

Amoxicillin / clavulanic acid in the treatment of severe pneumonia in children.

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Thirty-three children aged 2 months - 3 years with the presumptive diagnosis of bacterial pneumonia requiring oxygen therapy were treated with intravenous amoxicillin/clavulanic acid 30 mg./kg./dose every 8 hours followed by oral form. The drug had to be discontinued in 3 cases due to drug rash, mycoplasma infection and deterioration with S. aureus septicemia. Among the 30 cases, 5 cases had nosocomial pneumonia which were cured after amoxicillin/clavulanic acid therapy. The drug was also effective in the treatment of 25 cases with community-acquired pneumonia, but the outcome was not significantly different from the comparable group with conventional antibiotic therapy. The study suggested that amoxicillin/clavulanic acid had no more beneficial effect than the conventional antibiotics in community-acquired pneumonia; however, it appeared to be beneficial in pediatric patients with nosocomial pneumonia.

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ศึกษาผลของการใช้ยา *amoxycillin / clavulanic acid* ขนาด 30 มิลลิกรัม/กก./ครั้ง ทุก 8 ชั่วโมง ใน
การรักษาผู้ป่วยเด็กที่เป็นปอดอักเสบจากเชื้อแบคทีเรียอายุ 2 เดือน - 3 ปี จำนวน 33 ราย ทุกรายหายใจหอบต้องได้
รับออกซิเจน พบว่าได้ผลดีในผู้ป่วย 5 รายที่เป็นปอดอักเสบจากการติดเชื้อในโรงพยาบาล ผู้ป่วย 28 รายเป็นปอดอักเสบ
จากการติดเชื้อนอกโรงพยาบาล ในจำนวนนี้ 3 รายต้องหยุดยาเนื่องจากผลการตรวจเลือดคั่งถึงเชื้อมัยโคพลาสมา 1
ราย, มีผื่นที่ผิวหนังจากการแพ้ยา 1 ราย และอาการเลวลงเนื่องจากโลหิตเป็นพิษจากเชื้อ *staphylococcus* 1 ราย
ผู้ป่วยที่เหลืออีก 25 รายหายจากโรคหลังให้การรักษาค่าย *amoxycillin/clavulanic acid* โดยไม่มีอาการข้างเคียง
แต่อย่างใด เมื่อเปรียบเทียบผู้ป่วยกลุ่มนี้ กับผู้ป่วยปอดอักเสบอีก 25 รายที่ได้รับยาปฏิชีวนะชนิดอื่น พบว่าผลการ
รักษาไม่แตกต่างกัน

Antibiotic therapy for most children with pneumonia is empirically based on epidemiological data because the diagnostic methods to detect the etiologic agents are limited and inadequate.^(1,2) Either penicillin or ampicillin is recommended in children between 2 months and 5 years of age since *S.pneumoniae* and *H.influenzae* are the most common causes.^(2,3) Furthermore, broad-spectrum antibiotics or beta-lactamase resistant antibiotics should be considered in severe cases.⁽³⁾ The combination of amoxycillin and beta-lactamase inhibitor, clavulanic acid, has been successfully used in the treatment of lower respiratory tract infections in children.^(4,7) However, the comparative study to evaluate clinical use of amoxycillin/clavulanic acid in pediatric practice is scant, while this drug becomes available in Thailand. Therefore, we performed a study on amoxycillin/clavulanic acid in the treatment of severe pneumonia in young children as compared with conventional antibiotic therapy.

Materials and Methods

The patients enrolled in the study included children aged between 2 months and 3 years admitted with the following criteria:

1. respiratory rate 40 / min. or more
2. crepitations or rhonchi on chest auscultation
3. chest retractions requiring oxygen therapy
4. findings suggestive of bacterial pneumonia as one of the following :
 - 4.1 lobar infiltration on chest X-ray
 - 4.2 bronchopneumonia on chest X-ray with positive Gram's stain of sputum for polymorphonuclear leukocytes and bacteria
 - 4.3 bronchopneumonia with progression of pulmonary infiltrates within 4 days of initial treatment and increased leukocytosis.

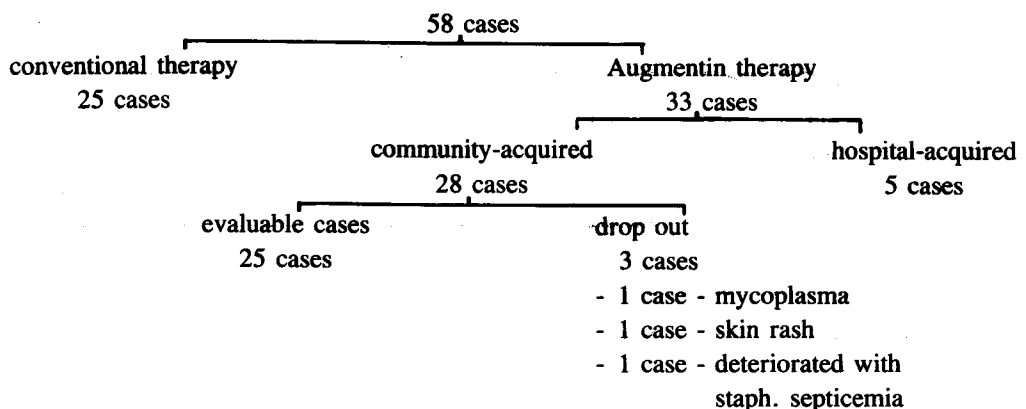
Those who did not required oxygen therapy and had negative chest X-ray were excluded from the study.

All the studied patients had demographic data, history and physical findings recorded and chest X-ray

done at the time of admission or within 24 hours after admission. Microbiological studies including hemocultures, sputum or nasopharyngeal secretion cultures for bacteria and fluorescent stain for respiratory syncytial virus (RSV) were performed in all cases. serological tests for mycoplasma pneumoniae and chlamydia trachomatis were done in suspected cases. Then, the patients were randomly allocated into 2 groups. The first group received amoxycillin/clavulanic acid 30 mg./kg./dose every 8 hours; the second group received conventional antibiotics. Each group received antibiotics intravenously followed by oral administration for at least 5 days after the patients become afebrile and were clinically improved. The minimum total course of treatment was 7 days. The effectiveness of treatment between the 2 groups were compared by using Chi-square and unpaired t - test.

Fifty - eight patients who fulfilled the above inclusion criteria were prospectively studied during January 1989 - September 1989. Twenty - five patients who received intravenous conventional antibiotics (ampicillin 17 cases, penicillin 4 cases, colxacillin 2 cases, ampicillin + gentamicin 1 cases, cloxacillin + gentamicin 1 cases) were previously healthy and had community - acquired pneumonia. Among the 33 cases in the amoxycillin/clavulanic acid group, 28 patients were previously healthy with community - acquired pneumonia while the remainder 5 cases had been hospitalized for more than 2 weeks due to their underlying conditions before acquiring pneumonia.

Of the 28 previously healthy patients in the amoxycillin/clavulanic acid (Augmentin) group, 25 patients were clinically evaluable. In the unevaluable patients, Augmentin therapy was discontinued because of serological diagnosis of mycoplasma pneumonia in 1 case, erythematous skin rash after 2 day - therapy in 1 case and clinical deterioration despite Augmentin treatment for 3 days in 1 case. The case with clinical deterioration had positive blood culture for *S.aureus*, as shown in the diagram.



Results

By using Chi-square and unpaired t - test in comparing the clinical characteristics before treatment of the 25 patients in the Augmentin group with the

conventional group, there were no statistically significant differences except for higher body temperature in the Augmentin group (table 1).

Table 1. Demographic and clinical characteristics prior to treatment.

characteristics	Augmentin gr. (n=25)	Conventional gr. (n=25)
mael : female	2.1 : 1	2.6 : 1
age (months)		
X ± SD	12.3 ± 8.3	12.3 ± 9.4
body weight by age :		
> 50 percentile	7/25 (28%)	7/25 (28%)
3-50 percentile	13/25 (52%)	13/25 (52%)
< percentile	5/25 (20%)	5/25 (20%)
body temperature (°C)		
X ± SD	38.5 ± 1.0*	37.8 ± 0.8
respiratory rate (/min.)		
X + SD	57 ± 10	54 ± 10
ventilator treatment at admission (%)	4.0	0.0

* = statistical significance at $\alpha=0.05$

There was also no significant difference between the two groups in terms of radiological chest findings and microbiological data (table 2 & 3). Hemophilus influenzae represented the most common organism

isolated from nasopharyngeal secretion. In addition, beta-lactamase producing H.influenzae comprised 12% (3/25) and 16% (4/25) in the Augmentin group and the conventional group respectively.

Table 2. Radiological chest findings.

chest X-ray	Augmentin gr. cases (%)	Conventional gr. cases (%)
lobar pneumonia	12 (48%)	11 (44%)
bronchopneumonia	11 (44%)	11 (44%)
lobar pneumonia with pleural effusion	2 (8%)	3 (12%)
total	25 (100%)	25 (100%)

No statistically significant difference between the two groups at $\alpha=0.05$

Table 3. Microbiological characteristics.

	Augmentin gr. cases (%)	Conventional gr. cases (%)
Hemocultures		
+ve <i>S.pneumoniae</i>	0 (0 %)	1 (4 %)
+ve <i>Streptococcus gr.A</i>	0 (0 %)	1 (4 %)
+ve <i>Salmonella A.</i>	1 (4 %)	0 (0 %)
negative	24 (96 %)	23 (92 %)
total	25 (100%)	25 (100%)
Nasopharyngeal secretion cultures		
<i>H.influenzae</i> :		
-ve beta-lactamase	8 (32 %)	7 (28 %)
-ve beta-lactamase + RSV	2 (8 %)	1 (4 %)
+ve beta-lactamase	1 (4 %)	3 (12 %)
+ve beta-lactamase + RSV	2 (8 %)	1 (4 %)
<i>S.pneumoniae</i> :	4 (16 %)	3 (12 %)
<i>S.aureus</i> :	0 (0 %)	2 (8 %)
<i>S.aureus</i> + RSV	0 (0 %)	1 (4 %)
<i>H.influenzae</i> + <i>S.pneumoniae</i>	1 (4 %)	2 (8 %)
<i>H.influenzae</i> + <i>Klebsiella</i>	1 (4 %)	0 (0 %)
others	0 (0 %)	3 (12 %)
negative	6 (24 %)	2 (8 %)
total	25 (100%)	25 (100%)

No statistic significance at $\alpha = 0.05$

The duration of oxygen therapy in the Augmentin group was comparable with the conventional group (2.4 ± 1.3 vs 2.1 ± 1.2 days), while the duration of hospitalization appeared to be longer in the Augmentin group (8.6 ± 4.8 vs 6.2 ± 5.3 days). However, there was no statistically significant difference (table 4).

Having analyzed the 5 patients with nosocomial pneumonia, all patients had previous treatment failure with other antibiotics before receiving amoxycillin/clavu-

lanic acid (Augmentin). Three cases had tracheostomy tubes for subglottic stenosis, Arnold Chari malformation and obliterative bronchiolitis on obligatory ventilation. The remaining 2 cases had patent ductus arteriosus and retropharyngeal mass. Nasopharyngeal cultures grew *H.influenzae* in 4 cases and *Klebsiella pneumoniae* in 1 case. Regardless of the duration of hospitalization which depended on the patients' underlying conditions, pneumonia in all cases was cured as shown in detail table 5.

Table 4. Outcome of treatment.

	Augmentin gr. (n=25)	Conventional gr. (n=25)
Days of oxygen therapy :		
range	1.0 – 6.0	1.0 – 5.0
X ± SD.	2.4 ± 1.3	2.1 ± 1.2
Days of hospitaization :		
range	3.0 – 21.0	2.0 – 21.0
X ± SD.	8.6 ± 4.8	6.2 ± 5.3
complications	0	0

Table 5. Details of nosocomial pneumonia treated with amoxicillin/clavulanic acid.

Nosocomial pneumonia 5 cases	
male : female	2 : 3
age (months) : range (X ± SD)	6 – 11 (12.6 ± 6.8)
body weight by age :	
>50 percentile	1/5 (20%)
3-50 percentile	2/5 (40%)
< 3 percentile	2/5 (40%)
chest X-ray : lobar pneumonia	4/5 (80%)
bronchopneumonia	1/5 (20%)
microbiologic studies :	
+ve hemocultures	0/5 (0%)
+ve nasopharyngeal secretion bacterial cultures	5/5 (100%)
+ve RSV	0/5 (0%)
response to treatment (days) : range (X ± SD)	
- disappearance of fever within	1–7 (2.6 ± 2.5)
- disappearance of dyspnea within	2–3 (2.2 ± 0.5)
- duration of oxygen therapy	2–14 (5.7 ± 5.6)

Discussion

As the definite etiologic agents of bacterial pneumonia in children could not be identified in most cases, broad - spectrum antibiotics tended to be used in the treatment of severe cases. Moreover, increasing number

of beta-lactamase producing organisms including H. influenzae, S.aureus and Branhamella catarrhalis had been isolated from pediatric patients with respiratory tract infections.^(8,9) From our study, 14% (7/50) of all isolated potential pathogens from previously healthy

children were beta-lactamase producing *H. influenzae*. Amoxicillin/clavulanic acid provided an attractive approach to the treatment of severe pneumonia in children since amoxicillin is a broad - spectrum antibiotic and clavulanic acid inhibited beta-lactamase enzyme.⁽⁷⁾ It should be effective against beta-lactamase producing bacteria which might be the causes of severe infections. Several studies demonstrated its efficacy and safety in pediatric patients.⁽⁴⁻⁷⁾ A comparative study done in patients over 12 years of age with chest infections revealed effective results similar to cefuroxime therapy.⁽¹⁰⁾

This study was conducted in two comparable groups with severe pneumonia requiring oxygen therapy in order to evaluate the effectiveness and safety of amoxicillin/clavulanic acid in young children. The overall success of treatment with both amoxicillin/clavulanic acid and conventional antibiotics was demonstrated. There was no significant difference between the two groups in the outcome of treatment of community - acquired pneumonia. When considering the therapy of nosocomial pneumonia which was not improved with ampicillin and aminoglycosides, amoxicillin/clavulanic acid could cure pneumonia in all 5 cases as confirmed by clinical improvement and clearing of pulmonary infiltrates.

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