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Poor compliance with antimicrobial guidelines for childhood pneumonia

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ABSTRACT

INTRODUCTION: Antimicrobial stewardship programmes recommend use of narrow-spectrum antibiotics as first-line treatment of childhood pneumonia in secondary care. The primary aim of the present study was to assess whether current guidelines are followed. A secondary aim was to assess if tracheal aspiration is a useful tool in the diagnostic process of suspected childhood pneumonia.

METHODS: This was a retrospective descriptive single-centre cohort study. Children between three months and 17 years with a pneumonia diagnosis were included. The children were divided into two groups based on whether or not they had been treated with antibiotics (TWA) by their general practitioner. We obtained information on blood samples, treatment and microbial findings. Finally, we compared the use of antibiotics and the microbiological diagnosis of children TWA prior to admittance with those of drug-naïve children (DN).

RESULTS: Guidelines were followed in 55% (n = 78) of the cases, which is comparable to results reported by other studies. Tracheal aspiration culture identified a bacterial pathogen in 54% (n = 77) of the cases; *Haemophilus influenzae* was the most prevalent. A larger percentage of tracheal aspirations was positive in the TWA group than in the DN group (66%; n = 31 versus 48%; n = 46).

CONCLUSIONS: Compliance with local guidelines was comparable to findings reported in similar single-centre studies. Airway aspiration may be a useful supplement to other investigations.

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TRIAL REGISTRATION: not relevant.

Community-acquired pneumonia (CAP) is a common cause of morbidity in children under five years of age [1, 2]. In many countries, including Denmark, respiratory infections are diagnosed and managed in primary care [3]; even so, CAP is a common cause of hospital admission in children [4].

The clinical presentation of CAP is often non-specific in young children [4], and bacterial and viral pneumonia may be clinically indistinguishable [3]. Empirical antibiotic therapy based on clinical presentation is therefore commonly applied [2, 3].

Since antibiotic treatment selects for antibiotic resistance, it is important to limit exposure to any antibiotic. Furthermore, it is difficult to identify the causative microorganisms and therefore to standardise the management of paediatric CAPs. At the time of the present study, lower airway aspiration culture was included as a diagnostic modality in local guidelines at the investigated centre [5], but airway aspiration culture was not recommended in current international guidelines [1, 3, 6]. Current Danish and international guidelines for treatment of CAP recommend the use of narrow-spectrum antibiotics as first-line treatment in both outpatients and hospitalised patients for children above three months of age [1, 3, 6]. This strategy has been confirmed by several studies showing comparable clinical outcomes of narrow-spectrum and broad-spectrum antibiotics for hospitalised children with CAP [7, 8]. In contrast, guidelines regarding non-responders to first-line treatment in CAP are not well established [9].

The primary goal of antimicrobial stewardship programmes is to improve patient outcome while reducing the negative consequences of antimicrobial treatment [10, 11]. Secondary goals include reduction of antibiotic acquisition costs. The two core strategies recommended to accomplish these goals are: 1) formulary restriction with preauthorisation and 2) prospective audit of antimicrobial use with immediate feedback to prescribers [10].

The aim of the present study was to analyse if childhood CAP is being treated according to local guidelines which recommend penicillin as first-line treatment. A second aim was to test the hypothesis that airway aspiration culture would be a better tool than blood culture for effectively guiding the choice of antibiotic regime. Children treated with antibiotics (TWA) prior to admittance were compared to drug-naïve children (DN). The samples from the DN group were expected to record a higher number of pathogens than the other group.

METHODS

This was a retrospective cohort study on inpatients admitted to the Department of Paediatrics at Herlev Hospital, Denmark. Information about the subjects is pro-

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Pneumonia is a common cause of morbidity in young children. Colourbox.



tected in accordance with the Danish Act on Processing of Personal Data. The study was approved by the Danish Data Protection Agency (r. no. 2007-58-0015).

The cohort was obtained as shown in **Figure 1**. All children between one month and 17 years of age who had been TWA between January and March 2012 were screened for inclusion. Children who received drugs given strictly as prophylaxis were excluded. Patients diagnosed with pneumonia at discharge were included in the final cohort. The final cohort was divided into two groups: 1) Children who had been TWA prescribed by a general practitioner before admission to hospital and 2) Children who were DN.

We identified the children through the Electronic Patient Medication module, which holds information on all in-hospital drug administrations. Information on drugs prescribed by the general practitioner was obtained from the unified Danish eHealth Portal, where it is possible to identify prescribed drugs dispensed at community pharmacies.

Information on biochemical parameters was obtained from the clinical laboratory information system LABKA. Information on microbiological findings (blood culture, airway aspiration culture) was gathered from the laboratory information system wwBakt. Patient records were reviewed in the electronic patient-continuation system OPUS.

We performed chart-audits on all patients. Baseline information included date of birth, sex, date of diagnosis, length of stay (LOS) in hospital, vital parameters at admittance (temperature, respiration frequency, heart rate, oxygen saturation) and prescribed antibiotics before and after admittance.

Vital parameters that are age-specific, respiration frequency and heart rate were stratified into age-defined subgroups (one month to one year of age, > 1 year to 11 years of age and > 11 years of age).

Biochemical parameters (white blood cell count (WBC) and C-reactive protein (CRP)) were registered. CRP levels within the normal range (< 10 mg/l) were listed as 0. Results from blood and airway aspiration culture were registered.

The initial empiric antibiotic therapy was compared to antibiotics given at discharge in order to analyse whether microbial findings in airway aspiration and blood culture led to a change in treatment.

To distinguish narrow-spectrum from broad-spectrum treatment, antibiotics prior to admittance were divided into three groups: penicillin, amoxicillin (with/without clavulanic acid) and others.

Descriptive statistics were used, and results were summarised as median and range for continuous variables, and as percentages for nominal variables.

Data management and all statistical analyses were performed using SAS, version 9.4 (SAS Institute, Cary, N.C.).

Trial registration: not relevant.

RESULTS

Clinical characteristics of the patients

A total of 152 patients between one month and 17 years of age with pneumonia were included. The youngest patient was three months old. Demographic data are shown in **Table 1**. The mean age was 3.8 years, and 81 (53%) of the children were boys. A total of 141 (93%) of the patients admitted were under 11 years of age. There was no difference in LOS between sexes.

The median CRP at time of admittance was 14 mg/l for girls and 5 mg/l for boys (reference range: 0-10 mg/l). The median WBC was $11.6 \times 10^3/\mu\text{l}$ for both males and females (reference range: $4.5 \times 10^3 - 11 \times 10^3/\mu\text{l}$).

Blood culture was performed in 58 cases (38%). Of these, only four were positive. The findings included: *Staphylococcus hominis*, *Staphylococcus warneri*, *Streptococcus parasanguinis* and "different streptococcus and staphylococcus species". The authors found it most likely that these isolates represented a contamination of the sample.

Airway aspiration and X-ray

Airway aspiration culture was performed from 142 patients out of a total of 152 patients (93%). No airway aspiration was performed for the remaining ten patients. One or more potential pathogens were identified in 54% (n = 77) of the cases. The airway aspiration cultures were divided into a DN and a TWA group. In the TWA group, a pathogen was found in 66% (n = 31) of the cases. In the DN group, a pathogen was found in 48% (n = 46).

Haemophilus influenzae was the most prevalent microorganism identified in both groups of airway aspiration culture. It appeared in 61% (n = 47) of the positive cases and as a monoculture in 39% (n = 30). *Moraxella catarrhalis* was identified in 32% (n = 25) of the positive cases, and as a monoculture in 12% (n = 9). *Streptococcus pneumoniae* was isolated in 17% (n = 13) of the positive cases, monoculture in 5% (n = 4).

Chest X-ray (CXR) was performed in 95% (n = 145) of cases. Only 6% (n = 8) were described as normal. In all, 48/145 patients (33% of the CXR-positive patients) had findings that were positive for bilateral lung consolidation; 42/145 patients (29% of the CXR-positive patients) had findings that were positive for unilateral consolidations. Only one patient showed pleural effusion. The rest had primarily perihilar linear opacities or consolidation 29/145 (20%).

Treatment with antibiotics in primary care and after admittance

Table 2 presents the type of antibiotics prescribed before and at admittance at the Department of Paediatrics in the 142 cases with airway aspirations.

Penicillin was the most frequently prescribed drug during admission (55%, n = 78), followed by clarithromycin (13%, n = 18), amoxicillin (11%, n = 16), cefuroxime (10%, n = 14), amoxicillin with clavulanic acid (6%, n = 9) and other antibiotics (5%, n = 7).

Overall, broad-spectrum antibiotics at admittance (cefuroxime, clarithromycin and others) were prescribed in 27% of all cases. For the TWA group, the prescription rate was 28% and for the DN group 27%.

We investigated the association between the microorganisms and the antibiotics that the patients received when discharged from the hospital. Out of 14 (30%) diagnosed with *H. influenzae* in monoculture in the DN group, eight were discharged with amoxicillin and five with amoxicillin with clavulanic acid. Among the 16 patients in the TWA with *H. influenzae* in monoculture, five were discharged with amoxicillin and three with amoxicillin with clavulanic acid. In total, 43% (n = 13) of the children with *H. influenzae* in monoculture were treated with amoxicillin at discharge.

Patients with a *M. catarrhalis* monoculture were discharged with amoxicillin with clavulanic acid in three out of nine cases.

When *S. pneumoniae* was identified in monoculture, three out of four of the children were discharged with penicillin.

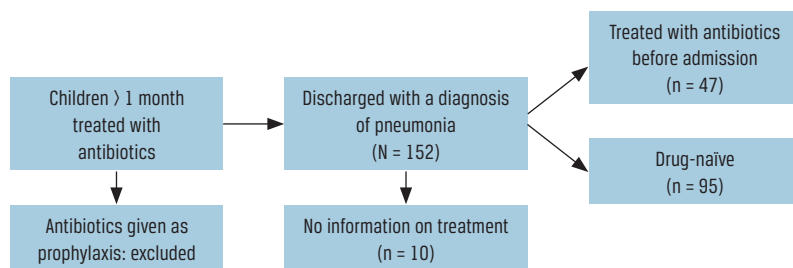
DISCUSSION

Local clinical guidelines were followed in 55% of the cases where penicillin was used as first-line treatment on admission. This is comparable to results reported from multiple international surveys: In a British review



FIGURE 1

Flow chart of how the cohort was obtained.



comprising three years of national data, the recommended first-line treatment (amoxicillin) was prescribed in only 17.6-21.1% of the cases [12]. In a similar single-centre report from the USA, the recommended first-line drug (ampicillin) was prescribed in 63% of the cases [13].

CXR was performed in almost all cases, although guidelines [7] do not recommend routine CXR in uncomplicated CAP, since viral, bacterial or atypical organisms such as *Chlamydia* or *Ureaplasma* are indistinguishable on the basis of radiographic findings [14].

In the current guidelines from the British Thoracic Society, microbiological investigations are recommended only in severe cases, and airway aspiration is



TABLE 1

General clinical characteristics of the study population. The values are median (range).

	Female (n = 71 (47%))	Male (n = 81 (53%))	Total (N = 152)
Age, yrs	2.0 (0.3-17.8)	1.7 (0.2-16.2)	3.8 (0.2-17.8)
LOS, days	4.0 (1-14)	4.0 (1-11)	4.0 (1-14)
SAT, %	94 (82-100)	95 (75-100)	95
Temperature, °C	38.9 (36.5-40.6)	38.4 (36.4-41.5)	38.7 (36.4-41.5)
<i>Respiratory rate, /min.</i>			
1 mo.-1 yr (n = 29)	60.0 (36-75)	52.0 (30-100)	52 (30-100)
1-11 yrs (n = 112)	50 (18-82)	40 (18-80)	44
> 11 yrs (n = 11)	37 (22-52)	28 (24-33)	28
<i>Heart rate, /min.</i>			
1 mo.-1 yr	163 (140-184)	156.5 (125-190)	159
1-11 yrs	152 (113-200)	148.5 (88-203)	150
> 11 yrs	118.5 (97-140)	119 (78-138)	119
WBC, × 10 ³ /µl	11.6 (4.1-29.8)	11.6 (3.8-37.3)	11.6 ^a
CRP concentration, mg/l	14 (0-187)	5 (0-305)	9.0

CRP = C-reactive protein; LOS = length of stay; SAT = oxygen saturation in the blood; WBC = white blood cell count.
a) Reference: 4.5-16.3 × 10³/µl.

TABLE 2

Choice of treatment with antibiotics prior to and after admittance to hospital. The values are n.

Prior to admittance	After admittance						total (N = 142)
	penicillin (n = 78)	amoxicillin (n = 16)	amoxicillin with clavulanic acid (n = 9)	cefuroxime (n = 14)	clarithromycin (n = 18)	other antibiotics (n = 7)	
Penicillin	16	6	3	3	5	1	34
Amoxicillin with clavulanic acid	-	-	2	-	-	-	2
Other	6	-	1	2	2	-	11
None	56	10	3	9	11	6	95

not mentioned [3]. Blood culture is, however, recommended even though the rate of positive findings is very low [1, 4]. A Finnish study found two positive blood cultures compared to 16 positive lung aspirates in 34 patients [15]. In this study, less than 7% of the blood cultures tested positive, but they were not clinically relevant since the positive result was very likely due to contamination. In other studies, bacteraemia is also rarely found [1, 4, 15].

In contrast, one or more potential pathogens were identified in 54% of the airway aspiration cultures. There is a risk that the aspirations contain upper-airway material instead of the intended lower-airway material. Since upper respiratory tract secretions often include bacteria that are commonly responsible for pneumonia [1], this is an important consideration when evaluating the results.

S. pneumoniae is considered the main cause of bacterial childhood CAP [3] even in the post-pneumococcus vaccine era [16]. We found that *H. influenzae* was the most isolated pathogen followed by *M. catarrhalis*. This can most easily be explained in the TWA group, since these patients have often been treated with penicillin prior to their admission. It has also been shown in another study that *H. influenzae* was the most common pathogen among children with CAP who had previously been TWA [17]. The high rate of *H. influenzae* in the DN group indicates that *S. pneumoniae* may not be as frequent as expected, at least not in hospitalised children. To the best of our knowledge, this has not been reported in previous studies [12].

M. catarrhalis has not previously been shown to cause pneumonia in otherwise healthy children, and the finding in this study may simply be a result of contamination from the upper airways. However, the microorganism is acknowledged as a common pathogen in other infections in children, such as otitis media and sinusitis [18], and we have chosen to include it as a potential pathogen in the present study.

Children in the TWA group presented with a higher percentage of positive aspirations than the other group. Possibly, the antibiotic treatment that

the children received in the primary care setting selected for an extended growth of the bacteria found in the aspirations.

A limitation in our study is the lack of viral diagnosis. Viral infection has been shown to account for 45–63.4% of pneumonias in hospitalised children [19], but viral infection is clinically distinguishable from bacterial infection [3]. There is also an indication that mixed viral and bacterial infections are common.

An older Danish study found no reason to treat infants and young children with antibiotics since there was no difference in their tracheal secretions and the course of acute disease when the authors compared children who were given antibiotics with children who did not receive antimicrobial treatment [20]. This raises an important question about the value of airway aspiration and even antibiotics in young children.

Another limitation of the present study is that we relied on diagnoses given to children at discharge. We used no objective criteria to establish the diagnosis. On the other hand, pneumonia is a clinical diagnosis [3, 6], and discharge diagnoses are given retrospectively with all information available.

We obtained no information about suspected allergy reactions towards penicillin or the presence of chronic pulmonary disease. Both might explain why broad-spectrum antibiotics were chosen in some of the cases, and chronic pulmonary disease could lead to a pathogen shift in the individual. Finally, the relatively limited size of the cohort might cause selection bias.

CONCLUSIONS

Compliance with local guidelines was comparable to the findings reported in similar single-centre studies but may be further improved. In the present study, we did not find that blood culture was diagnostic of CAP. Airway aspiration may be useful as a supplement to other investigations.

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