International Archives of Allergy and Immunology

Clinical Allergy – Research Article

Int Arch Allergy Immunol 2020;181:926–933
DOI: 10.1159/000507857

Received: January 22, 2020
Accepted: April 14, 2020
Published online: October 22, 2020

Recent Practice Patterns and Variations in Children Hospitalized for Asthma Exacerbation in Japan

Yusuke Okubo[a, b, c] Kenta Horimukai[d] Nobuaki Michihata[e] Kojiro Morita[c] Hiroki Matsui[c] Kiyohide Fushimi[f] Hideo Yasunaga[c]

[a]Department of Epidemiology, University of California, Fielding School of Public Health, Los Angeles, CA, USA; [b]Department of Social Medicine, National Center for Child Health and Development, Tokyo, Japan; [c]Department of Clinical Epidemiology and Health Economics, School of Public Health, The University of Tokyo, Tokyo, Japan; [d]Department of Pediatrics, Jikei University Katsushika Medical Center, Tokyo, Japan; [e]Department of Health Services Research, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan; [f]Department of Health Policy and Informatics, Tokyo Medical and Dental University Graduate School of Medicine, Tokyo, Japan

Keywords
Pediatric asthma · Treatment pattern · Machine learning

Abstract
Background: High antibiotic prescribing rates for adults with an asthma exacerbation have been reported in developed countries, but few studies have assessed the variation of antibiotic and adjunctive treatment in the routine care of children. ***Objective:*** We evaluated the trends in health resource utilization for children hospitalized for asthma exacerbation, ascertained the variations of practices across hospitals and geographic location, and classified these different patterns at hospital levels. ***Methods:*** Using data on Japanese children hospitalized for asthma exacerbation with no indication of bacterial infection during 2010–2018, we conducted a retrospective observational study to assess the trends in initial treatment patterns and their variations. Mixed-effect generalized linear models were used to investigate the treatment trends. Hierarchical cluster analyses were performed to classify the treatment variations across hospitals. ***Results:*** Overall, 54,981 children were eligible for the study. Proportions of antibiotic use decreased from 47.2% in 2010 to 26.9% in 2018. Similarly, utilization of antitussives, antihistamines, and methylxanthine showed decreasing trends over the period, whereas the use of mucolytics and ambroxol increased. These treatment variations were more considerable in hospital levels than in 47 prefecture levels. Hierarchical cluster analyses classified these patterns into 6 groups, mostly based on mediator release inhibitor, ambroxol, and antitussives. ***Conclusions:*** Wide variations in antibiotics and adjunctive treatments were observed across hospital levels. Our findings support the improvement in reducing inappropriate antibiotic use and highlight the need for comparative effectiveness research of the adjunctive treatments among children hospitalized for asthma.

© 2020 S. Karger AG, Basel

Edited by: H.-U. Simon, Bern.

karger@karger.com
www.karger.com/iaa

© 2020 S. Karger AG, Basel

Yusuke Okubo
Department of Epidemiology, UCLA Fielding School of Public Health
650 Charles E. Young Dr. S
Los Angeles, CA 90095 (USA)
sunning_dale@yahoo.co.jp

Downloaded by: C. Alessandri - 87218
84.220.48.124 - 11/15/2020 8:18:46 AM

Introduction

Asthma is the most common chronic lung condition in children. Asthma exacerbation cases are responsible for a large number of emergency department visits, hospitalization, and healthcare expenditures each year in the most developed countries [1, 2]. In Japan, asthma affects 8–13% of children [3, 4]. Among them, approximately 15% were uncontrolled, and <5% experienced severe wheeze in the past year [4, 5].

According to most guidelines for the treatment of patients hospitalized for asthma exacerbation [6, 7], the standard treatments consist of oxygen administration, short-acting β_2 agonists, and corticosteroids. Some current guidelines [6, 8] recommended against a routine antibiotic prescription for asthma exacerbations in the absence of concurrent bacterial infections because respiratory viral infections are the major cause of asthma exacerbations [9, 10]. Methylxanthine, inhaled ipratropium bromide, and oral leukotriene receptor antagonist (LTRA) are not recommended for pediatric inpatients with asthma exacerbation based on insufficient evidence.

A previous study based on a large database reported adherence to those guidelines and variations in treatment patterns in adults [11]. According to the data from the USA, antibiotics were prescribed on the first day in 61% of cases with extremely wide variations across hospitals, ranging from 0% to approximately 90% of inpatients with asthma exacerbation. However, little is known about the use of antibiotics and adjunctive treatments in routine clinical practice among children at a national level, including Japan and other developed countries. Identifying practice patterns across hospitals and investigating geographic differences in medical utilization are essential for recognizing unwarranted variations and developing health policies and clinical guidelines that increase the value of healthcare. Therefore, we evaluated the trends in health resource utilization for children hospitalized for asthma exacerbation, ascertained the variations of practices across hospitals and geographic location, and classified these different patterns at hospital levels.

Methods

Study Design and Data Source

We conducted a retrospective observational study using the Diagnosis Procedure Combination inpatient database between July 1, 2010, and March 31, 2018. The details of the database have been described elsewhere [12]. Briefly, it contains data collected from >1,000 hospitals and covers up to 55% of all inpatient admissions to acute-care hospitals in Japan. The database stores hospital discharge records and administrative claims data for approximately 7 million inpatients per year. Approval for the present study was obtained from the institutional review board at the University of Tokyo. The board waived the requirement for informed consent because of the anonymous nature of the data.

We included pediatric inpatients aged between 6 months and 15 years with a diagnosis of asthma exacerbation. Hospitalizations for asthma exacerbation were defined using the International Classification of Diseases, tenth revision (ICD-10) code, as a primary diagnosis of asthma or principal diagnosis of acute respiratory failure combined with a secondary diagnosis of asthma (see online suppl. Table 1; see www.karger.com/doi/10.1159/000507857 for all online suppl. material). To avoid misclassification and maximize the accuracy of the asthma diagnosis, we restricted the analyses to inpatients treated with systemic corticosteroids and short-acting β_2 stimulant inhalation because these medications are currently considered the standard therapy for moderate to severe asthma exacerbation [13]. We excluded patients with potential indications for bacterial infections based on the diagnoses at admission (online suppl. Table 1), diagnostic procedures (computed tomography and blood culture), and treatments (neuraminidase inhibitors and antifungal agents). Patients treated with neuraminidase inhibitors were excluded because children hospitalized for influenza treatment could have concurrent bacterial infections [14]. Patients with chronic medical conditions were also excluded from the analyses. Chronic medical conditions were defined according to the pediatric complex chronic conditions classification system version 2 [15]. When a patient had more than 1 admission during the study period, we randomly selected 1 admission.

Measurements of Variables

The patient characteristics included age, sex, weight status (thin, normal, overweight, or obese), preexisting comorbidities (food allergy, allergic rhinitis, and atopic dermatitis), admission to academic hospitals, ambulance use, and medications used within the first 2 days of hospitalization. These variables were selected based on our best prior knowledge from previous study findings [16–19]. The weight status was determined using *z*-scores of weight-for-length (for patients aged <2 years), weight-for-height (for patients aged 2–5 years), or body mass index for age (for patients aged >5 years) calculated from the child growth references of the World Health Organization [20]. Preexisting comorbidities were identified based on ICD-10 codes (online suppl. Table 1).

We defined the initial treatment patterns as any antibiotics and adjunctive treatments that started during the first 2 days of hospitalization. Antibiotics were categorized into the following groups: penicillin, macrolides, cephalosporins, quinolones, tetracyclines, and other types (online suppl. Table 2). The adjunctive treatments used within the first 2 days of hospitalization included antitussives, mucolytics, antihistamines, LTRAs, xanthine, and inhaled corticosteroid (online suppl. Tables 2 and 3). Healthcare resource utilization consisted of the length of hospital stay in days, hospitalization costs in Japanese yen, and invasive or noninvasive mechanical ventilation during hospitalization.

Statistical Analysis

Baseline characteristics are summarized as means and proportions for continuous and categorical variables. We calculated the proportions of patients who received the initial antibiotics and ad-

Downloaded by: C. Alessandri - 87218
84.220.48.124 - 11/15/2020 8:18:46 AM

Table 1. Trends in patient characteristics, healthcare utilization, and antiepileptic drug use

Year of admission: *N:*	2010 5,560	2011 7,338	2012 6,517	2013 7,811	2014 6,374	2015 8,839	2016 5,759	2017 6,147	2018 636	% Increase
Healthcare cost, mean JPY	221,662	220,758	228,430	228,044	231,285	231,632	234,710	232,111	230,395	0.3%
(SE)	(1,304)	(1,249)	(1,280)	(1,155)	(1,308)	(1,057)	(1,328)	(1,320)	(3,992)	(0.2%, 0.5%)
LOS, mean days	5.7	5.7	5.7	5.7	5.7	5.6	5.6	5.5	5.5	−0.7%
(SE)	(0.1)	(0.1)	(0.1)	(0.1)	(0.1)	(0.1)	(0.1)	(0.1)	(0.1)	(−0.8%, −0.5%)
Mechanical ventilation, *N*	44	47	44	64	75	85	63	57	5	10.5%
(%)	(0.8)	(0.6)	(0.7)	(0.8)	(1.2)	(1.0)	(1.1)	(1.0)	(0.8)	(4.5%, 16.9%)

SE, standard error; JPY, Japanese yen, LOS, length of stay; % Increase, % increase of proportion per year for health resource utilization in ratio scale.

Table 2. Trends in early antibiotic use

Year of admission: *N:*	2010 5,560	2011 7,338	2012 6,517	2013 7,811	2014 6,374	2015 8,839	2016 5,759	2017 6,147	2018 636	% Increase
Total, *N*	2,622	3,272	2,894	3,176	2,459	3,413	2,121	1,958	171	−11.7%
(%)	(47.2)	(44.6)	(44.4)	(40.7)	(38.6)	(38.6)	(36.8)	(31.9)	(26.9)	(−12.6%, −10.8%)
Macrolide, *N*	1,288	1,627	1,225	1,288	794	1,209	770	689	60	−15.5%
(%)	(23.2)	(22.2)	(18.8)	(16.5)	(12.5)	(13.7)	(13.4)	(11.2)	(9.4)	(−16.6%, −14.4%)
Cephalosporin, *N*	768	914	716	717	555	714	447	399	30	−15.9%
(%)	(13.8)	(12.5)	(11.0)	(9.2)	(8.7)	(8.1)	(7.8)	(6.5)	(4.7)	(−17.4%, −14.6%)
Third generation, *N*	382	447	396	443	356	472	309	270	20	−6.8%
(%)	(6.9)	(6.1)	(6.1)	(5.7)	(5.6)	(5.3)	(5.4)	(4.4)	(3.1)	(−8.7%, −4.8%)
Penicillin, *N*	410	489	460	624	568	882	512	585	64	6.6%
(%)	(7.4)	(6.7)	(7.1)	(8.0)	(8.9)	(10.0)	(8.9)	(9.5)	(10.1)	(4.7%, 8.5%)
Quinolone, *N*	9	21	99	77	70	108	100	49	6	12.5%
(%)	(0.2)	(0.3)	(1.5)	(1.0)	(1.1)	(1.2)	(1.7)	(0.8)	(0.9)	(7.5%, 17.6%)
Tetracycline, *N*	21	57	90	50	23	50	38	15	0	−9.4%
(%)	(0.4)	(0.8)	(1.4)	(0.6)	(0.4)	(0.6)	(0.7)	(0.2)	(0)	(−14.5%, 4.0%)

% Increase, % increase of proportion per year for health resource utilization in ratio scale.

junctive therapy, given all inpatients with asthma. The annual trends were investigated in terms of total hospitalization costs, length of stay, and practice patterns from 2010 to 2018. To evaluate the trends, we constructed multivariable mixed-effect generalized linear models that contained the year of admission as a continuous variable. All models included fixed effects for patient characteristics and random effects for hospitals. The trends were reported in relative scales for a 1-year increase with 95% confidence intervals (CIs). All data were analyzed using Stata software version 15.1 (StataCorp LP, College Station, TX, USA).

We also investigated the practice pattern variations across the hospitals and 47 prefectures in Japan using dot plots for each treatment. To investigate the variations at hospital levels, we selected hospitals that had at least 50 patients hospitalized for asthma. Finally, we performed hierarchical cluster analyses with Ward's clustering criterion [21, 22]. Hierarchical cluster analysis is one of the unsupervised learning methodologies and creates hierarchically related sets of clusters to determine the natural groupings or clusters of the observations. This method is aimed to create clusters of hospitals that had similar clinical practice patterns (antibiotics and adjunctive treatment) and to capture the differences and variations across the clusters of hospitals using a heat map. This analysis was performed with R, version 3.6.1. Furthermore, we conducted subgroup analyses among children aged >5 years because the Japanese Guideline for the Diagnosis and Treatment of Allergic Disease 2017 (JAGL 2017) differs from the Global Initiative for Asthma Guideline in that JAGL emphasizes diagnosis and early intervention of children with asthma at <2 years or 2–5 years of age [6, 7].

Results

We identified a total of 54,981 children eligible for our study. Baseline characteristics are summarized in Table 1 and online suppl. Table 4. The trend analyses showed almost similar healthcare costs and length of hospital stay

Downloaded by: C. Alessandri - 87218
84.220.48.124 - 11/15/2020 8:18:46 AM

Table 3. Trends in adjunctive treatments

Year of admission: *N:*	2010 5,560	2011 7,338	2012 6,517	2013 7,811	2014 6,374	2015 8,839	2016 5,759	2017 6,147	2018 636	% Increase
Adjunctive treatments, *N*										
Antitussives	1,951	2,605	2,199	2,554	2,132	2,812	1,692	1,661	174	−8.7%
(%)	(35.1)	(35.5)	(33.7)	(32.7)	(33.5)	(31.8)	(29.4)	(27.0)	(27.4)	(−9.2%, −7.6%)
Mucolytics	3,761	4,948	4,562	5,450	4,517	6,314	4,151	4,543	482	6.0%
(%)	(67.6)	(67.4)	(70.0)	(69.8)	(70.9)	(71.4)	(72.1)	(73.9)	(75.8)	(4.8%, 7.1%)
Ambroxol	2,110	2,727	2,504	3,183	2,574	3,822	2,442	2,721	285	5.9%
(%)	(38.0)	(37.2)	(38.4)	(40.8)	(40.4)	(43.2)	(42.4)	(44.3)	(44.8)	(4.7%, 7.2%)
Antihistamines	963	1,279	1,000	1,021	790	977	602	677	74	−15.0%
(%)	(17.3)	(17.4)	(15.3)	(13.1)	(12.4)	(11.1)	(10.5)	(11.0)	(11.6)	(−16.2%, −13.7%)
LTRA	3,784	4,884	4,510	5,601	4,540	6,288	4,186	4,691	499	9.0%
(%)	(68.1)	(66.6)	(69.2)	(71.7)	(71.2)	(71.1)	(72.7)	(76.3)	(78.5)	(7.8%, 10.1%)
Mediator release inhibitors	2,242	2,986	2,628	3,095	2,713	3,695	2,357	2,580	266	1.6%
(%)	(40.3)	(40.7)	(40.3)	(39.6)	(42.6)	(41.8)	(40.9)	(42.0)	(41.8)	(−0.2%, 3.5%)
Xanthine	912	949	641	640	427	543	228	211	15	−30.6%
(%)	(16.4)	(12.9)	(9.8)	(8.2)	(6.7)	(6.1)	(4.0)	(3.4)	(2.4)	(−32.1%, −29.2%)
Inhaled corticosteroids	574	860	755	884	671	927	592	688	81	−1.8%
(%)	(10.3)	(11.7)	(11.6)	(11.3)	(10.5)	(10.5)	(10.3)	(11.2)	(12.7)	(−3.3%, −0.2%)

LTRA, leukotriene receptor antagonist; % Increase, % increase of proportion per year for health resource utilization in ratio scale.

from 2010 to 2018. The risk of mechanical ventilation had a slightly increasing trend. Table 2 demonstrates the trends in proportions of antibiotic use within 2 days of hospitalization for children with asthma exacerbation. Decreasing trends were observed in total antibiotics, macrolide, cephalosporin, and tetracycline, whereas penicillin and quinolone showed increasing trends. Macrolide was the most frequently used antibiotics in 2010, but penicillin and macrolide had almost similar utilization in 2018. Table 3 and online suppl. Table 5 shows the trends in adjunctive treatments. The commonly prescribed adjunctive treatments were mucolytics, LTRAs, and mediator release inhibitors. Proportions of initial treatments with antitussives, antihistamine, and xanthine decreased from 2010 to 2018, while treatments with mucolytics, ambroxol, and LTRAs increased over the period.

Figure 1a demonstrates the variations of antibiotic use across 330 hospitals (1A) and 47 prefectures (online suppl. Fig. 1a) during 2010–2018. The variations of antibiotics were more considerable in between-hospital levels than those in between-prefecture levels. Similarly, higher variabilities for adjunctive treatments were observed in between-hospital levels (Fig. 1b) than those in between-prefecture levels (online suppl. Fig. 1b) during 2010–2018.

To classify the difference in treatment patterns, we performed a hierarchical cluster analysis and presented the result with heat map (Fig. 2). Based on the dendrogram, we categorized the hospitals into 6 groups and checked their practice patterns at hospital levels. Mediator release inhibitor use differentiated the hospital groups 4–6 from hospital groups 1–3. Antitussives, ambroxol, and antibiotics were different across these groups. For example, hospitals in group 3 and group 5 did not prefer to use antitussives and ambroxol. Hospitals in groups 1 and 6 were more likely to use antitussives and antibiotics. Hospitals in groups 2 and 4 were less likely to use antitussives, but preferred to use ambroxol.

We conducted subgroup analyses among children aged >5 years. We observed similar treatment trends during 2010–2018 (online suppl. Tables 6–8) and variations of antibiotic and adjunctive treatment across hospitals and geographic locations (online suppl. Fig. 2–3). Furthermore, the hierarchical clustering also showed similar clustering patterns of hospitals based on their practice patterns (online suppl. Fig. 4).

Discussion

In this large observational study based on a national database with approximately 58,000 children hospitalized for asthma exacerbation, we found decreasing trends in antibiotic use, antitussives, antihistamine, and xan-

Downloaded by: C. Alessandri - 87218
84.220.48.124 - 11/15/2020 8:18:46 AM

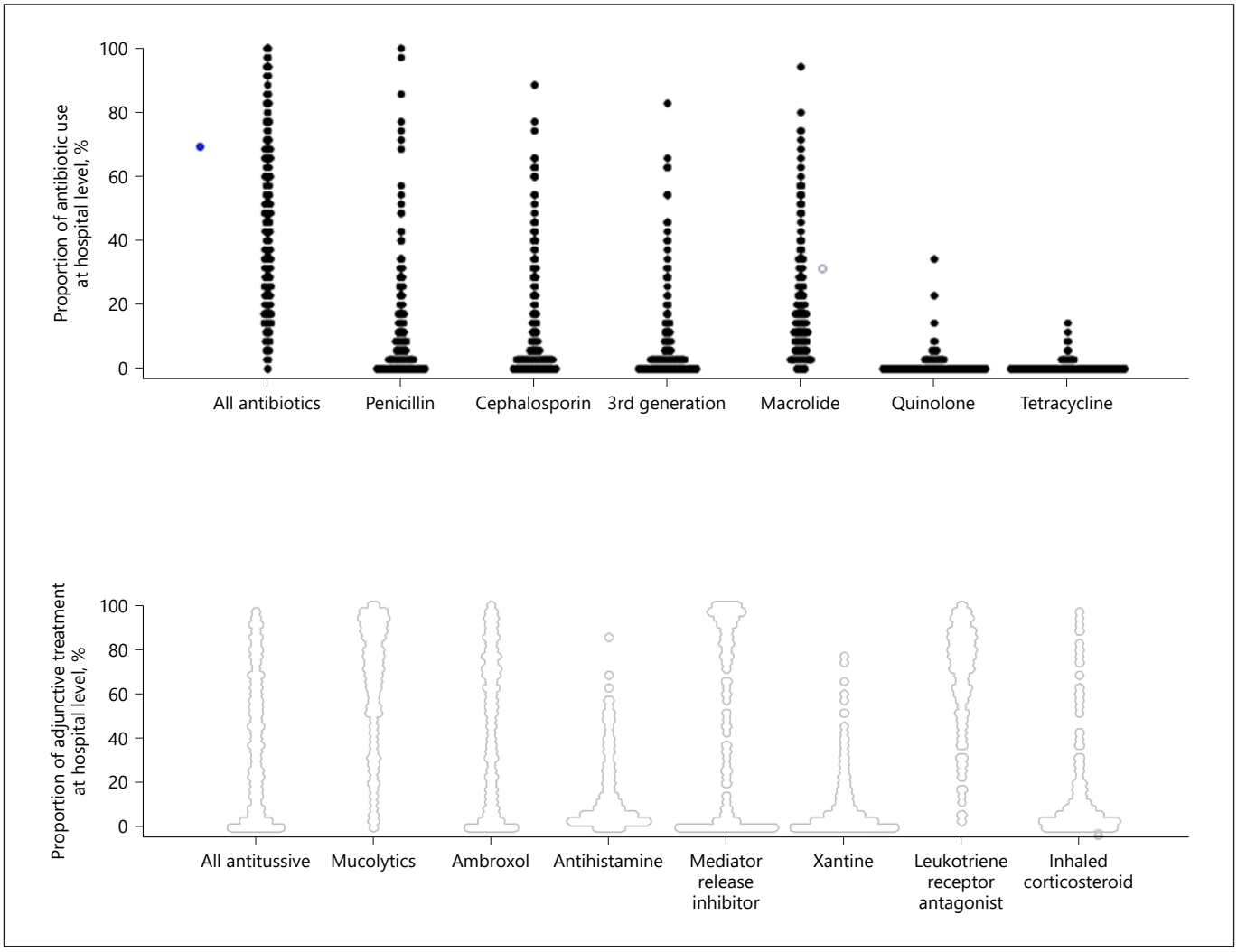


Fig. 1. Proportions of antibiotic use (1A) and adjunctive treatment (1B) among children hospitalized for asthma at the hospital level during 2010–2018.

thine. We observed wide variations in antibiotic use and adjunctive treatment at the hospital level rather than prefecture levels. Our findings reflect the setting of routine care for children with asthma, support the improvement of antibiotic use, and highlight the need for further studies to promote clinical trials for widely varying treatments in the setting of pediatric asthma exacerbation.

Evidence about antibiotic treatment for asthma exacerbation has been limited and derived from randomized controlled trials, mainly in adults [1, 23, 24]. Although several small studies in preschool children with a history of wheeze showed that early administration of azithromycin reduced the duration of symptoms and mitigated the illness severity [25, 26]; these findings were limited due to the small sample size and 1 class of antibiotics (macrolide). A prior study found that antibiotics were used for 60% of adults hospitalized for asthma exacerbation with wide variation across hospitals [11]. Similarly, our results also demonstrated that 40% of children with asthma received antibiotic treatment with high variability. However, the utilization of total and broad-spectrum antibiotics decreased from 2010 to 2018, with a slight increase in narrow-spectrum antibiotic use (penicillin). The trend could be multifactorial, such as the epidemiological evidence on the role of viral infections in asthma exacerbation [9], a nation-wide action plan to reduce antibiotic use led by a government [27–30], and the Choosing Wisely campaign [31], which is spreading globally

Downloaded by: C. Alessandri - 87218
84.220.48.124 - 11/15/2020 8:18:46 AM

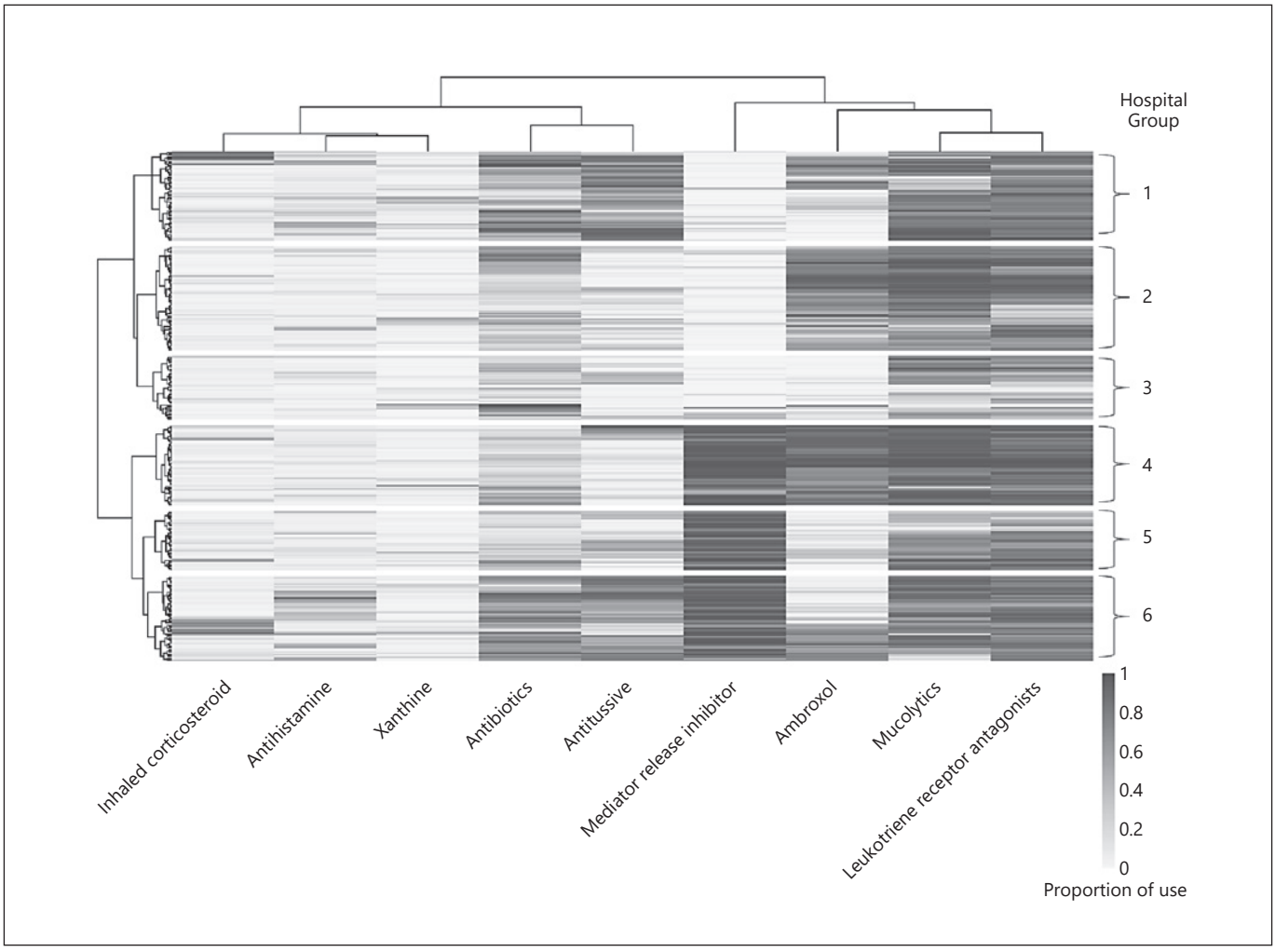


Fig. 2. Hierarchical clustering with heat map for classification of hospitals based on antibiotic and adjunctive treatment patterns during 2010–2018.

and inspiring many countries including Japan. Further efforts are needed to decrease unnecessary antibiotic use, especially for the intervention to hospitals that almost always used antibiotics.

We found widely different patterns in adjunctive treatments across hospitals at a national level. The decreasing trends in sedative antihistamine and methylxanthine could be explained by a lack of data to improve clinical outcomes and the incidence of side effects [32]. Although methylxanthine could be helpful in treating critically ill children in a single randomized controlled trial [33], the findings of its wide variation were hard to justify because our study excluded severe patients who required intensive care, suggesting the routine use for pediatric inpatients with moderate severity in some hospitals. We observed the highest variability of mediator release inhibitors (e.g., sodium cromoglicate). This variability could be merely due to practical reasons, rather than previous study findings because it can be more comfortable and convenient for physicians and nurses to use 1 bottle of sodium cromoglicate (2 mL) than to measure 2 mL of normal saline from the bottle and use it. Whereas antitussives, ambroxol, and mucolytics did not have sufficient evidence for effectiveness to treat children hospitalized for asthma, utilization of these adjunctive treatments differed widely across hospitals. To investigate the necessity and justification for these adjunctive treatments in children with asthma exacerbation, future clinical trials and observational studies for routine care settings are warranted. Also, our findings suggest that improving these

Downloaded by: C. Alessandri - 87218
84.220.48.124 - 11/15/2020 8:18:46 AM

treatment variabilities could have the potentials to reduce the unnecessary healthcare costs and improve healthcare outcomes at a national level.

This study had several limitations. The diagnoses of asthma exacerbation and preexisting comorbidities may have been underestimated because of possible underreporting or potential misclassification of ICD-10 codes. The detailed clinical presentation, laboratory data, and patient information (e.g., environmental pollution and passive smoking) were unavailable in the Diagnosis Procedure Combination database. However, we restricted our data to children who treated with corticosteroid and bronchodilators to maximize the diagnostic accuracy of asthma. In addition, we conducted subgroup analyses on children aged >5 years and obtained similar results, suggesting the robustness of our findings. Although the utilization of a national representative inpatient database was the strength of our study, the generalizability of our finding to the total population in Japan and transportability to external populations may still be uncertain.

In summary, our findings highlight the decreasing trends in antibiotic use and wide variations of practice patterns across hospitals. Further comparative effectiveness research is needed to reduce and justify these different treatment patterns in children hospitalized for asthma exacerbation.

Statement of Ethics

Approval for the present study was obtained from the institutional review board at the University of Tokyo. The board waived the requirement for informed consent because of the anonymous nature of the data.

Conflict of Interest Statement

The authors have no conflicts of interest relevant to this article to disclose.

Funding Sources

This work was supported by grants from the Ministry of Health, Labor, and Welfare, Japan. Yusuke Okubo is supported by the Wagatsuma Fellowship from the University of California, Los Angeles, Asia Pacific Center.

Author Contributions

Drs. Okubo and Michihata designed the data collection instruments, coordinated the data, drafted the initial manuscript, and performed the initial analyses. Drs. Horimukai, Matsui, and Morita and Profs. Fushimi and Yasunaga supervised the data collection, revised the manuscript, and approved the final manuscript as submitted. Each author has seen and approved the submission of the manuscript and takes full responsibility for its contents.

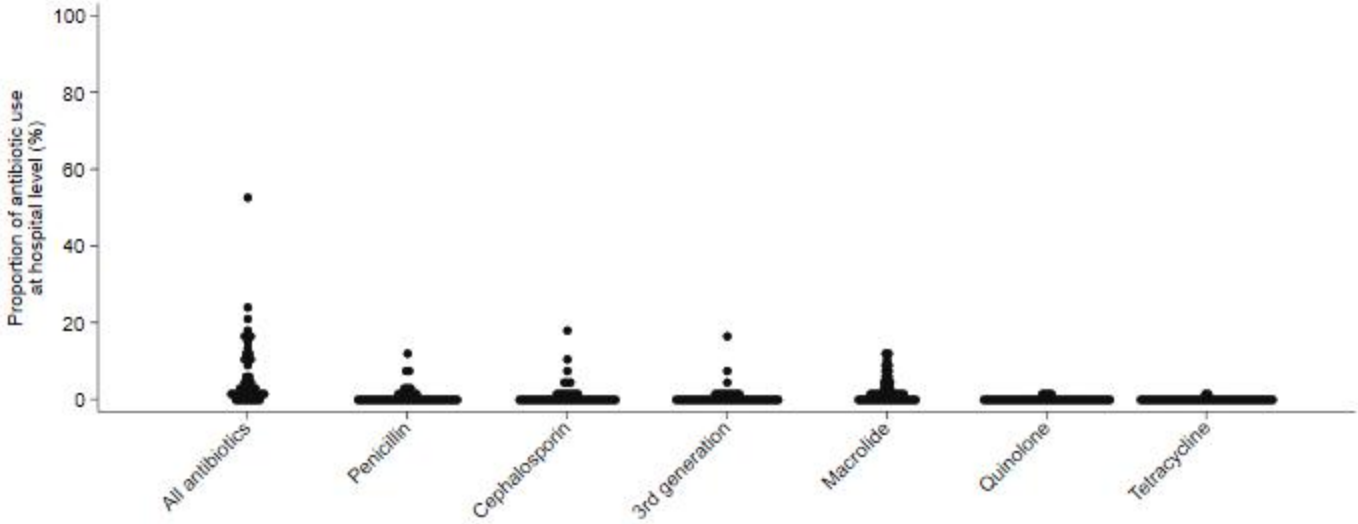
References

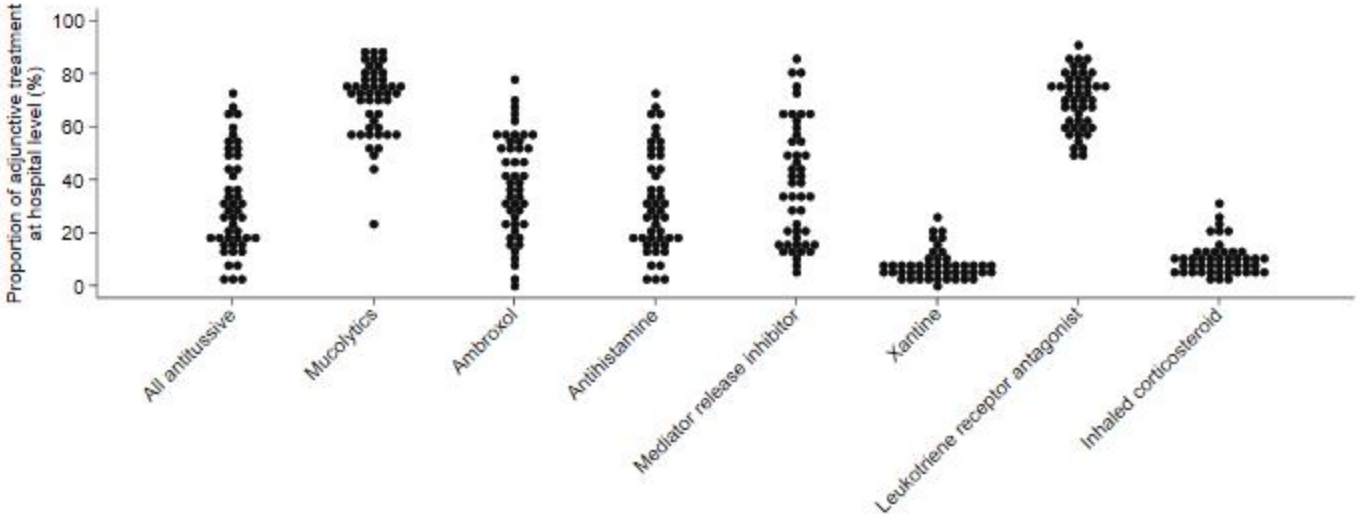
1 Stefan MS, Shieh MS, Spitzer KA, Pekow PS, Krishnan JA, Au DH, et al. Association of antibiotic treatment with outcomes in patients hospitalized for an asthma exacerbation treated with systemic corticosteroids. JAMA Intern Med. 2019;179(3):333–9.
2 Rabe KF, Vermeire PA, Soriano JB, Maier WC. Clinical management of asthma in 1999: the Asthma Insights and Reality in Europe (AIRE) study. Eur Respir J. 2000;16(5):802–7.
3 Morikawa E, Sasaki M, Yoshida K, Adachi Y, Odajima H, Akasawa A. Nationwide survey of the prevalence of wheeze, rhino-conjunctivitis, and eczema among Japanese children in 2015. Allergol Int. 2019;69(1):98–103.
4 Sasaki M, Morikawa E, Yoshida K, Adachi Y, Odajima H, Akasawa A. The change in the prevalence of wheeze, eczema and rhino-conjunctivitis among Japanese children: findings from 3 nationwide cross-sectional surveys between 2005 and 2015. Allergy. 2019;74(8):1572–5.
5 Yoshida K, Sasaki M, Adachi Y, Itazawa T, Odajima H, Saito H, et al. Childhood asthma control in Japan: a nationwide, cross-sectional, web-based survey. Asian Pac J Allergy Immunol. 2018;36(1):16–21.
6 Global Initiative for Asthma. Global strategy for asthma management and prevention. Global strategy for asthma management and prevention. 2018. Accessed April 28, 2019. Available from: https://ginasthma.org/wp-content/uploads/2018/04/wms-GINA-2018-report-tracked_v1.3.pdf.
7 Arakawa H, Hamasaki Y, Kohno Y, Ebisawa M, Kondo N, Nishima S, et al. Japanese guidelines for childhood asthma 2017. Allergol Int. 2017;66(2):190–204.
8 British Thoracic Society/Scottish Intercollegiate Guideline Network. British Guideline on the Management of Asthma. 2016. Accessed November 11, 2019. Available from: http: //www.globalasthmanetwork.org/management/guides/bosnia and herzegovina/British guideline for asthma.pdf.
9 Johnston SL, Pattemore PK, Sanderson G, Smith S, Lampe F, Josephs L, et al. Community study of role of viral infections in exacerbations of asthma in 9–11 year old children. BMJ. 1995;310(6989):1225–9.
10 Chauhan AJ, Inskip HM, Linaker CH, Smith S, Schreiber J, Johnston SL, et al. Personal exposure to nitrogen dioxide (NO2) and the severity of virus-induced asthma in children. Lancet. 2003;361(9373):1939–44.
11 Lindenauer PK, Stefan MS, Feemster LC, Shieh MS, Carson SS, Au DH, et al. Use of antibiotics among patients hospitalized for exacerbations of asthma. JAMA Intern Med. 2016;176(9):1397–400.
12 Matsuda S, Fujimori K, Kuwabara K, Ishikawa KB, Fushimi K. Diagnosis procedure combination as an infrastructure for the clinical study. Asian Pac J Dis Manag. 2013;5(4):81–7.
13 Arakawa H, Hamasaki Y, Kohno Y, Ebisawa M, Kondo N, Nishima S, et al. Japanese guidelines for childhood asthma 2017. Allergol Int. 2017;66(2):190–204.
14 Uda K, Okubo Y, Shoji K, Miyairi I, Morisaki N, Michihata N, et al. Trends of neuraminidase inhibitors use in children with influenza related respiratory infections. Pediatr Pulmonol. 2018;53(6):802–8.
15 Feudtner C, Feinstein JA, Zhong W, Hall M, Dai D. Pediatric complex chronic conditions classification system version 2: updated for ICD-10 and complex medical technology dependence and transplantation. BMC Pediatr. 2014;14(1):199–7.

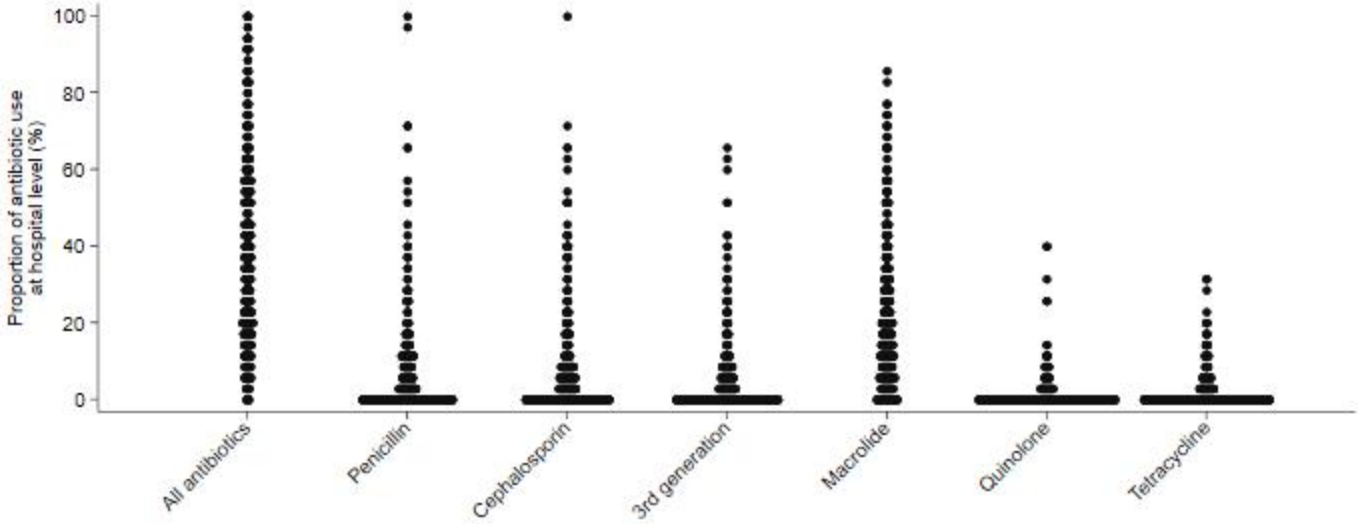
Downloaded by: C. Alessandri - 87218
84.220.48.124 - 11/15/2020 8:18:46 AM

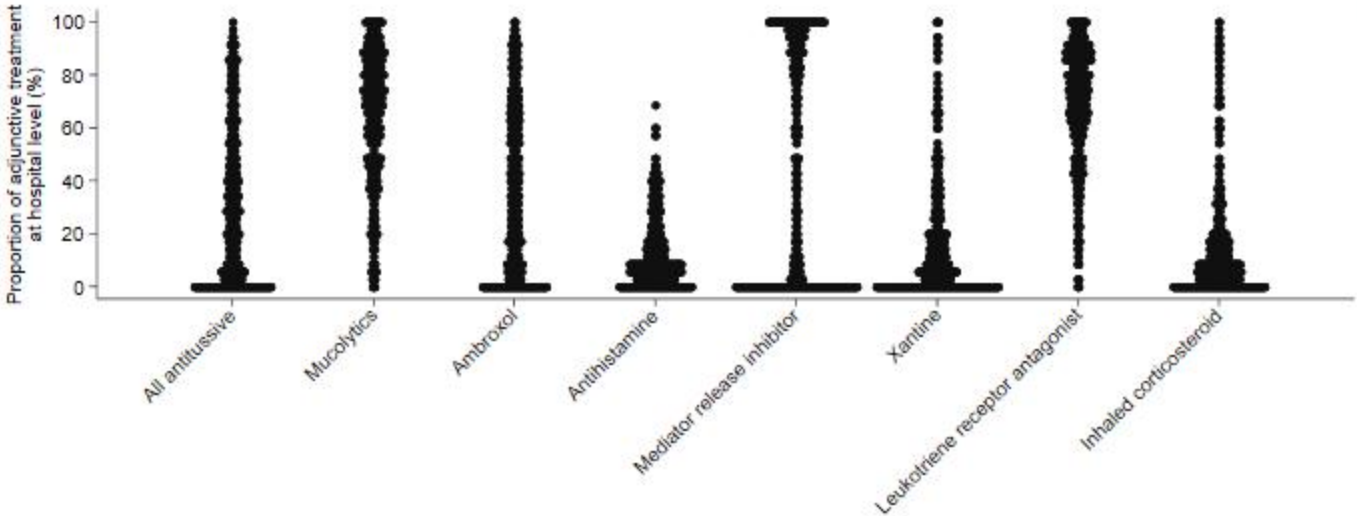
16 Sasaki M, Yoshida K, Adachi Y, Furukawa M, Itazawa T, Odajima H, et al. Factors associated with asthma control in children: findings from a national Web-based survey. Pediatr Allergy Immunol. 2014;25(8):804–9.
17 Okubo Y, Michihata N, Yoshida K, Morisaki N, Matsui H, Fushimi K, et al. Impact of pediatric obesity on acute asthma exacerbation in Japan. Pediatr Allergy Immunol. 2017;28(8):763–7.
18 Okubo Y, Nochioka K, Testa MA. The impact of pediatric obesity on hospitalized children with lower respiratory tract infections in the United States. Clin Respir J. 2018;12(4):1479–84.
19 Okubo Y, Nochioka K, Hataya H, Sakakibara H, Terakawa T, Testa M. Burden of obesity on pediatric inpatients with acute asthma exacerbation in the United States. J Allergy Clin Immunol Pract. 2016;4(6):1227.
20 WHO. The World Health Organization (WHO) Child Growth Standards.
21 Ward JH. Hierarchical grouping to optimize an objective function. J Am Stat Assoc. 1963;58(301):236.
22 Murtagh F, Legendre P. Ward's hierarchical agglomerative clustering method: which algorithms implement ward's criterion? J Classif. 2014;31(3):274–95.
23 Johnston SL, Blasi F, Black PN, Martin RJ, Farrell DJ, Nieman RB. The effect of telithromycin in acute exacerbations of asthma. N Engl J Med. 2006;354(15):1589–600.
24 Gibson PG, Yang IA, Upham JW, Reynolds PN, Hodge S, James AL, et al. Effect of azithromycin on asthma exacerbations and quality of life in adults with persistent uncontrolled asthma (AMAZES): a randomised, double-blind, placebo-controlled trial. Lancet. 2017;390(10095):659–68.
25 Bacharier LB, Guilbert TW, Mauger DT, Boehmer S, Beigelman A, Fitzpatrick AM, et al. Early administration of azithromycin and prevention of severe lower respiratory tract illnesses in preschool children with a history of such illnesses: a randomized clinical trial. JAMA. 2015;314(19):2034–44.
26 Stokholm J, Chawes BL, Vissing NH, Bjarnadóttir E, Pedersen TM, Vinding RK, et al. Azithromycin for episodes with asthma-like symptoms in young children aged 1–3 years: a randomised, double-blind, placebo-controlled trial. Lancet Respir Med. 2016;4(1):19–26.
27 Okubo Y, Michihata N, Morisaki N, Kinoshita N, Miyairi I, Urayama KY, et al. Recent patterns in antibiotic use for children with group A streptococcal infections in Japan. J Glob Antimicrob Resist. 2018;13:55–9.
28 Okubo Y, Michihata N, Morisaki N, Uda K, Miyairi I, Ogawa Y, et al. Recent trends in practice patterns and impact of corticosteroid use on pediatric Mycoplasma pneumoniae-related respiratory infections. Respir Investig. 2018;56(2):158–65.
29 Okubo Y, Miyairi I, Michihata N, Morisaki N, Kinoshita N, Urayama KY, et al. Recent prescription patterns for children with acute infectious diarrhea. J Pediatr Gastroenterol Nutr. 2019;68(1):13–6.
30 Uda K, Okubo Y, Kinoshita N, Morisaki N, Kasai M, Horikoshi Y, et al. Nationwide survey of indications for oral antimicrobial prescription for pediatric patients from 2013 to 2016 in Japan. J Infect Chemother. 2019;25(10):758–63.
31 Ametican Acedemy of Pediatrics. Five Things Physicians and Patients Should Question. 2018. Accessed April 5, 2019. Available from: http: //www.choosingwisely.org/societies/american-academy-of-pediatrics-committee-on-infectious-diseases-and-the-pediatric-infectious-diseases-society/.
32 Mitra A, Bassler D, Goodman K, Lasserson TJ, Ducharme FM. Intravenous aminophylline for acute severe asthma in children over two years receiving inhaled bronchodilators. Cochrane database Syst Rev. 2005;1(2):CD001276.
33 Wheeler DS, Jacobs BR, Kenreigh CA, Bean JA, Hutson TK, Brilli RJ. Theophylline versus terbutaline in treating critically ill children with status asthmaticus: a prospective, randomized, controlled trial. Pediatr Crit Care Med. 2005;6(2):142–7.

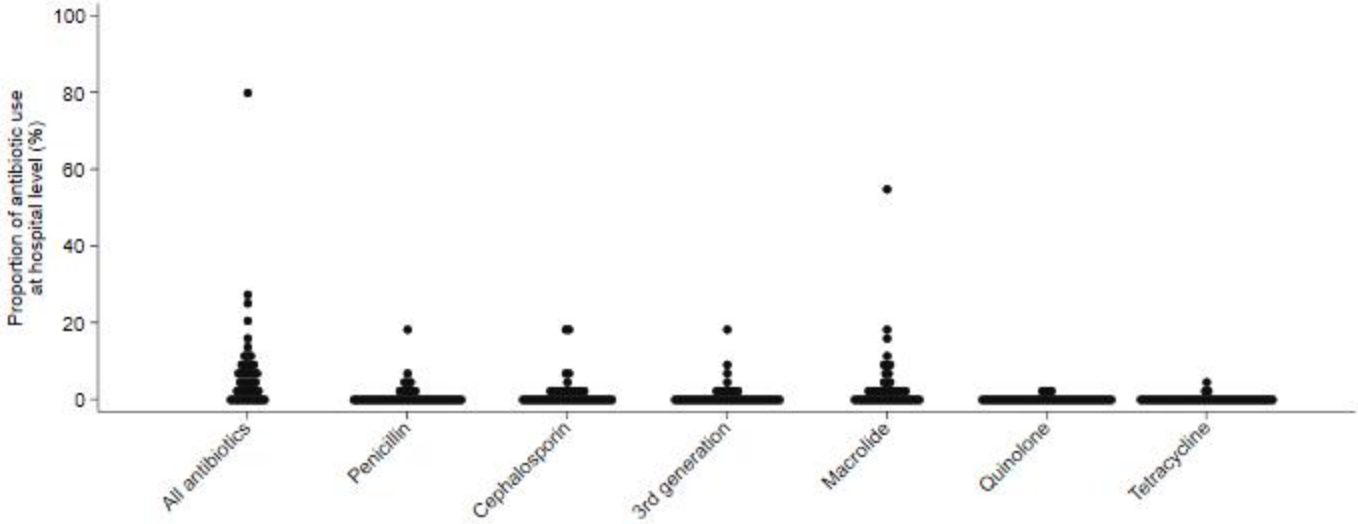
Downloaded by: C. Alessandri - 87218
84.220.48.124 - 11/15/2020 8:18:46 AM

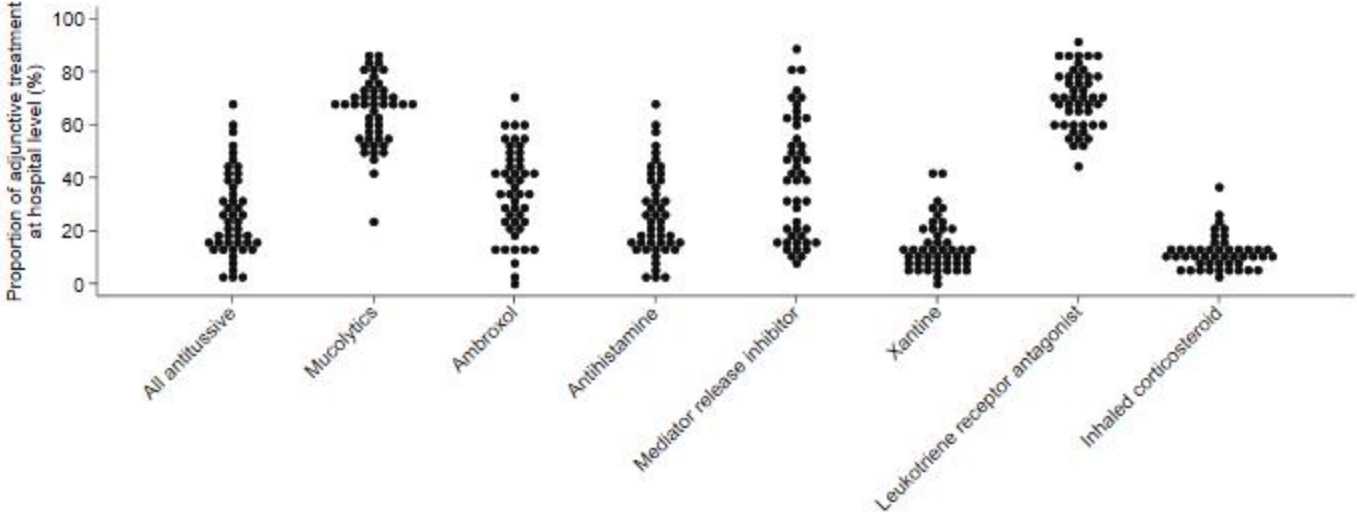

Proportion of antibiotic use at hospital level (%)
100
80
60
40
20
0
All antibiotics
Penicillin
Cephalosporin
3rd generation
Macrolide
Quinolone
Tetracycline

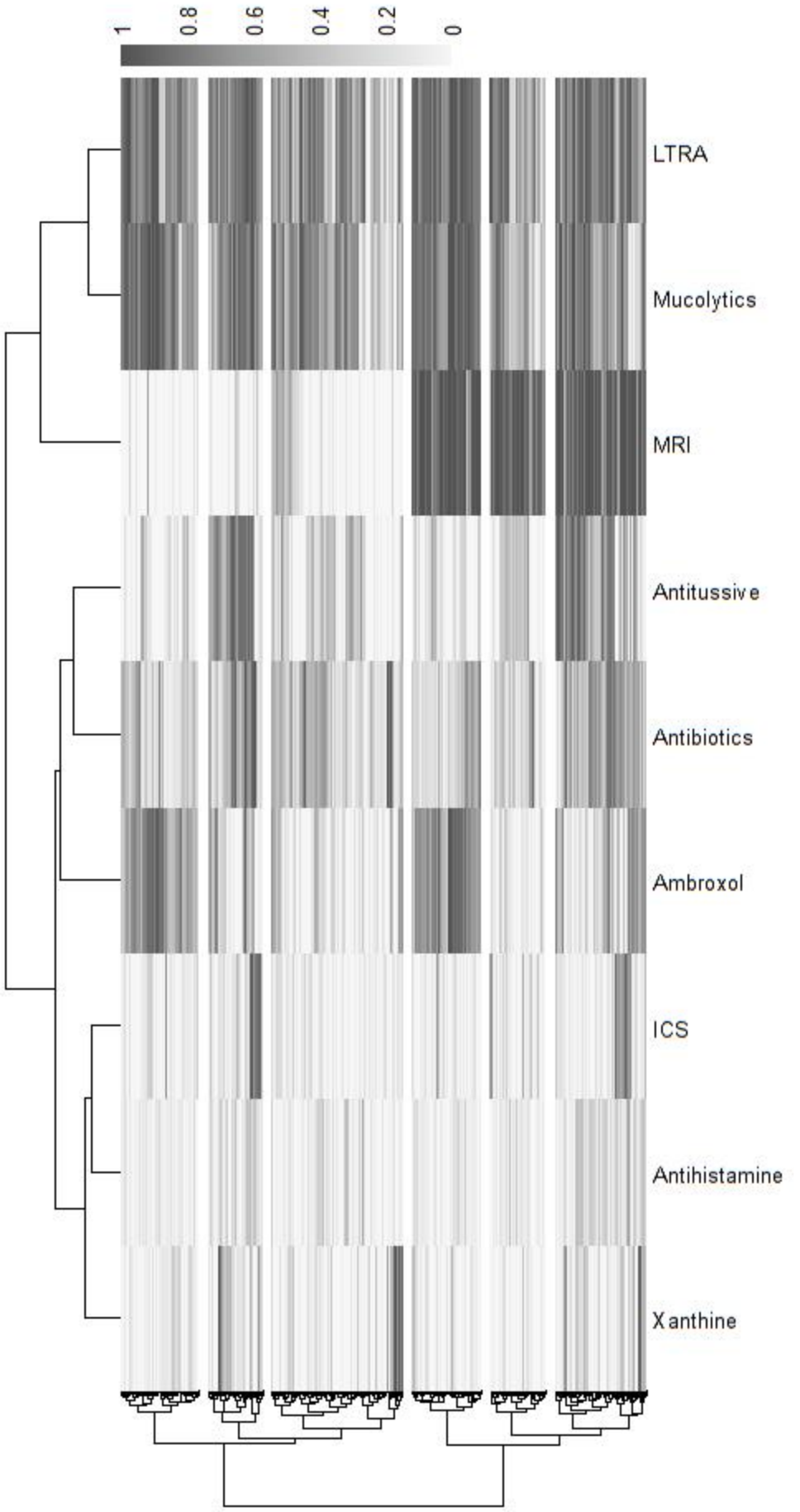

Proportion of adjunctive treatment at hospital level (%)
100
80
60
40
20
0
All antitussive
Mucolytics
Ambroxol
Antihistamine
Mediator release inhibitor
Xanthine
Leukotriene receptor antagonist
Inhaled corticosteroid


Proportion of antibiotic use at hospital level (%)
100
80
60
40
20
0
All antibiotics
Penicillin
Cephalosporin
3rd generation
Macrolide
Quinolone
Tetracycline


Proportion of adjunctive treatment at hospital level (%)
100
80
60
40
20
0
All antitussive
Mucolytics
Ambroxol
Antihistamine
Mediator release inhibitor
Xantine
Leukotriene receptor antagonist
Inhaled corticosteroid


Proportion of antibiotic use at hospital level (%)
100
80
60
40
20
0
All antibiotics
Penicillin
Cephalosporin
3rd generation
Macrolide
Quinolone
Tetracycline


Proportion of adjunctive treatment at hospital level (%)
100
80
60
40
20
0
All antitussive
Mucolytics
Ambroxol
Antihistamine
Mediator release inhibitor
Xantine
Leukotriene receptor antagonist
Inhaled corticosteroid


1
0.8
0.6
0.4
0.2
0
LTRA
Mucolytics
MRI
Antitussive
Antibiotics
Ambroxol
ICS
Antihistamine
Xanthine

Supplemental Figure 1. Proportions of antibiotic use (1A) and (1B) adjunctive treatment use among children hospitalized for asthma at 47 prefecture level during 2010–2018.

Supplemental Figure 2. Proportions of antibiotic use among children aged > 5 years hospitalized for asthma at the hospital level (2A) and 47 prefecture level (2B) during 2010–2018.

Supplemental Figure 3. Proportions of adjunctive treatment use among children aged > 5 years hospitalized for asthma at the hospital level (3A) and 47 prefecture level (3B) during 2010–2018.

Supplemental Figure 4. Hierarchical clustering with heatmap for classification of hospitals based on antibiotic and adjunctive treatment patterns among children aged > 5 years during 2010–2018.

Supplemental Table 1.

Diagnoses and the International Classification of Diseases, Tenth Revision code (ICD-10 code)

Diagnoses	Lists of ICD-10 code
Inclusion criteria	
Asthma	J45x, J46
Acute respiratory failure	J96x
Exclusion criteria	
Pneumonia	A010, A022, A162, A379, A48x, A49x, A500, A548, A698, A70, B012, B052, B068, B206, B221, B250, B371, B38x, B39x, B441, B49, B583, B59, B778, C349, J110, J12x, J13x, J14, J15x, J160, J18x, J202, J440, J67x, J680, J69x, J70x, J82, J83x, J85x, J958, K650, M0019, M0510, M32x, M33x, M351, 0290, P23x, Ps49, P361, U049
Sinusitis	J014, J019, J111, J32x, T701, T889
Lymphadenitis	A182, A210, A318, D763, D898, I88x, L04x
Abscess formation	A06x, A16x, A178, A18x, A54x, B43x, D733, E060, E236, E321, G06x, G09, H043, H050, H163, H278, H440, H600, H700, J329, J340, J36, J38x, J39x, J85x, K04x, K05x, K102, K113, K122, K130, K140, K20, K353, K572, K578, K610, K612, K614, K630, K650, K750, K810, K859, L02x, L030, L040, L100, L663, L748, M0099, N151, N288, N308, N340, N412, N450, N482, N492, N61, N709, N719, N732, N735, N751, N760, N764, 0860, 091x. T814
Sepsis	A021, A207, A227, A241, A267, A282, A327, A394, A40x, A41x, A427, A548, B007, B349, B377, D71, I301, I330, I400, I776, J020, J039, J209, J950, L029, L080, O080, O753, O85, O883, P36x, T814, R880
Bacteremia	A39x, A499, B49
Influenza	J09, J10x, J11x
Urinary tract infection	N30x, N390, 0862, P393, T835, N10, N11x, N12, N209, A003, A191, T835, A181, A540, A560, B374, B901
Skin and subcutaneous infection	L089, P394, H0x, H601, K340, J36, J387, J391, K122, K291, K358, L03x, L983, N450, N730, N731
Septic arthritis	M009
Osteomyelitis	A022, A180, A318, A544, B672, D898, H050, K102, M462x, M86x,
Pre-existing comorbidity	
Food allergy	T781, T782
Atopic dermatitis/eczema	L208, L209,
Allergic rhinitis	J301–304

Supplemental Table 2. Classifications and lists of antibiotics

Classification	Details
Penicillin	Benzylpenicillin potassium, benzylpenicillin benzathine hydrate, ampicillin, bacampicillin hydrochloride, amoxicillin hydrate
Penicillin with beta-lactamase inhibitors	Amoxicillin clavulanate, ampicillin sulbactam, piperacillin sodium, piperacillin tazobactam
First-generation cephalosporin	Cephazolin, cefalexin, cefroxadine, cefaclor
Second-generation cephalosporin	Cefotiam, cefmetazole, cefminox, flomoxef, cefuroxime
Third-generation cephalosporin	Cefotaxime, cefmnoxime, ceftriaxione, ceftadizime, cefdinir, ceftibuten, cefditren pivoxil, cefixime, cefteram pivoxil, cefpodoxime proxetil, cefcapene pivoxil, ceftizoxime,
Fourth-generation cephalosporin	Cefpirome, cefozopran, cefepime
Carbapenem and oral penem	Inipenem cilastatin, panipenem betamipron, meropenem, biapenem, doripenem, tebipenem pivoxil, faropenem
Macrolide	Erythromicin, clarithromycin, roxithromycin, azithromycin, josamycin
Tetracycline	Tetracycline, doxycycline, minocycline, tigecycline
Quinolone	Norfloxacin, ofloxacin, levofloxacin, ciproxacin, lomeofloxacin, tosufloxacin, pazufloxacin, prulifloxacin, moxifloxacin, garenoxacin, sitafloxacin
Trimethoprim-sulfamethoxazole	Trimethoprim-sulfamethoxazole
Aminoglycoside	Streptomycin, kanamycin, gentamicin, tobramycin, dibekacin, amikacin, isepamicin, arbekacin
Lincomycin	Lincomycin, clindamycin,
Glycopeptide and lipopeptide	Vancomycin, teicoplanin, daptomycin
Fosfomycin	Fosfomycin
Other types	Quinoupristin dalfopristin, linezolid, chloramphenicol, colistin, polymyxin B, azreonam, metronidazole,

Supplemental Table 3. List of medications other than antibiotics

Classification	Details
Antitussives	Codeine (*55 observation; excluded from the analyses), dextromethorphan hydrobromide hidrate. tipepidine hibenzate, others (dimemorphan phosphate, eprazinone hydrochloride, pentoxyverine citrate, cloperastine, clofedanol, noscapine, guaifenesin, Senega®, cheery bark extract)
Mucolytics	L-cysteine hydrochloride, bromhexine hydrochloride, dornasealfa, carbocisteine, fudosteine
Airway lubricant	Ambroxol hydrochloride
First-generation antihistamine[1]	Diphenhydramine, clemastine fumarate, chlorpheniramine maleate, promethazine hydrochloride, alimemazine tartrate, hydroxyzine, homochlorcyclizine hydrochloride, cyproheptadine hydrochloride
Second-generation sedative antihistamine[1]	Ketotifen fumarate, azelastine hydrochloride, oxatomide, mequitazine
Second-generation non-sedative antihistamine[1]	Fexofenadine hydrochloride, epinastine hydrochloride, ebastine, cetiridine hydrochloride, levocetirizine hydrochloride, bepotastine besilate, emedastine fumarate, olopadadine hydrochloride, loratadine, desloratadine, bilastine rupatadine fumarate
Leukotriene receptor antagonist	Montelukast, pranlukast
Other types of antiallergic medications	Thromboxane A1 receptor antagonist (seratrodast, ramatroban), Th2 cytokine inhibitors (suplatast tosilate), mediator release inhibitors (sodium cromoglicate, tranilast, amlexanox, ibudilast, pemirolast potassium)
Xanthine	Theophylline, diprophylline, proxyphylline, aminophylline
Short-acting beta-stimulant inhaler	Isoprenaline hydrochloride, salbutamol sulfate, fenoterol hydrobromide, procaterol hydrochloride,
Intravenous beta-stimulant	Isoprenaline hydrochloride, terbutaline sulfate,
Oral beta-stimulant	Isoprenaline hydrochloride, salbutamol sulfate, terbutaline sulfate, fenoterol hydrobromide, procaterol hydrochloride, turobuterol
Tape beta-stimulant	Turobuterol
Inhaled corticosteroid	Beclomethasone dipropionate, fluticasone propionate, budesonide, ciclesonide, mometasone furoate, fluticasone furoate
Long-acting beta-stimulant inhaler	Clebuterol hydrochloride, salmeterol xinafoate, indacaterol malate, formoterol fumarate hydrate (*8 observations were excluded)
Anticholinergics inhalers	Tiotropium bromide hydrate, glycopyronium bromide, aclidinium bromide, umeclidinium bromide (*only 16 patients used anticholinergic inhalers; we excluded these patients from the analyses)
Intravenous magnesium	Magnesium sulfate (*Only 7 patients received NSAIDs; we excluded these patients from the analysis)

Supplemental Table 4. Baseline characteristics of children hospitalized with asthma from 2010 to 2018

Year pf admission	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**2018**	**%Increase**
N	5560	7338	6517	7811	6374	8839	5759	6147	636	
Age, mean year	5.0	4.6	4.6	4.6	4.4	4.7	4.4	4.4	4.2	
(SE)	(3.3)	(3.5)	(3.5)	(3.4)	(3.4)	(3.3)	(3.4)	(3.3)	(3.4)	
Male, N	3478	4595	4096	4890	3932	5504	3563	3766	397	
(%)	(62.6)	(62.6)	(62.9)	(62.6)	(61.7)	(52.4)	(61.9)	(61.3)	(64.2)	
Atopic dermatitis, N	129	173	198	226	215	279	183	243	24	
(%)	(2.3)	(2.4)	(3.0)	(2.9)	(3.4)	(3.2)	(3.2)	(4.0)	(3.8)	
Allergic rhinitis, N	189	299	324	396	376	534	378	434	45	
(%)	(3.4)	(4.1)	(5.0)	(5.0)	(5.9)	(6.0)	(6.6)	(7.1)	(7.1)	
Food allergy, N	55	74	68	105	106	132	72	115	9	
(%)	(1.0)	(1.0)	(1.0)	(1.3)	(1.7)	(1.5)	(1.3)	(1.9)	(1.4)	
Obesity, N	419	547	514	621	573	730	485	484	63	
(%)	(7.5)	(7.5)	(7.9)	(8.0)	(9.0)	(8.3)	(8.4)	(7.9)	(9.9)	
Ambulance use, N	252	264	299	396	313	572	346	454	42	
(%)	(4.5)	(3.6)	(4.6)	(5.1)	(4.9)	(6.5)	(6.0)	(7.4)	(6.6)	
Academic hospital, N	442	527	604	764	563	760	470	444	57	
(%)	(8.0)	(7.2)	(9.3)	(9.8)	(8.8)	(8.6)	(8.2)	(7.2)	(9.0)	
Season, N										
Spring	–	1567	1666	1866	1542	1678	1584	1416	293	
(%)	–	(21.4)	(25.6)	(23.9)	(24.2)	(19.0)	(27.5)	(23.0)	–	
Summer	1657	1654	1445	1757	1268	1892	1362	1366	–	
(%)	–	(22.5)	(22.2)	(22.5)	(22.5)	(21.4)	(23.7)	(22.2)	–	
Fall	3457	2972	2368	3087	2634	4195	2000	2440	–	
(%)	–	(40.5)	(36.3)	(39.5)	(41.3)	(47.5)	(34.7)	(39.7)	–	
Winter	446	1145	1038	1101	930	1074	813	925	343	
(%)	–	(15.6)	(15.9)	(14.1)	(14.6)	(12.2)	(14.1)	(15.1)	–	

Supplemental Table 5. Trends in adjunctive treatments for children hospitalized with asthma

Year of admission	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**2018**	**%Increase**
Total, N	5560	7338	6517	7811	6374	8839	5759	6147	636	
Adjunctive treatments, N										
Antitussives	1951	2605	2199	2554	2132	2812	1692	1661	174	-8.7%
(%)	(35.1)	(35.5)	(33.7)	(32.7)	(33.5)	(31.8)	(29.4)	(27.0)	(27.4)	(-9.2%, -7.6%)
Dextromethorphan	170	158	135	125	93	207	86	73	8	-5.4%
(%)	(3.1)	(2.2)	(2.1)	(1.6)	(1.5)	(2.3)	(1.5)	(1.2)	(1.3)	(-8.9%, -2.7%)
Tipepidine	1651	2185	1827	2168	1872	2374	1452	1472	152	-8.4%
(%)	(29.1)	(29.8)	(28.0)	(27.8)	(29.4)	(26.9)	(25.2)	(24.0)	(23.9)	(-8.5%, -6.2%)
Mucolytics	3761	4948	4562	5450	4517	6314	4151	4543	482	6.0%
(%)	(67.6)	(67.4)	(70.0)	(69.8)	(70.9)	(71.4)	(72.1)	(73.9)	(75.8)	(4.8%, 7.1%)
Ambroxol	2110	2727	2504	3183	2574	3822	2442	2721	285	5.9%
(%)	(38.0)	(37.2)	(38.4)	(40.8)	(40.4)	(43.2)	(42.4)	(44.3)	(44.8)	(4.7%, 7.2%)
Antihistamines	963	1279	1000	1021	790	977	602	677	74	-15.0%
(%)	(17.3)	(17.4)	(15.3)	(13.1)	(12.4)	(11.1)	(10.5)	(11.0)	(11.6)	(-16.2%, -13.7%)
FGAHs	576	719	497	433	328	323	152	152	17	-29.1%
(%)	(10.4)	(9.8)	(7.6)	(5.5)	(5.2)	(5.7)	(3.7)	(2.6)	(2.7)	(-30.8%, -27.4%)
Sedative SGAHs	230	301	233	270	168	169	105	90	7	-22.0%
(%)	(4.1)	(4.1)	(3.6)	(3.5)	(2.6)	(1.9)	(1.8)	(1.5)	(1.1)	(-24.3%, -19.6%)
Non-sedative SGAHs	191	289	291	345	314	514	354	457	53	11.1%
(%)	(3.4)	(3.9)	(4.5)	(4.4)	(4.9)	(5.8)	(6.2)	(7.4)	(8.3)	(8.7%, 13.5%)
LTRA	3784	4884	4510	5601	4540	6288	4186	4691	499	9.0%
(%)	(68.1)	(66.6)	(69.2)	(71.7)	(71.2)	(71.1)	(72.7)	(76.3)	(78.5)	(7.8%, 10.1%)
Mediator release inhibitors	2242	2986	2628	3095	2713	3695	2357	2580	266	1.6%
(%)	(40.3)	(40.7)	(40.3)	(39.6)	(42.6)	(41.8)	(40.9)	(42.0)	(41.8)	(-0.2%, 3.5%)
Xanthine	912	949	641	640	427	543	228	211	15	-30.6%
(%)	(16.4)	(12.9)	(9.8)	(8.2)	(6.7)	(6.1)	(4.0)	(3.4)	(2.4)	(-32.1%, -29.2%)
Inhaled corticosteroids	574	860	755	884	671	927	592	688	81	-1.8%
(%)	(10.3)	(11.7)	(11.6)	(11.3)	(10.5)	(10.5)	(10.3)	(11.2)	(12.7)	(-3.3%, -0.2%)

Supplemental Table 6. Trends in patient characteristics, healthcare utilization, and antiepileptic drug use among children aged > 5 years

Year pf admission	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**2018**	**%Increase**
N	2277	2584	2349	2791	2133	3336	1923	1994	190	
Age, mean year	8.3	8.6	8.6	8.5	8.5	8.3	8.5	8.3	8.7	
(SE)	(2.5)	(2.6)	(2.6)	(2.6)	(2.6)	(2.5)	(2.6)	(2.6)	(2.6)	
Male, N	1364	1498	1356	1682	1252	1984	1127	1169	110	
(%)	(59.9)	(58.0)	(57.7)	(60.3)	(58.7)	(59.5)	(58.6)	(58.6)	(57.9)	
Atopic dermatitis, N	47	51	68	90	68	108	62	89	7	
(%)	(2.3)	(2.0)	(2.9)	(3.2)	(3.2)	(3.2)	(3.2)	(4.5)	(3.7)	
Allergic rhinitis, N	91	127	165	197	162	261	162	163	14	
(%)	(4.0)	(4.9)	(7.0)	(7.1)	(7.6)	(7.8)	(8.4)	(8.2)	(7.4)	
Food allergy, N	14	26	16	37	26	42	20	28	3	
(%)	(0.6)	(1.0)	(0.7)	(1.3)	(1.2)	(1.3)	(1.0)	(1.4)	(1.6)	
Obesity, N	216	254	204	262	248	348	221	210	25	
(%)	(9.5)	(9.8)	(8.7)	(9.4)	(11.6)	(10.4)	(10.5)	(10.5)	(13.2)	
Ambulance use, N	121	125	150	195	137	261	152	185	19	
(%)	(5.3)	(4.8)	(6.4)	(7.0)	(6.4)	(7.8)	(7.9)	(9.3)	(10)	
Academic hospital, N	190	145	193	284	178	278	165	160	20	
(%)	(8.4)	(5.6)	(8.2)	(10.2)	(8.4)	(8.3)	(8.6)	(8.0)	(10.5)	
Season, N										
Spring	–	506	611	606	495	596	539	473	100	
(%)	–	(19.6)	(26.0)	(21.7)	(23.2)	(17.9)	(28.0)	(23.7)	–	
Summer	655	531	460	540	374	641	424	355	–	
(%)	–	(20.6)	(19.6)	(19.4)	(17.5)	(19.2)	(22.5)	(17.8)	–	
Fall	1486	1140	944	1256	964	1743	679	842	–	
(%)	–	(44.1)	(40.2)	(45.0)	(45.2)	(52.3)	(35.3)	(42.2)	–	
Winter	136	407	334	389	300	356	281	324	90	
(%)	–	(15.8)	(14.2)	(13.9)	(14.1)	(10.7)	(14.6)	(16.3)	–	
Healthcare cost, mean JPY	215.681	210,307	218,670	222,825	222,053	226,107	227,400	227,682	223,079	0.6%
(SE)	(2139)	(2113)	(2290)	(2008)	(2268)	(1696)	(2407)	(2424)	(7453)	(0.3%, 0.8%)
Length of stay, mean days	5.6	5.5	5.5	5.6	5.5	5.5	5.5	5.5	5.3	-0.6%
(SE)	(0.1)	(0.1)	(0.1)	(0.1)	(0.1)	(0.1)	(0.1)	(0.1)	(0.1)	(-0.9%, -0.4%)
Mechanical ventilation, N	23	15	12	19	26	24	20	13	2	-0.3%
(%)	(1.0)	(0.6)	(0.5)	(0.7)	(1.2)	(0.7)	(1.0)	(0.6)	(1.1)	(-10%, 10.1%)

SE, standard error; %Increase, %increase of proportion per year for health resource utilization in ratio scale

Supplemental Table 7. Trends in early antibiotic use among children aged > 5 years

Fiscal year	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**2018**	**%Increase**
N	2277	2584	2349	2791	2133	3336	1923	1994	190	
Total, N	959	972	871	938	677	1082	619	525	29	-11.1%
(%)	(42.1)	(37.6)	(37.1)	(33.6)	(31.7)	(32.4)	(32.2)	(26.3)	(15.3)	(-12.6%, -10.6%)
Macrolide, N	563	585	479	492	303	520	300	284	15	-12.4%
(%)	(24.7)	(22.6)	(20.4)	(17.6)	(14.2)	(15.6)	(15.6)	(14.2)	(7.9)	(-14.2%, -11.6%)
Cephalosporin, N	222	185	132	161	117	192	100	81	3	-15.9%
(%)	(9.8)	(7.2)	(5.6)	(5.8)	(5.5)	(5.8)	(5.2)	(4.1)	(1.6)	(-17.6%, -11.8%)
3rd generation, N	112	91	75	106	63	131	67	49	1	-9.1%
(%)	(4.9)	(3.5)	(3.2)	(3.8)	(3.0)	(3.9)	(3.5)	(2.5)	(0.5)	(-11.9%, -4.2%)
Penicillin, N	107	104	102	140	106	217	90	95	5	2.2%
(%)	(4.1)	(4.0)	(4.3)	(5.0)	(5.0)	(6.5)	(4.7)	(4.8)	(2.6)	(-1.4%, 6.0%)
Quinolone, N	3	5	36	25	17	41	40	15	1	15.0%
(%)	(0.1)	(0.2)	(1.5)	(0.9)	(0.8)	(1.2)	(2.1)	(0.8)	(0.5)	(6.5%, 24.1%)
Tetracycline, N	17	49	72	45	18	40	35	13	0	-7.1%
(%)	(0.8)	(1.9)	(3.1)	(1.6)	(0.8)	(1.2)	(1.8)	(0.7)	(0)	(-12.8%, -0.1%)

%Increase, %increase of proportion per year for health resource utilization in ratio scale

Supplemental Table 8. Trends in adjunctive treatments among children aged > 5 years

Year of admission	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**2018**	**%Increase**
Total, N	2277	2584	2349	2791	2133	3336	1923	1994	190	
Adjunctive treatments, N										
Antitussives	685	773	697	793	574	934	467	468	35	-6.9%
(%)	(30.1)	(29.9)	(29.7)	(28.4)	(26.9)	(28.0)	(24.3)	(23.47)	(18.4)	(-8.6%, -4.9%)
Dextromethorphan	76	73	67	76	52	113	57	46	3	3.7%
(%)	(3.3)	(2.8)	(2.9)	(2.7)	(2.4)	(3.4)	(3.0)	(2.3)	(1.6)	(-1.4%, 9.1%)
Tipepidine	501	549	490	561	431	664	324	351	22	-6.6%
(%)	(22.0)	(21.3)	(20.9)	(20.1)	(20.2)	(19.9)	(16.9)	(17.6)	(11.6)	(-8.7%, -4.5%)
Mucolytics	1427	1601	1493	1760	1354	2220	1229	1375	132	4.7%
(%)	(62.7)	(62.0)	(63.6)	(63.1)	(63.5)	(66.6)	(63.9)	(68.9)	(69.5)	(2.9%, 6.5%)
Ambroxol	823	880	792	999	756	1264	704	789	71	3.8%
(%)	(36.1)	(34.1)	(33.7)	(35.8)	(35.4)	(37.9)	(36.6)	(39.6)	(37.4)	(1.8%, 5.8%)
Antihistamines	316	358	321	374	249	388	221	275	21	-7.2%
(%)	(13.9)	(13.9)	(13.7)	(13.4)	(11.7)	(11.6)	(11.5)	(13.8)	(11.1)	(-9.4%, -5.0%)
FGAHs	151	144	105	103	62	88	36	36	2	-25.2%
(%)	(6.6)	(5.6)	(4.5)	(3.7)	(2.9)	(2.6)	(1.9)	(1.8)	(1.1)	(-28.4%, -21.7%)
Sedative SGAHs	65	65	63	69	33	32	12	19	2	-23.9%
(%)	(2.9)	(2.5)	(2.7)	(2.5)	(1.6)	(1.0)	(0.6)	(1.0)	(1.1)	(-28.4%, -19.0%)
Non-sedative SGAHs	114	157	163	215	160	284	177	230	18	10.1%
(%)	(5.0)	(6.1)	(6.9)	(7.7)	(7.5)	(8.5)	(9.2)	(11.5)	(9.5)	(6.9%, 13.4%)
LTRA	1531	1710	1588	1963	1463	2354	1339	1539	148	8.6%
(%)	(67.2)	(66.2)	(67.6)	(70.3)	(68.6)	(70.6)	(69.6)	(77.2)	(77.9)	(6.8%, 10.5%)
Mediator release inhibitors	907	1055	951	1106	905	1394	793	784	81	1.6%
(%)	(39.8)	(40.8)	(40.5)	(39.6)	(42.4)	(41.8)	(41.2)	(39.3)	(42.6)	(-0.2%, 3.5%)
Xanthine	575	592	415	406	280	333	138	113	10	-30.2%
(%)	(25.3)	(22.9)	(17.7)	(14.6)	(13.1)	(10.0)	(7.2)	(6.7)	(5.3)	(-32.1%, -29.2%)
Inhaled corticosteroids	263	355	312	381	249	384	229	261	32	-1.0%
(%)	(11.6)	(13.7)	(13.3)	(13.7)	(11.7)	(11.5)	(11.9)	(13.1)	(16.8)	(-3.4%, 1.5%)

FGAHs, first-generation antihistamines; SGAHs, second-generation antihistamines; LTRA, leukotriene receptor antagonists; %Increase, %increase of proportion per year for health resource utilization in ratio scale