotics, N = 39	Bacterial pneumonia with antibiotics, N = 41	*p*-values	Cohen's *d*
Mean age, years (SD)	4.85 (4.0)	5.45 (4.4)	4.27 (3.4)	0.187	
Female gender (%)	31 (39 %)	16 (41)	15 (37 %)	0.684	
Moreno BPS (SD)	6.2 (2.3)	6.38 (2.4)	6.1 (2.2)	0.516	
Number of secondary ICD-10 diagnoses (SD)	2.1 (0.2)	1.8 (1.6)	2.3 (2.3)	0.266	
Fever duration, anamnestic, days (SD)	4.5 (5.5) N = 77	5.8 (7.4) N = 38	3.1 (1.8) N = 39	0.033	0.59 (medium)
Temperature on admission, C° (SD)	39.3 (0.9) N = 80	39.2 (0.9) N = 39	39.3 (0.8) N = 41	0.671	
Antibiotics prior to admission (%)	10 N=80	3 (8%) N=39	7 (17 %) N = 41		
Abnormal general appearance,(%)	67 (92) N = 73	30 (86) N = 35	37 (97) N = 38	0.192	
Oxygen saturation %, minimum day 1 (SD)	90.9 (6.3) N = 56	89.9 (8.2) N = 26	91.8 (4.0) N = 30	0.252	
Oxygen saturation, %, minimum during stay (SD)	90.4 (6.9) N = 57	89.2 (8.2) N = 25	91.3 (5.6) N = 32	0.246	
Days with fever during stay (SD)	2.89 N = 80	2.27 N = 39	3.05 N = 41	0.477	
CRP mg/L, maximum	11.65 (8.8) N = 80	8.35 (8.3) N = 39	14.78 (8.2) N = 41	0.001 *	−0.78 (medium)
Leucocytes 10^9/L, maximum during stay (SD)	20.4 (8.8) N = 80	17.9 (7.5) N = 39	22.8 (9.3) N = 41	0.011	−0.59 (medium)
Neutrophils 10^9/L, maximum during stay (SD)	15.5 (7.6) N = 80	13.3 (6.6) N = 39	17.6 (7.9) N = 41	0.012	−0.58 (medium)
pH venous, minimum during stay (SD)	7.42 (0.19) N = 66	7.41 (0.1) N = 28	7.42 (0.1) N = 38	0.818	
pCO2 venous, maximum during stay (SD)	37.1 (7.0) N = 66)	38.6 (7.9) N = 28	36.0 (6.0) N = 38	0.136	
Base excess (SD)	0.53 (3.5) N = 66	1.18 (3.1) N = 28	0.06 (3.7) N = 38	0.200	
Complementary medicine : medications, (%)	80 (100) N = 80	39 (100) N = 39	41 (100) N = 41		
Hospital duration, days (SD)	6.0 (3.2) N = 80	4.9 (2.2) N = 39	7.0 (3.6) N = 41	0.003	−0.71 (medium)

Selected parameters shown. Strength of effect for Cohen's d: small = 0.2, medium = 0.5, and large = 0.8. Asterisks: significant after adjustment with the method of Bonferroni-Holm.

positive tests (positive rate: 12 out of 28 viral pneumonia episodes, 1 out of 2 bacterial pneumonia episodes). 11 blood cultures were collected among bacterial pneumonia cases, with five each growing one of the following pathogens: *Haemophilus influenza*, *Mycoplasma pneumoniae*, *Streptococcus anginosus*, *Streptococcus oralis* and *Staphylococcus hominis* (a contaminant). Antibiotics used included ampicillin, amoxicillin, co-amoxicillin, cefaclor, cefuroxime, ceftriaxone, cefotaxime, azithromycin, clarithromycin and gentamicin.

4. Discussion

The antibiotic treatment rate among children hospitalized for community-acquired pneumonia was 32 % which is very low when compared to the literature reported treatment rate of 88–98% in the inpatient setting [8,17] and 68 % in the outpatient setting [18].

The low prescription rate cannot be explained by an unusually high proportion of viral pneumonia in this cohort and the prescription rate was even low in presumed bacterial pneumonia—51 %. Delayed antibiotic prescriptions were needed in only 13 % of patients with presumed bacterial pneumonia, suggesting significant potential to reduce antibiotic use even for bacterial pneumonia in the inpatient setting.

Baseline characteristics and clinical severity of disease in the non-antibiotic and antibiotic subgroups of bacterial pneumonia were comparable except for higher CRP levels, possibly suggesting physician predilection for antibiotic therapy in cases of more pathological laboratory values. Very good outcomes in terms of clinical improvement and complications were observed in both non-antibiotic and antibiotic treatment subgroups for presumed bacterial pneumonia. Longer hospitalizations in bacterial pneumonia episodes managed with antibiotics than those without further point to the children in the antibiotic-managed group being more ill. Children receiving delayed prescriptions (i.e., those not improving with the non-antibiotic approach), recovered quickly, thus facing no adverse symptoms. Clinical judgment in the hands of experienced clinicians appeared to accurately distinguish between high and low risk patients.

Several differences were found between patients categorized as having viral versus bacterial pneumonia. As expected, mean age among presumed viral pneumonia patients was much lower and a substantial difference was found with respect to CRP values (CRP is not included in BPS calculation).

Except for one death from aspiration pneumonia in the antibiotic-treated bacterial pneumonia subgroup, no complications, such as septicemia or pleural effusion with persistent fever, were observed; however, the sample size was too small to make any definitive statements regarding the rates of rare complications, such as empyema or necrotizing pneumonia. The tolerant attitude to fever at this hospital – we recorded only 12 administrations of paracetamol (acetaminophen) or ibuprofen in 350 episodes of pneumonia – may potentially have contributed to the low incidence of complications: we note the presence of several reports of pneumonia complication rates linked to ibuprofen use. [19–22] In summary, children hospitalized for community-acquired pneumonia were safely managed without antibiotics when considered appropriate by physician judgment.

A strength of this study is that it occurred in an institution making an active effort to avoid antibiotics, while in most institutions physicians prescribe antibiotics almost universally for community acquired

Table 3a
Delayed prescription and follow up. Delayed prescription. Patients with bacterial pneumonia started without antibiotics, requiring antibiotics after > 2 days.

Age yrs	Sex m/f	Hospital day of antibiotic start	Reason for starting antibiotics	Bacterial Pneumonia Score	Further clinical development
4	f	4	Continued fever and oxygen dependence, rising leucocytes and CRP	5	Defeverfescence, improvement
1	f	4	Continued fever, reduced general appearance, intermittent oxygen dependence	5	Defeverfescence, improvement
2	m	5	Continued fever	4	Defeverfescence, improvement
1	f	9	Higher fever, worsening general appearance and laboratory parameters	4	Defeverfescence, improvement
3	m	11	Renewed fever, rising CRP, continued leukocytosis	5	Defeverfescence 3 days later, improvement
5	m	3	Clinical deterioration	5	Defeverfescence, improvement

pneumonia for fear of missing a bacterial pneumonia. A weakness, however, is that the department has no clear decision criteria for antibiotic prescribing, leaving this decision to clinical judgement.

Two controlled studies have evaluated antibiotics versus placebo in childhood pneumonia [23,24], but neither differentiated between viral and bacterial infection. An open-label, randomized study among children with clinical and radiographic confirmed pneumonia found no difference in length of stay, readmission rate or pulmonary complications between antibiotic and placebo groups; although 2 children in the placebo group required antibiotics in accordance to predefined criteria. [23] A randomized controlled trial carried out in India with children diagnosed with "non-severe pneumonia and wheeze" that specifically excluded children with radiologic confirmed pneumonia reported a slightly increased likelihood of treatment failure in children assigned to the placebo group [24]. However, the selection criteria biased the sample to over-include children with viral pneumonia and obstructive airway disease.

A self-limited course of bacterial pneumonia is fully within the capacity of the immune system of an otherwise healthy individual, with recent attempts in immunomodulation as an alternative to antimicrobial therapy being reported in the literature. [25] The possible self-limited course of pneumonia is also known from historic records: in the pre-antimicrobial era of the early 20th century in New York City the pneumonia fatality rate was sharply age dependent, > 30 % in children < 12 months and < 5% in children > 3 years. [26]. The Moreno Bacterial Pneumonia Score is imperfect and cannot determine the true microbiologic etiology, but it was useful in verifying that low antibiotic prescribing did not just apply to viral pneumonia episodes.

Differentiating viral and bacterial pneumonia remains exceedingly difficult as neither a consensus nor a gold standard exists, even for research. [27] The BPS, the only validated score for this purpose, does not take advantage of CRP scores [28]. It also has 2 distinct disadvantages: it requires a chest radiograph, which is not needed in routine care [29], and a neutrophil band count that involves labor-intensive manual microcopy counting. New blood-based tools, such as the TRAIL – IP-10 – CRP biomarker signature, hold promise [30,31] and should be validated for childhood pneumonia.

Absent a control condition, our retrospective analysis does not allow us to determine the degree to which the hospital's integrative medicine approach contributed to the observed outcomes; however, any potential contributory effect presumably would have benefited all groups evenly.

Further, limitations inherent in retrospective cohort study designs apply: data were sometimes incomplete (we only included parameters where we had data for at least 65 % patients) and follow up was possible in only 53 % of presumed cases of bacterial pneumonia. Recall bias applies for the follow up questionnaire, although it is likely that parents remember pneumonia episodes after several years. Additionally, this is a single center study with uncertain generalizability of results.

The study design, which required chest radiographs for BPS calculations, biased the sample in the direction of including more severe cases of pneumonias (i.e., those that triggered ordering of radiographs) and higher antibiotic usage; this bias thus increases confidence in the results of low antibiotic usage. [32] Also the more stringent application of the BPS biased towards higher antibiotic use in the bacterial pneumonia group, further contributing to confidence in the results.

5. Conclusions

Our data provide preliminary support for the hypothesis that restrictive antibiotic use in otherwise healthy children hospitalized for pneumonia is feasible, regardless of viral or bacterial etiology. Controlled studies of a delayed antibiotic prescription strategy for pneumonia appear warranted. Such research should examine the characteristics of children most suitable for this approach, develop monitoring guidelines and empirically determine the optimal antibiotic

Table 3b
Follow up interviews. Pneumonia relapses and subsequent pneumonia incidence among 80 bacterial pneumonia cases: results from telephone follow up and chart reviews.

	Non-antibiotic subgroup	Antibiotic subgroup
Interview responders	23	19
Relapse $\leq$ 4 weeks	2	3
Relapse $\leq$ 4 weeks, antibiotic treated	1	2
Relapse $\leq$ 4 weeks, hospital admission	2	2
Relapse $\leq$ 4 weeks, intensive care admission	0	1
New pneumonia episodes > 4 weeks later	2	4
New pneumonia, episodes per child	3 children with each 1 pneumonia (1 identified through chart review)	3 children with 1 pneumonia; 1 child with 2 pneumonias
Disease observations since hospitalization (number of children)	Allergic rhinitis; atopic dermatitis and other allergy (3); asthma (1); recurrent otitis (1); skin problems (1)	Recurrent pneumonia in context of spinal muscular atrophy (1); asthma/ bronchitis (4); otitis (2); influenza (1); recurrent otalgia & cephalgia (1); frequent common cold (2); recurrent eye infections (1)

delay period.

Declarations

Ethics approval and consent to participate: The study was carried out in accordance with the Declaration of Helsinki and approved by the ethics committee of Tübingen University. Patients contacted by telephone for follow up were asked for verbal consent; consent was not applicable for the retrospective chart review.

Authors

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Declaration of Competing Interest

The authors declare they have no conflicts of interest.

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