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**ARAŞTIRMA/RESEARCH**

# Effect of healthcare associated infections and broad spectrum antibiotic use in newborn period on development of asthma, allergic rhinitis and atopic dermatitis in early childhood

## Yenidoğan döneminde sağlık bakımı ile ilişkili enfeksiyon geçirmiş ve geniş spektrumlu antibiyotik kullanmış olmanın erken çocukluk döneminde gözlenen astma, allerjik rinit ve atopik dermatit üzerine etkisi

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**Abstract**

**Purpose:** The iam of this study was to investigate the effect of healthcare associated infections (HAIs) and broad spectrum antibiotic use in newborn period on asthma, allergic rhinitis and atopic dermatitis.

**Material and Methods:** Seventy three children treated for HAIs in newborn period in Neonatal Intesive Care Unitin a 6 years period, and their 41 siblings who were healthy in newborn period were included in the study. Parents answered a detailed questionnaire, children were examined and complete blood count, serum total Ig E and specific Ig E levels were studied.

**Results:** Ventilator associated pneumonia was observed in 32 (45.2%), blood stream infection in 28 (38.4%) and clinic sepsis in 12 (16.4%) of 73 children with HAIs. Asthma was significantly higher in HAIs group compared to sibling group (32.9% vs. 4.9), whereas there was no significant difference in allergic rhinitis (4.1% vs.2.4%) and atopic dermatitis (6.8% vs. 0%) among groups. When non-allergic 85 subjects and allergic 29 children compared, children who had been hospitalised and treated with broad-spectrum antibiotics in newborn period were almost 11.5 times as likely to have an allergic disease.

**Conclusion:** Asthma was significantly higher in HAI group, and allergic disease risk seems to increase in children treated with broad-spectrum antibiotics for HAIs in newborn period.

**Key words:** Antibiotics, allergic disease, healthcare associated infection, newborn period.

**Öz**

**Amaç:** Bu çalışmadaki amacımız yenidoğan döneminde sağlık bakımı ilişkili enfeksiyon (SBİE) geçiren ve geniş spektrumu antibiyotik kullanan çocuklarda astma, allerjik rinit ve atopic dermatit sıklığını araştırmaktır.

**Gereç ve Yöntem:** Çalışmaya Yenidoğan Yoğun Bakım Ünitesi'nde 6 yıl içinde izlenen 73 SBİE olan çocuk ile bu çocukların yenidoğan döneminde sağlıklı olan 41 kardeşi alındı. Ebeveynlere detaylı bir anket uygulandı ve çocuklardan tam kan sayımı, serum total Ig Eve spesifik IgE için kan örnekleri alındı.

**Bulgular:** SBİE olan 73 çocuğun 32'sinde (%45.2) ventilator ilişkili pnömoni, 28'inde (%38.4) kan dolaşımı enfeksiyonu, 12'sinde (%16.4) klinik sepsis gözlenmişti. Astma SBİE grubunda belirgin daha fazla (%32.9'a karşın %4.9) iken allerjik rinit (%4.1'e karşın %2.4) ve atopik dermatit sıklığı farklı değildi (%6,8'e karşın %0). Allerjisi olmayan 85 çocuk ile allerjisi olan 29 çocuk kıyaslandığında, yenidoğan döneminde SBİE geçirmek ve antibiyotik kullanmak allerjik olma oranını 11.5 kat arttırmaktaydı.

**Sonuç:** SBİE grubunda astma daha sık gözlenmiş olup, yenidoğan döneminde SBİE geçirmek ve geniş spektrumlu antibiyotik kullanmak erken çocukluk döneminde allerji riskini arttırmaktadır.

**Anahtar kelimeler**: Antibiyotik, allerjik hastalıklar, sağlık bakımı ilişkili enfeksiyon, yenidoğan dönemi

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## INTRODUCTION

Epidemiologic studies have demonstrated a significant increase of allergic diseases over the past decades, particularly in industrialized countries[1]. It is accepted that increase in the prevalence in western countries can not be explained solely by genetic factors. Environmental changes and environment-gene interactions are thought to be responsible for this increase[2].

Hygiene hypothesis postulates that the lack of early childhood infection agents modulates the immune system, increasing the susceptibility of individuals to atopic diseases, particularly asthma[3]. In newborn period, T helper (Th) 2 immune response is predominant. According to hygiene hypothesis, infections early in life may protect against the development of asthma by generating predominant Th1 immune responses. However antibiotic use for an infection may shorten the duration and intense of infections; nevertheless may cause major disruptions to the intestinal bacterial flora. These are the suggested risk factors to increase risk of atopic diseases[3,4].

There are conflicting results about the relationship between antibiotic use in early childhood and atopic diseases. Although several studies have suggested that antibiotic exposure in the first year of life has been a risk factor for the development of asthma[5-7], this relationship could not be shown in other studies[8,9] .

In this study we aimed to investigate whether broad spectrum antibiotics for healthcare associated infections (HAIs) in newborn period is a risk factor for subsequent asthma, allergic rhinitis and atopic dermatitis in early childhood.

## MATERIAL AND METHODS

The Ethical Committee of the Çukurova University, Faculty of Medicine approved the study at 2nd meeting on 10th Feb., 2009, decision 3. After approval study was initiated. The Newborn Intensive Care Unit (NICU) of Cukurova University is a tertiary centre with 31 beds. The medical files of 4538 patients admitted in 6 years period were reviewed and 190 infants with HAIs ≥ 24 months (HAI group) were asked to admit Newborn Outpatient Clinic by letter. Infants ≤ 33 gestational age, with congenital anomaly, neurologic disorders and chronic lung disease were not included. HAI site definition was adopted according to the Center of Disease Control definition system[10,11]. HAI was considered if a patient had an infection after the first 72 h of admission.

The nearest age sibling ≥ 24 months not treated with antibiotics during newborn period were asked to enroll to the study as 'Sibling group'. Three days later, parents were called. 27 parents refused to come and 82 parents could not be reached probably due to address or phone number change. 8 patients were exluded (1 for not fully vaccinated, 4 due to underlying disease- tracheal web, tuberculosis, leucemia, and congenital cataract-, 3 due to exitus). 73 patients (HAI group) and 41 siblings were enrolled to the study.

All subjects were examined and 5 ml of blood was drawn for complete blood count, total Ig E, allergen-specific Ig E and eosinophil count. Allergen-specific IgE antibodies were determined in ImmunoCAP 100 by using Phadiatop and fx5 (Phadia AB, Uppsala, Sweden). A value of ≥0.35 kU/L was considered positive. The total serum IgE was assayed by microparticle enzyme immunoassay (Abbott Laboratories, USA). A questionnaire about demographic factors, physician diagnosed allergic disease, parental asthma, enviromental exposures, vaccination and other diseases were asked to the parents by one of the physicians. The Ethical Committee of the Çukurova University, Faculty of Medicine approved the study and written consent was gained from the parents.

All patients and questionnaires were evaluated by a pediatric allergist who did not know whether the patient was from HAI group or Sibling group. Asthma and rhinitis were diagnosed according to the guidelines of the Global Initative for Asthma and Allergic Rhinitis and Its Impact on Asthma, respectively[12,13]. Atopic dermatitis was diagnosed by Hanifin and Rajka criteria[14].

### Statistical analysis

SPSS 17.0 was used for data analysis. Categorical variables were summarized using count and percent whereas continuous variables were summarized in mean ± standard deviation, median, min and max values. The chi-square test was used for comparisons of categorical variables. The Kolmogrov-Smirnov test was used to check for normality of continuous variables. Group

comparisons of these variables were done using the t-test for normally distributed and Mann-Whitney test for non normal distributed variables. Variables found to be statistically significant in the univariate analysis were used in the multivariate logistic regression analysis. A p-value≤ 0.05 was accepted as statistically significant.

## RESULTS

43 (58.9%) of the 73 patients were boys. The underlying diseases of the subjects are shown in Table 1. The mean hospitalisation day in NICU was 20.31±8.45 days. 51 (69.9%) patients were supported on ventilator. 33 (45.2%) patients had ventilator associated pneumonia (VAP), 28 (38.4%) had blood stream infection (BSI) and 12 (16.4%) had clinical sepsis. 4 patients in VAP group and 5 patients in BSI group also had necrotising enterocolitis (NEC). Gram negative microorganisms were predominant in tracheal aspirate fluid in VAP: 48.5% was K.pneumonia, 33.3% was A.baumannii and 33.3% was P.aeruginosa. S.epidermidis was the leading microorganism in BSIs (16/28 patients, 57.1%). Empiric antibiotic treatment for early neonatal sepsis prophylaxis was begun to 59 patients (81.9%) in the first day of life. For HAIs, 63 (91.8%) patients had been treated with aminoglycoside, 40 patients (54.8%) with carbapenem, 26 patients (35.6%) with vancomycin and 4 patients (5.5%) with teicoplanin.

18 children in HAI group have not got a sibling in 24-144 months old age and 14 children had no sibling. There were 41 siblings in Sibling group. The mean gestational age, birth weight and age of the subjects in HAI group were significantly lower ($p<0.001$). Delivery by caesarean section was significantly high in HAI group (84.9% vs. 43.9%), ($p<0.001$). There was no difference among gender between groups ($p=0.588$). There were no significant difference among household size, parental occupation, monthly income, parental education level, parental smoking, maternal and paternal atopic disorders between groups ($p>0.05$). Sibship size was higher in Sibling group ($p=0.017$), however 14 children in HAI group have got no sibling and there was no significant difference among sibship size in the remaining 59 children compared with Sibling group ($p=0.990$). Although the amount of exclusively breastfeeding period was significantly shorter in HAI group, there was no significant difference in terms of total duration of breastfeeding and time of weaning. Formula use was higher in HAI group. History of food allergy was similar between groups (16.4% in HAI group vs. 14.6% in Sibling group, $p=0.799$). Subjects in the HAI group had significantly received more antibiotics, they more frequently had lower respiratory tract infections (RTIs), and had been more frequently hospitalised for RTIs in 1-12 months of age, Table 2. 27 (23.6%) of 114 subjects had at least one atopic disease (allergic children). The rate of an allergic disease was significantly higher in HAI group ($p<0.001$) (Table 3).

Total Ig E levels were higher in HAI group (133.90±230.00 vs. 56.67±69.10 IU/ml), ($p=0.003$). There was no significant difference among eosinophil count (327.2 ±310.5/mm³ vs. 251.9±174.5/mm³), ($p=0.202$). Specific IgE was positive in 4 subjects (9.8%) in Sibling group: f1 was positive in 2 subjects, f4 was positive in 1 subject and f13 was positive in 2 subjects. Of these 4 subjects, one had asthma and allergic rhinitis, one had atopic dermatitis and one had asthma, one had no symptom. 9 children (12.3%) had specific Ig E and 3 subjects had both positive phadiotop and fx5 (f1 was positive in 4 subjects, f2 in 2, f5 in one and f13 was positive in one patient) in HAI group. There was no allergic disease in 4 of these children.

Children with allergic diseases had significantly higher rates of HAIs in the newborn period. Frequent (≥ 3) RTI and hospitalisation for RTI were more common. Rate of antibiotic use in the first year after newborn period was similar. Sibling size was similar ($p>0.05$). Major risk factors for an allergic disease were lower age, HAIs in newborn period, high C/S delivery rate, frequent RTI and hospitalisation for RTI in 1-12 months as shown in Table 4. There were 24 allergic and 49 non-allergic subjects in HAI group. There were no significant difference in duration of hospitalisation, ventilator treatment, total parenteral nutrition and antibiotic treatment and supplementation time among them ($p>0.05$). Compared with the children without an allergic disease in terms of age, gestational age, gender, birth weight, delivery (C/S), prenatal/natal factors, sibship size, antibiotic use in 1-12 months, frequent RTI and hospitalisation for RTI in the first year of life and total Ig E levels, children with allergic diseases had significantly higher ratios of RTI and hospitalisation after newborn period ($p=0.001$, $p=0.009$, respectively). In multivariate models of univariate risk factors, higher ratios of

RTI after newborn period increases the risk of allergic diseases for 8.5 times (95% CI: 2.26-32.6, p=0.002). 13 (39.4%) of the patients with VAP, 9 (32.1%) of the patients with BSI and 2 (16.7%) of the patients with clinical sepsis had an allergic disease (p=0.328). Although asthma was higher in patients with VAP and atopic dermatitis was higher in patients with BSIs, the differences were not statistically significant (Table 5).

**Table 1. Underlying diseases of subjects in Health-care Associated Infection group**

| **Diseases*** | **n (73)** | **%** |
|---|---|---|
| Prematurity (≤ 37 gestational age) | 57 | 78.1 |
| Respiratory distress | 57 | 78.1 |
| Respiratory distress syndrome | 44 | 60.3 |
| Respiratory distress syndrome treated with surfactant | 13 | 17.8 |
| Maternal risk factors/ infections (pPROM, UTI, vaginal discharge etc.) | 26 | 35.6 |
| Maternal hypertension (preeclampsia, eclampsia, chronic hypertension) | 22 | 30.1 |

*infant may have more than one disease, pPROM: prolonged premature rupture of membranes, UTI: Urinary tract infection

**Table 2. Characteristics of subjects in Sibling and Health-care Associated Infection (HAI) groups**

| | **Sibling group (n=41)** | **HAI group (n=73)** | |
|---|---|---|---|
| | mean±SD<br>median (min-max) | mean±SD<br>median (min-max) | P |
| Age (month) | 85.07±34.66<br>90 (24-144) | 52.48±18.63<br>48 (24-94) | <0.001 |
| Gestational age (weeks) | 37.34±2.11<br>38 (33-40) | 35.16±2.11<br>34 (33-40) | <0.001 |
| Birth weight (g) | 2968±653.96<br>3000 (1770-4300) | 2294±592.10<br>2180 (1400-3870) | <0.001 |
| Exclusively breastfeeding (months) | 5.37±4.05<br>6 (0-12) | 2.04±2.71<br>0 (0-12) | <0.001 |
| Start of supplementation, weaning (month) | 6.27±2.3<br>6 (3-12) | 6.64±2.82<br>6 (3-18) | 0.664 |
| Total amount of breastfeeding (months) | 12.54±6.54<br>12 (1-24) | 11.37±10.57<br>9 (0-36) | 0.177 |
| | n (%) | n (%) | |
| Delivery (C/S) | 18 (43.9) | 62 (84.9) | <0.001 |
| Gender (male) | 22 (53.7) | 43 (58.9) | 0.588 |
| Formula use | 14 (34.1) | 58 (79.5) | 0.001 |
| Parental smoking | 25 (61.0) | 46 (63.0) | 0.843 |
| Antibiotics (1-12 months) | 23 (56.1) | 56 (76.7) | 0.023 |
| Frequent (≥3) RTIs (1-12 months) | 14 (34.1) | 43 (58.9) | 0.011 |
| Hospitalisation for RTIs (1-12 months) | 6 (14.6) | 24 (32.9) | 0.028 |

**Table 3. Allergic diseases of subjects**

| | **Sibling group (n=41)<br>n (%)** | **HAI group (n=73)<br>n (%)** | **p** |
|---|---|---|---|
| Asthma | 2 (4.9) | 22 (30.1) | 0.001 |
| Allergic rhinitis | 1 (2.4) | 3 (4.1) | 0.999 |
| Atopic dermatitis | 1 (2.4) | 5 (6.8) | 0.417 |
| Allergic disease (total)* | 3 (7.3) | 24 (32.9) | 0.002 |

* Child may have more than one disease

**Table 4. Characteristics of allergic and non-allergic children**

| | **Non-allergic Children (n=87)** | **Allergic Children (n=27)** | |
|---|---|---|---|
| | mean±SD<br>median (min-max) | mean±SD<br>median (min-max) | p |
| Age (months) | 68.03±31.49<br>60 (24-144) | 51.85±19.89<br>45 (24-88) | 0.021 |
| Gestational age | 36.16±2.36<br>36 (33-40) | 35.26±2.21<br>35 (33-40) | 0.109 |
| | n (%) | n (%) | |
| Healhtcare-associated infections | 49 (56.3) | 24 (88.9) | 0.002 |
| Delivery (C/S) | 56 (64.4) | 24 (88.9) | 0.016 |
| Formula use | 51 (58.6) | 21 (77.8) | 0.109 |
| Exclusively breastfeeding (months) | 3.46±3.24<br>4 (0-12) | 2.07±2.61<br>0 (0-6) | 0.059 |
| | | | |
| Antibiotic use (1-12 months) | 58 (66.7) | 21 (77.8) | 0.344 |
| Frequent (≥3) RTI | 34 (39.1) | 23 (85.2) | <0.001 |
| Hospitalisation for RTI | 17 (19.5) | 13 (48.1) | 0.005 |

**Table 5. Allergic diseases in ventilator-associated pneumonia (VAP) and bloodstream infection (BSI)**

| | **VAP (n=33)<br>n (% )** | **BSI (n=28)<br>n (% )** | **p** |
|---|---|---|---|
| Asthma | 13 (39.4) | 7 (25.0) | 0.281 |
| Allergic rhinitis | 1 (3.0) | 1 (3.6) | 0.999 |
| Atopic dermatitis | 1 (3.0) | 4 (14.3) | 0.170 |
| Atopic disease (total) | 13 (39.4) | 9 (32.1) | 0.602 |

## DISCUSSION

In this study, we have shown that asthma was significantly high in children with HAI. In developed countries, asthma incidence by International Study of Asthma and Allergies in Childhood (ISAAC) survey was reported as 4-23%[15,16]. Atopic diseases are characterised by dominant Th2 mechanisms and the production of Ig E. [17] Th2 cells are dominant in newborn period. In non-atopic individuals, Th2 cells are suppressed, whereas Th1 immune responses predominate. Postnatal infections may be protective against atopic diseases by rebalancing Th1/Th2 immunity. However, microbial exposure, especially gastrointestinal tract flora is a keypoint in promoting normal postnatal maturation. There are conflicting results from studies about early antibiotic use and the development of atopic disease. In a meta-analysis study about antibiotic exposure during infancy and childhood asthma development, only the pooled results from the retrospective studies showed a positive association[6]. In a prospective study, Droste et al.[7] showed increased risk of asthma, hay fever and eczema in 7- 8 aged children treated with antibiotics during first year of life. However after strafication for the presence of parental hay fever, children without parental hay fever did not show any significant association between antibiotic use and asthma or allergy whereas antibiotic exposure significantly related with asthma, hay fever and eczema. They concluded that antibiotic exposure may cause Th2 skew in children who are predisposed to atopic immune responses. However this result may be due to reverse caution, as subjects predisposed to atopic diseases, particulary asthmatics are likely to have more often symptomatic and more severe respiratory diseases and treated with antibiotics[18]. More recently several studies found no association between early antibiotic use and subsequent atopic diseases[8,19]. A large longitudinal study of more than 4000 subjects from birth to 5 years found no association between antibiotic use and asthma at 5 years but concluded

that antibiotic exposure in early life was much more in asthmatic children[8]. Ultimately the results showing an association between antibiotic use and atopic diseases seem to be a result rather than a cause. In a study about antibiotic sales and atopic diseases seroprevalence in 56 countries, Foliaki et al.[20] showed that the amount of antibiotic use does not explain the increased prevalence of asthma in developed world. In our study, HAIs and broad spectrum antibiotic use during newborn period was related with increased risk of asthma. It may be concluded that the results may not be reliable as 27 parents denied the study and possibly they were healthy. But if we assume these 27 children had no atopic illnesses, atopy incidence would still be significantly higher (24/100 subjects, 24%). The subjects in the present study were from the same genetic and environmental backgrounds. So we may suggest that healthcare-associated infections and broad spectrum antibiotic use in newborn period may be significant risk factors for asthma. We could not find any other study dealing with newborn infenctions and allergic disease except for Cetinkaya et al.'s study[21]. However, in Cetinkaya et al.'s study[21], sepsis in neonatal life was inversely related with the development of asthma in childhood.

Approximately 80-90% of asthmatics report disease onset before 5 years of age, 50% in two years and 30% in the first year of life[22]. In the present study, although the mean age of HAI group was 32 months younger than sibling group, asthma rate was significantly higher in HAI group. In our study we could not show an association between atopic dermatitis and allergic rhinitis and healthcare-associated infections similar to other studies[21,23,24].

Well-known risk factors for atopy such as low birth weight, low gestational age, caserean delivery and formula feeding[25-29] were significantly higher in HAI group; however there was no difference in allergic and non-allergic subjects in HAI group. In the present study, gestational age and birth weight of subjects in HAI group were significantly lower than sibling group; however there was no significant difference either among allergic and non-allergic children in all, and among allergic and non-allergic individuals in HAI group. So we suggest that gestational age and birth weight were not effective in atopic disease in our study groups. Protective effect of breastfeeding on development of asthma and recurrent wheezing has been shown in studies and a dose response effect was observed with breastfeeding duration[28,29]. In the HAI group, duration of exclusively breastfeeding was shorter compared to sibling group; however the mean duration of breastfeeding and start of supplementation were similar. Also rate of C/S delivery and duration of exclusively breastfeeding were similar between allergic and non-allergic children in HAI group.

There is consistent evidence of an inverse association between sibship size and allergic rhinitis but conflincting findings about number of siblings and asthma[30]. In this study as both the rate of allergic disease of children with and without sibling and number of siblings of allergic and non allergic children were similar; we suggest that sibling size had no effect on allergic disease rate in our study.

Pneumonia and severe bronchiolitis are important risk factors for asthma. We have shown that subjects in HAI group had significantly higher exposure to antibiotics in 1-12 months of age, significantly more recurrent respiratory diseases and hospitalised for RTIs. In a birth cohort of 13116 children, an association with asthma at age 7 years was observed for antibiotic use in non- respiratory tract infections in the first year of life. The risk of asthma was highest in children with more than 4 courses of antibiotics[31]. All children in HAI received broad spectrum antibiotics in newborn period. However we could not exactly know afternewborn period as we have gained the information about antibiotic use, courses of antibiotics and illnesses particulary from parents, and if possible from their hospital files if they had. The limitation of this study is it is not a prospective study. However healthcare associated infections and broadspectrum antibiotic exposure seem to cause an increase in asthma rate.

In conclusion, newborns hospitalised in NICUs should be protected from healthcare associated infections and broad spectrum antibiotics exposure as much as possible. Large, prospective controlled studies are needed to clarify the role of neonatal healthcare associated infections and antibiotic use on asthma and other allergic diseases.

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