Risk factors for intensive care admission in children with severe acute asthma in the Netherlands: a prospective multicenter study

Shelley A. Boeschoten[1], Annemie L. Boehmer[2,3], Peter J. Merkus[4], Joost van Rosmalen[5], Johan C. de Jongste[6,] Pieter Fraaij[7], Corinne M. Buysse[1], Matthijs de Hoog[1]; Dutch collaborative PICU research network (SKIC) and Dutch collaborative paediatric respiratory network (SKL)

Online Data Supplement

Methods

Ethnicity was defined as Caucasian or non-Caucasian (if black, Turkish, Moroccan, Asian, Latin-American, Surinamese, or two or more parental races). We determined the SES by using the highest educational level of the parents (low, middle or high, according to Statistics Netherlands; statline.cbs.nl). The postal code was used to quantify the neighborhood SES, with a mean of zero. A lower (negative) score is associated with a lower SES. National guidelines for PICU admission did not change during the study period and included respiratory failure and imminent exhaustion, no clinical benefit after continuous nebulization with the need for intravenous (IV) salbutamol (which is a PICU indication according to Dutch guidelines (1)), and/or the need for mechanical ventilation.

Medication adherence

Pharmacy records were obtained, containing all prescriptions actually retrieved by the patient. Adherence to ICS was assessed by measuring the proportion of days covered (PDC) in the period preceding the index admission (2). PDC was calculated by dividing the number of days patients had ICS on hand (since first ICS prescription) by the total number of days in the period, with a minimum of 30 days and a maximum of 365 days. Continuous and categorical (≥80%) measures of ICS adherence were used. The cutoff values were chosen based on previous studies (E3, E4).

Detection of viruses

From every patient we acquired a nasal swab which was examined by real-time transcriptase PCR (RT-PCR) for the detection of viruses. A viral pathogen was defined if a cycle threshold value (Ct-value) <40 was detected for adenoviruses, human bocavirus, coronaviruses (OC43, 229E and NL 63), enteroviruses, human metapneumovirus, influenza A and B, parainfluenza viruses 1–4, respiratory syncytial virus (RSV) and/or human rhinoviruses (HRV). Ct-values represents the number of cycles required for the fluorescent signal to cross the threshold, and is inversely related to viral load (7). For subtyping of rhinovirus a Ct-value <30 was required (in-house protocol).

Analyses

Our main study outcome is the prevalence of undertreatment, defined as no treatment with or ICS. We estimated that 70% of the children admitted to a PICU was undertreated, versus 50% of the general ward children; a difference of 20%. Based on this assumption, we have computed the required sample size to detect a difference between groups in the prevalence of undertreatment using a chi-square test. Hundred patients per group is a sufficient sample size to detect a difference between groups in the prevalence of undertreatment, with a power of 80% and a significance level of 5%. To account for the effects of missing data and/or dropouts, we increased the sample size by 10%. For a power of 80%, this yields the following group sizes: 110 PICU patients vs. 110 MC patients, total sample size: 220. For the PICU we included children between August 2016 and September 2018. For the general ward we included children between November 2016 and May 2018.

Multivariate analysis was performed using logistic regression to evaluate the relationship between covariates and the probability of PICU admission for SAA. Covariates included in analysis were: age, sex, ethnicity, steroid-naïve, previous PICU admissions, duration of symptoms prior to admission, positive PCR for at least one virus or multiple viruses and level of cotinine. For cotinine we used the multiple imputation by chained equations (MICE) method for missing data (16% was missing). All statistical analyses were carried out in SPSS version 25 (Chicago, IL, USA), and a two-sided significance level of 0.05 was used. Informed

written consent was obtained prior to participation. The study was approved by the Research Ethics Committee of the Erasmus Medical Center Rotterdam (MEC 2015-709).

References

E1. Nederlandse Vereniging voor Kindergeneeskunde N, https://www.nvk.nl/Portals/0/richtlijnen/acuut%20astma/Methodenacuutastma.pdf. 2012.

E2. Peterson AM, Nau DP, Cramer JA, Benner J, Gwadry-Sridhar F, Nichol M. A checklist for medication compliance and persistence studies using retrospective databases. *Value Health* 2007; 10: 3-12.

E3. Camargo CA, Jr., Ramachandran S, Ryskina KL, Lewis BE, Legorreta AP. Association between common asthma therapies and recurrent asthma exacerbations in children enrolled in a state Medicaid plan. *Am J Health Syst Pharm* 2007; 64: 1054-1061.

E4. Engelkes M, Janssens HM, de Jongste JC, Sturkenboom MC, Verhamme KM. Medication adherence and the risk of severe asthma exacerbations: a systematic review. *Eur Respir J* 2015; 45: 396-407.

E5. Herndon JB, Mattke S, Evans Cuellar A, Hong SY, Shenkman EA. Anti-inflammatory medication adherence, healthcare utilization and expenditures among Medicaid and children's health insurance program enrollees with asthma. *Pharmacoeconomics* 2012; 30: 397-412.

E6. Rust G, Zhang S, Reynolds J. Inhaled corticosteroid adherence and emergency department utilization among Medicaid-enrolled children with asthma. *J Asthma* 2013; 50: 769-775.

E7. Moesker FM, van Kampen JJ, van der Eijk AA, van Rossum AM, de Hoog M, Schutten M, Smits SL, Bodewes R, Osterhaus AD, Fraaij PL. Human bocavirus infection as a cause of severe acute respiratory tract infection in children. *Clin Microbiol Infect* 2015; 21: 964 e961-968.

E8. GSA-MD, version 2 array. http://glimdna.org/global-screening-array.html. 2016.