ASSOCIATION BETWEEN USE OF ASTHMA DRUGS IN CHILDREN AND LIVER INJURY

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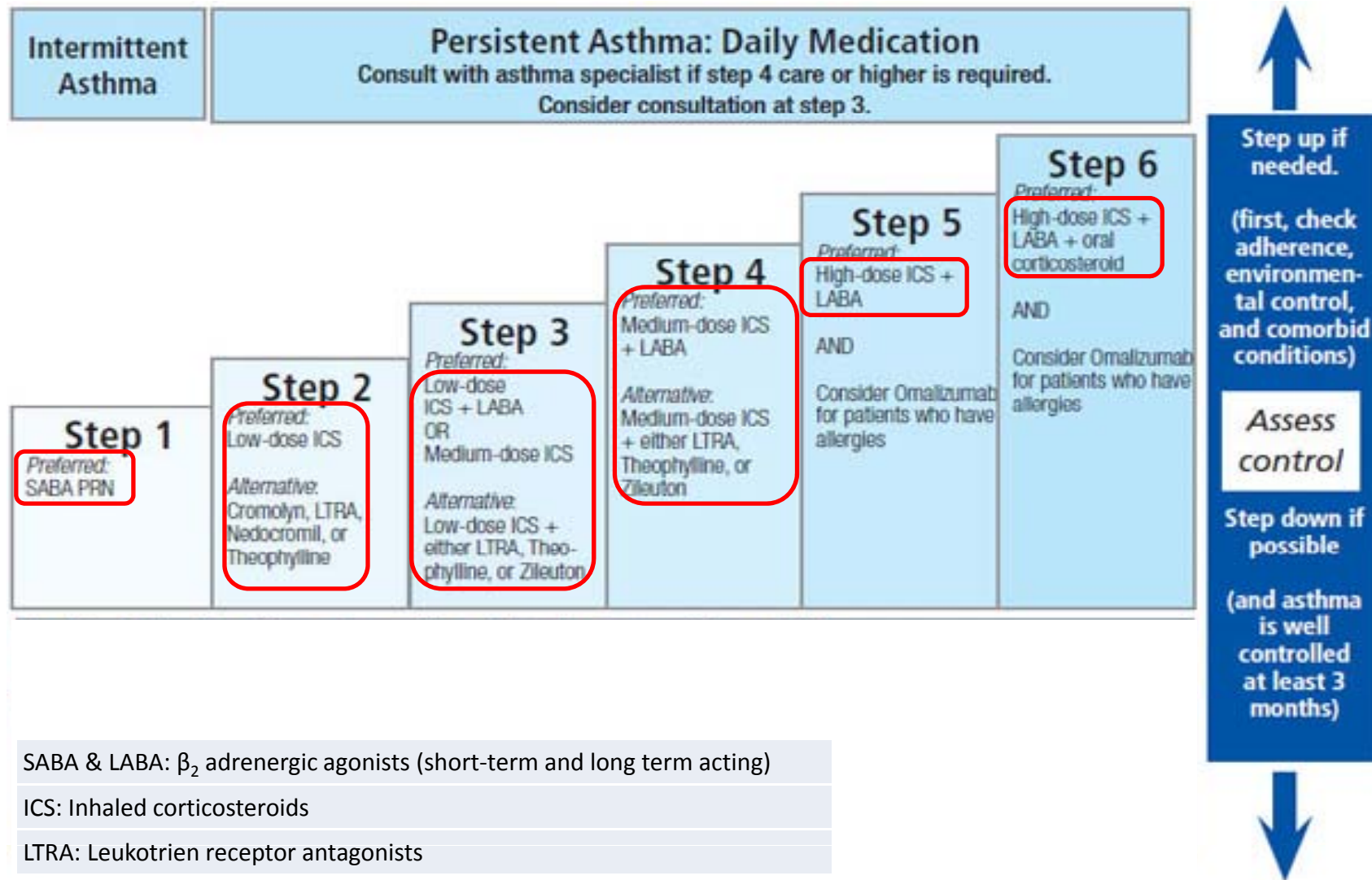
ASTHMA

- Asthma is the most **common chronic airway disease** among **children** and first symptoms occur at around 5 years. [1]

- US: >10 million children under age 18 (14%) ever suffered asthma ATTACK; 6.8 million children still have chronic asthma (9%).[2]

- Asthma is characterized by two components, either **inflammatory** or **functional alteration**, thus it requires a dual treatment, including **steroids** and/or **bronchodilators**

1. http://www.who.int/respiratory/asthma/en/
2. CDC http://www.cdc.gov/nchs/data/series/sr_10/sr10_258.pdf

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GLOBAL INITIATIVE FOR ASTHMA (GINA 2010) GUIDELINES IN CHILDREN

Intermittent Asthma

Persistent Asthma: Daily Medication
Consult with asthma specialist if step 4 care or higher is required.
Consider consultation at step 3.

Step 1
Preferred:
SABA PRN

Step 2
Preferred:
Low-dose ICS

Alternative:
Cromolyn, LTRA, Nedocromil, or Theophylline

Step 3
Preferred:
Low-dose ICS + LABA
OR
Medium-dose ICS

Alternative:
Low-dose ICS + either LTRA, Theophylline, or Zileuton

Step 4
Preferred:
Medium-dose ICS + LABA

Alternative:
Medium-dose ICS + either LTRA, Theophylline, or Zileuton

Step 5
Preferred:
High-dose ICS + LABA

AND

Consider Omalizumab for patients who have allergies

Step 6
Preferred:
High-dose ICS + LABA + oral corticosteroid

AND

Consider Omalizumab for patients who have allergies

Step up if needed.
(first, check adherence, environmental control, and comorbid conditions)

Assess control

Step down if possible
(and asthma is well controlled at least 3 months)

SABA & LABA: β₂ adrenergic agonists (short-term and long term acting)

ICS: Inhaled corticosteroids

LTRA: Leukotrien receptor antagonists

INHALED MEDICINES AND SYSTEMIC ABSORPTION

>10 μm: mouth
<0.5 μm: exhaled
1-5 μm: small airways

Mouth and pharynx

Lung deposition (10% to 30%)

Lung

Absorption from the lung (A)

Swallowed fraction (70% to 90%)

GI tract

Absorption from the gut

Liver

Inactivation in the liver "first pass"

Active drug from the gut (B)

Systemic circulation

Systemic concentration = A + B
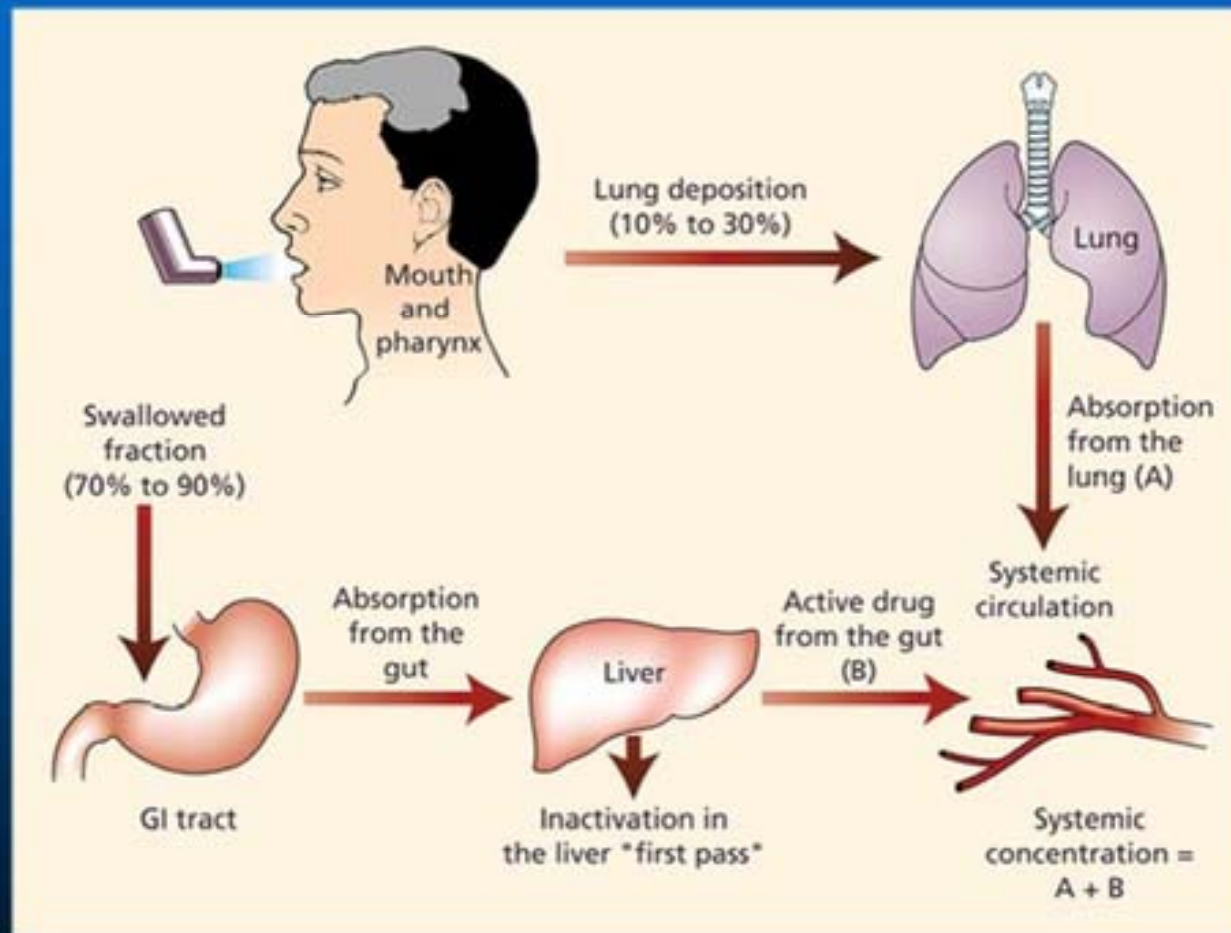
LIVER INJURY

LEUKOTRIENES RECEPTORS ANTAGONISTS (LTRA)

• mild, asymptomatic **ALT elevations occur in 1.5%** of patients receiving **zafirlukast**;

• **Rarely severe hepatic failure, resulting in liver transplantation or death**;

• Onset typically within **2 to 6 months** of starting therapy;

• One case of **montelukast -induced liver toxicity** in **children[1]**.

B$_2$-ADRENERGIC AGONISTS

• **ALT elevations occur in less than 1% of patients**;

• After **long term oral** therapy with B$_2$-adrenergic bronchodilators.

CORTICOSTEROIDS (CS)

• Oral CS have been reported to be associated with liver toxicity, while **inhaled** CS are thought to be much lower associated than orally intake.

Incecik et al. Ann Saudi Med 2007; 27(6)

SIGNAL DETECTION IN EU-ADR NETWORK

Table 2. Comparison of different methods applied for signal detection concerning acute liver injury

ATC	Drugs	No. of cases	Exposure (PYs)	Crude IR/10,000 PY (95% CI)	RR_{LGPS} (95% CI)	RR_{SCCS} (95% CI)	LEOPARD[#]
A02	Ranitidine	7	3,833.86	18.3 (8.14-35.8)	43.7 (17.7-87.6)	12.9 (4.9-34.0)	yes
	Omeprazole	7	5,583.97	12.5 (5.6-24.6)	29 (9.5--60.9)	13.3 (4.9-35.6)	yes
	.....						
R03	Flunisolide*	4	27,548.87	1.5 (0.5-34.5)	3.4 (1.3-7.6)	2.7 (0.9-8.1)	no
R06	Cetirizine	5	43,255.13	1.2 (0.4-2.5)	2.5 (1.0-5.1)	3.0 (1.2-7.7)	yes

Drugs with ≥3 exposed cases of ALI and a lower band of 95% CI of RR >1 when applying LGPS method.

*not statistically significant association when using SCCS method;

[#]Yes= protopathic bias is likely to be present, No= protopathic bias is unlikely to be present.

Ferrajolo C. et al. Drug Safety 2013

OBJECTIVE

By combining multiple healthcare databases from two EU Countries, we **assessed the risk of liver injury associated with anti-asthma medications**, as a whole class and by therapeutic classes and individual compounds, **in children and adolescents outpatients**.

METHODS

Design: Case-control analysis

Period: Jan 2001 – Dec 2008

Setting: General Practitioner and Family Pediatrician healthcare databases from Netherlands and Italy

Study population: Children and adolescents outpatients (<18 years)

POOLING OF ELECTRONIC MEDICAL RECORD DATABASES

Integrated Primary Care Information

- **300 Family Paediatricians (FP)**
- **145,706 children (<14y)**
- **400 GPs**
- **93,307 children (<18y)**

Health Search/Thales

- **900 General Practitioners (GPs)**
- **190,772 children (14-17 y)**   **> 400,000 children**

CASE OF LIVER INJURY ASCERTAINMENT

1. Initial broad case selection through search based on:

   a) terminology specific diagnostic codes (ICPC and ICD9) related to liver disease

   b) free text

   a) laboratory data (i.e. Alanine/Aspartate Amino Transferases, OR Alkaline phosphatase OR Total Bilirubin)

2. Manual review of all potential cases by medically trained researchers using common algorithm (*blinded to the drug exposure*)

EXCLUSION CRITERIA

- Liver injury due to other specified causes:
  - ➤ viral infections; alcohol abuse; autoimmune, or metabolic disorders or abdominal trauma)
  - • Neonatal hepatitis
- Isolated jaundice and hepatomegaly
- Chronic liver disease
- Small elevation of liver tests (≤ 2xULN)
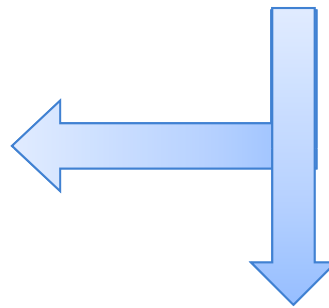
CASE
diagnosis of liver injury by one of those:
- Specialist;
-GP/FP confirmed by diagnostic tests;
-lab data (>2xULN)

3. Doubtful cases reviewed by two experts to reach consensus
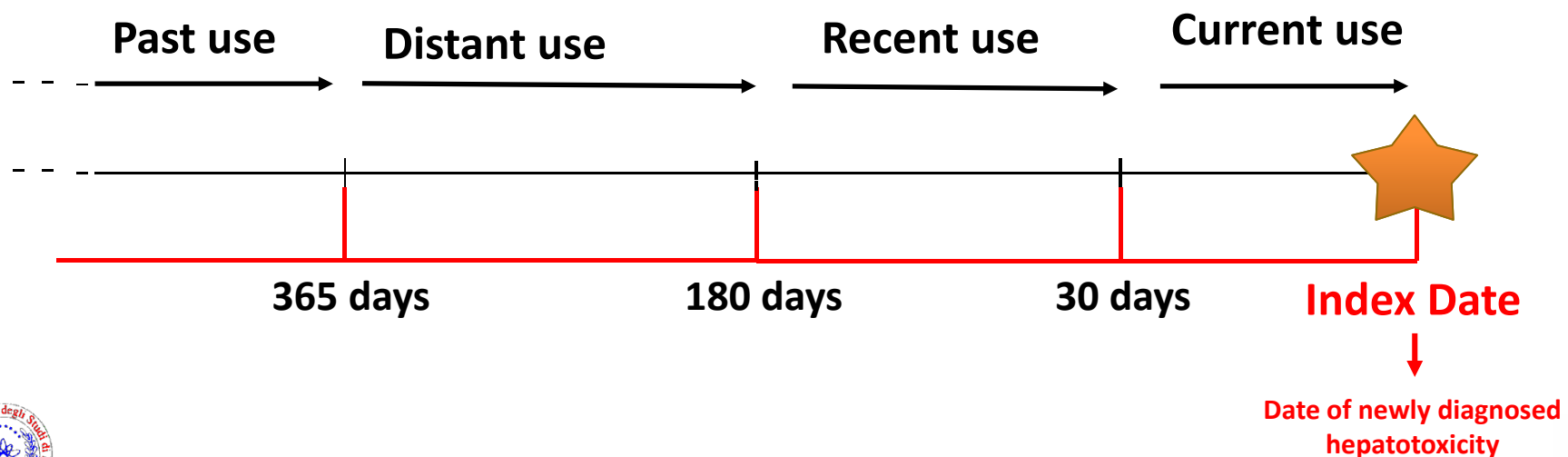
SELECTION OF CONTROLS

- 100 controls for each case (**incidence density sampling**) matched by:
    - index date (date of case onset)
    - Age
    - Sex
    - Database

ANTI-ASTHMA DRUGS EXPOSURE DEFINITION

Prescriptions of any R03:

- β_2-adrenergic agonists short and long acting (SABA & LABA) and in combination;
- Inhaled and Oral corticosteroids (ICS and CS);
- Anticholinergics;
- Chromones;
- Theophyllines;
- Leukotriene receptor antagonists (LTRA).

Exposure categories based on regency of

Past use Distant use Recent use Current use

365 days 180 days 30 days **Index Date**

Date of newly diagnosed hepatotoxicity

STATISTICAL ANALYSIS

Main analysis:

❑ By conditional logistic regression we measured the Crude OR (95% CI) as the probability to develop liver injury in children and adolescents with the use of class/individual anti-asthma drugs, as **compared to no use of these medications**

❑ Adjusted OR for all covariates (P>0.10)

Sensitivity analyses:

❑ **Restricted analysis among R03 users** to control for confounding by indication

❑ Stratified the analyses by duration of the therapy

❑ Removal of carry-over period to explore the possible effect of misclassification of the exposure

CHARACTERISTICS OF CASES AND CONTROLS

	Cases N=938 (%)	Controls N=93,665 (%)	
Gender			
Girls	392 (41.8)	39,106 (41.8)	Matching factor
Age cat. (yrs)			
<2	88 (9.4)	8811 (9.4)	Matching factor
2-5	101 (10.8)	9704 (10.4)	
6-11	260 (27.8)	26,060 (27.7)	
12-18	489 (52.1)	49,090 (52.4)	
Database			
HSD	478 (51)	47,480 (51)	Matching factor
Pedianet	382 (40.7)	38,159 (40.7)	
IPCI	78 (8.3)	7706 (8.2)	

RISK FACTOR

	Cases N=938 (%)	Controls N=93,665 (%)	OR* (95% CI)	p-value^
Comorbidities				
Diabetes	16 (1.7)	264 (0.3)	6.2 (3.7-10.3)	<0.001
Obesity	57 (6.1)	1767 (1.9)	3.5 (2.6-4.5)	<0.001
Hyperlipidaemia	7 (0.7)	177 (0.2)	4.0 (1.9-8.5)	<0.001
Thyroid hormone abn.	9 (1.0)	395 (0.4)	2.3 (1.2-4.5)	0.014
Nutrition-related issues	10 (1.1)	762 (0.8)	1.3 (0.7-2.5)	0.390
Hypertension	1 (0.1)	89 (0.1)	NA	
Congenital diseases	18 (1.9)	871 (0.9)	2.1 (1.3-3.4)	0.002
Concomitant hepatotoxic drug [ATC]				
Antibiotics [J01]	117 (12.5)	3398 (3.6)	3.5 (2.8-4.3)	<0.001
Anti-mycotics [J02]	1 (0.0)	41 (0.1)	NA	
Anti-tubercolosis [J04]	2 (0.2)	9 (0.1)	NA	
Anti-acids [A02]	8 (0.9)	141 (0.2)	5.8 (2.8-11.9)	<0,001
Anti-convulsants [N03]	12 (1.3)	323 (0.3)	3.7 (2.1-6.7)	<0.001
Anti-inflammatory [M01]	10 (1.1)	320 (0.3)	3.4 (1.8-6.3)	<0.001
Hormon preparations [G03]	10 (1.1)	678 (0.7)	1.8 (0.8-3.8)	0.133
Paracetamol [N02BE]	4 (0.4)	128 (0.1)	3.2 (1.2-8.7)	0.022
Psycoleptics [N05]	3(0.3)	93 (0.1)	3.3 (1.0-10.4)	0.043
Psycoanaleptics [N06]	3 (0.3)	107 (0.1)	2.9 (0.9-9.1)	0.075

RISK OF LIVER INJURY WITH ANTIASTHMA MEDICATIONS

|	CASES (N= 938)	CONTROLS (N= 93665)	OR (CI 95%)
NO USE	572 (61%)	67539 (72%)	REF.
CURRENT USE (<30dys)	52 (6%)	2491 (3%)	2.51 (1.88-3.35)
RECENT USE (30-180dys)	43 (5%)	2174 (2%)	2.12 (1.67-2.69)
DISTANT USE (180-365dys)	99 (11%)	6749 (7%)	1.73 (1.32-2.28)
PAST USE (≥ 365dys)	172 (18%)	14712 (16%)	1.41 (1.18-1.68)

No further analyses within age group because of low exposure

Risk of liver injury and different classes of anti-asthma medications*

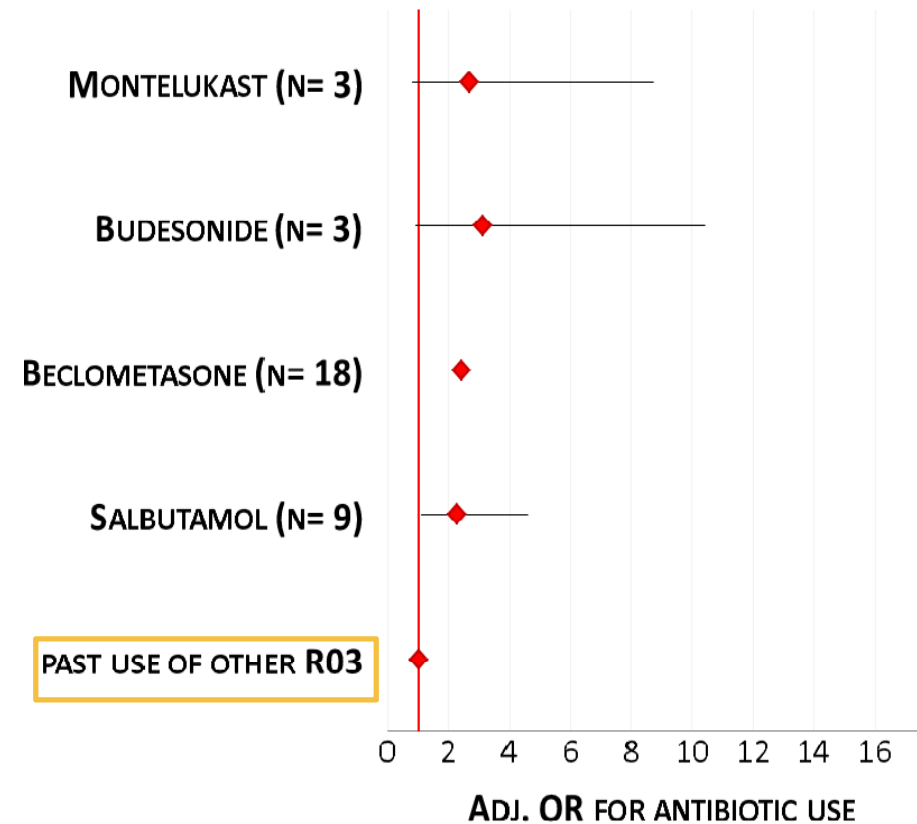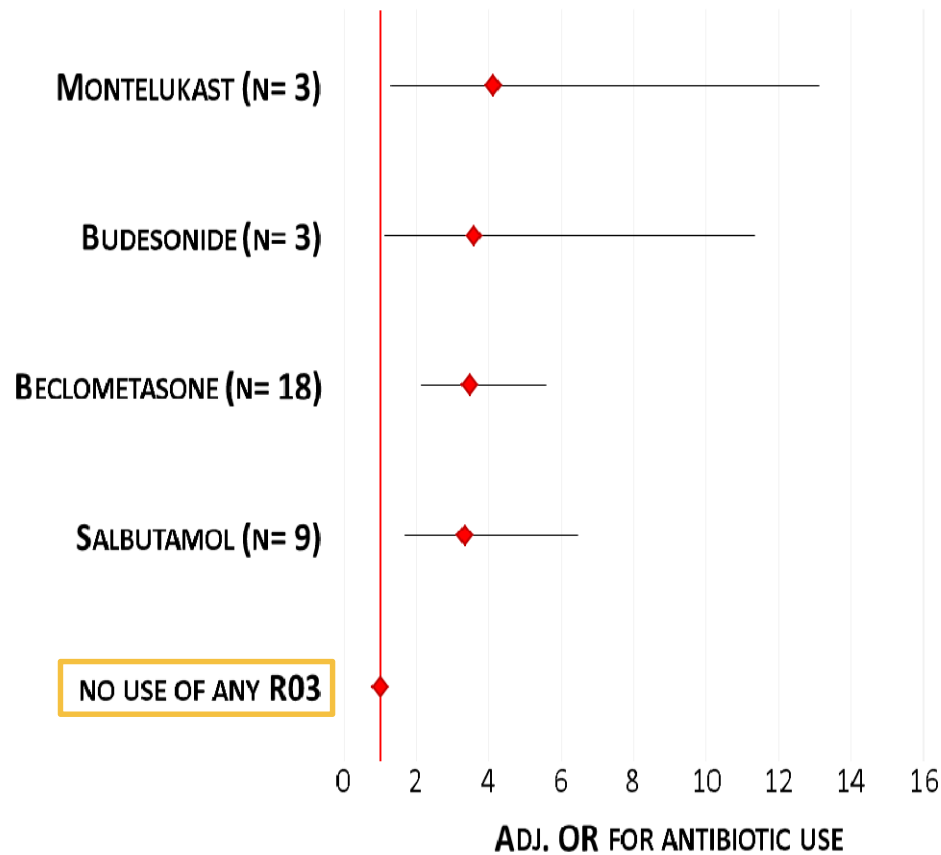**whole cohort**
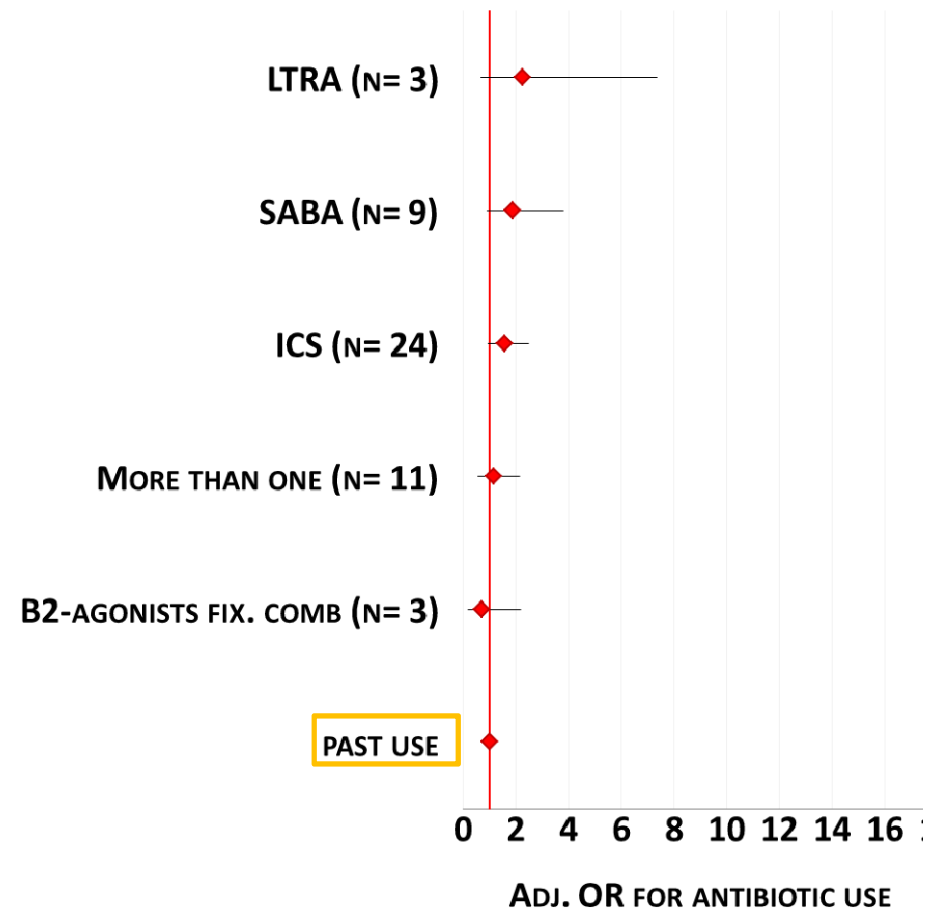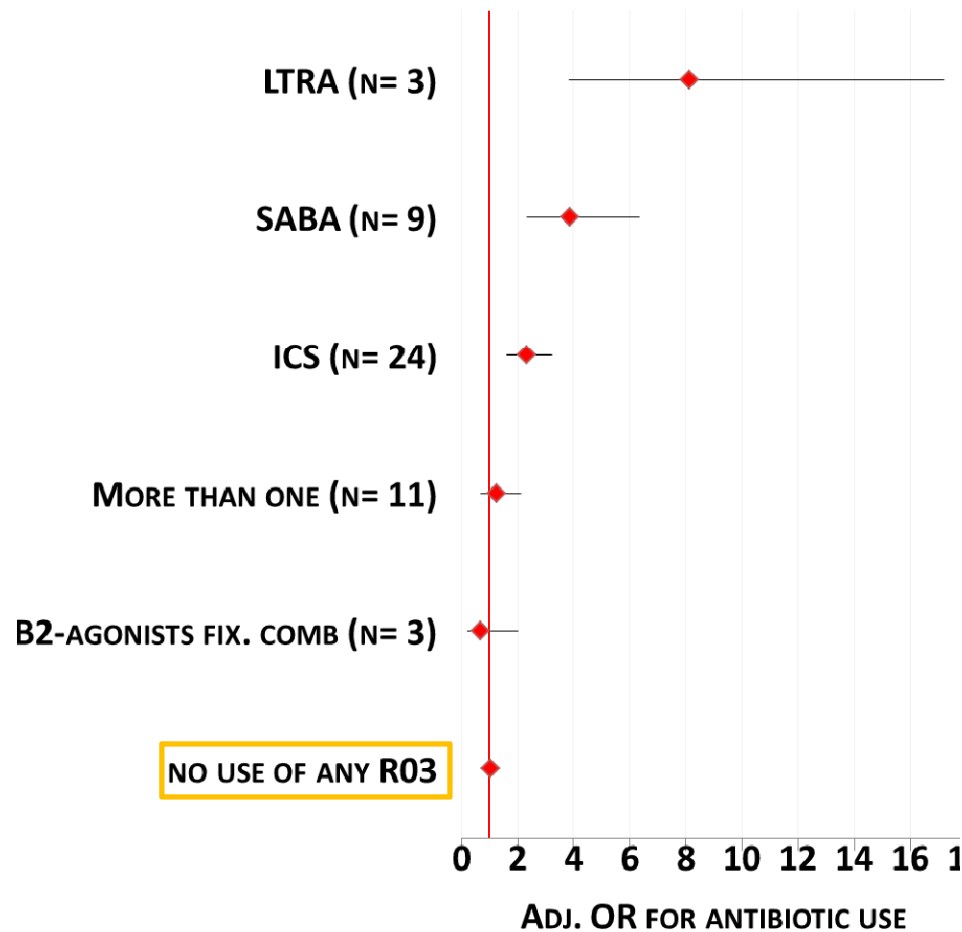
R03 users cohort

*No cases for anticholinergics, cromons, and systemic drugs (B2-adreniergics, CS, Xanthines, and comb)

RISK OF LIVER INJURY AND SPECIFIC ANTI-ASTHMA MEDICATIONS*

whole cohort

R03 users cohort

*with at least 3 exposed cases of liver toxicity

LIMITATIONS

Misclassification

- outcome: unlikely, as manually validated cases
- exposure: adherence to the therapy (?)
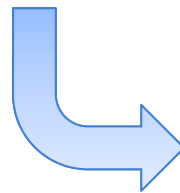 → possible risk underestimation

Confounding by indication

- restricted analysis within R03 users to control for it;

Residual confounding

- due to unmeasured severity of disease can never be excluded

CONCLUSIONS

➢ Liver injury seems to be associated with the use of some classes of anti-asthma medications in children and adolescents beyond the effect of the indication of use.

➢ Results need to be interpreted with caution:

  ✓ β_2-agonists, ICS and LTRA showed a trend of association with hepatotoxicity but the effect of long/short treatment requires further investigation

➢ Larger exposure set is needed to estimate these potential associations as well as the effect of duration of treatment and of risk factors.

GRiP

Global Research in Paediatrics

SEVENTH FRAMEWORK PROGRAMME

Erasmus MC