Antibiotic Exposure Prior To Hospital Admission For Acute Liver Injury

A. Grolleau[1], S. Duret[1], N. Thurin[1], M. Duong[1], R. Lassalle[1], P. Blin[1], C. Droz-Perroteau[1], SE. Gulmez[1], N. Moore[1]

[1] Bordeaux PharmacoEpi, INSERM CIC1401, Université de Bordeaux, Bordeaux, France

Abstract

Background: Hepatic injury is a major safety issue. Several antibiotics (AB) have been concerned, and antimycobacterials (AMB) are known hepatotoxic drugs. **Objectives:** To quantify exposure to AB or AMB prior to hospital admission for acute liver injury (ALI) in the French National healthcare systems database, SNDS. **Methods:** All hospital admissions for acute liver injury (K71.1,.2,.6,.9, K72.0) over 2009-2014 were identified in SNDS (66 million persons). Previous diagnoses of liver disease/liver injury were excluded. Exposures of interest were AB (ATC codes J01AA to J01MA) and AMB (J04) dispensed from 7 to 60 days before hospital admission. Reference populations were a) the French population over the study period, extrapolated from the 1/97th permanent representative sample, EGB in a case-population analysis. b) 5 controls/case from EGB, matched on age, gender, and index date, for case-control analysis. Results are provided as a) number of cases per million users (MPt) or ten thousand patient-years (TPY), with 95% confidence intervals [95%CI]; b) Odds Ratios [95% CI], compared to non-exposure. **Results:** 4807 ALI were matched to 24035 controls, with 3619 cases and 12793 controls exposed (OR 3.1 [2.9-3.4]). 1108 cases had been exposed to at least one AB, vs. 2606 controls (OR 2.47 [2.29-2.68]). All AB together had 1.3 [1.2-1.5] cases per TPY, 22.7 [20.2-25.2] per MPt. Individual drugs ranged from 28.8 /TPY [21.8-37.5] for erythromycin to Doxycycline 0.4 [0.2-0.6]. Other commonly used drugs were amoxicillin 0.9 [0.8-1.0], co-amoxiclav 1.5 [1.3-1.7], clarithromycin 1.9 [1.5-2.5] /TPY. Per MPt rates were erythromycin 189 [141-242], clindamycin 31 [15-58], cotrimoxazole 26 [20-34], Co-amoxiclav 15 [13-18]. Odds ratios ranged from 93 [29-298] for erythromycin to 1.36 [0.85-2.18] for roxithromycin. Co-amoxiclav's OR was 3.55 [3.05-4.13], amoxicillin 1.76 [1.5-2.1]. AMB had higher risks, from 108/TPY for the triple association isoniazid, rifampicin, ethambutol to 17/TPY for isoniazid alone; per patient rates were 1728/MPt for the triple association, to 780 for isoniazid. The OR for all AMB pooled was 73 [31-164]. Individual AMB were mostly not evaluable because there were no exposed controls. Estimated OR went from 174 for triple therapy, ethambutol 125, isoniazid 35. **Conclusion:** The risk of hospital admission for hepatic injury with AB was similar for most AB, with some outliers: in addition to AMB, erythromycin was associated with a clearly much higher risk of admission for hepatic injury.

1. *Gulmez SE, et al. Transplantation for acute liver failure in patients exposed to NSAIDs or paracetamol (acetaminophen): the multinational case-population SALT study. Drug Saf. 2013;36(2):135-44.*
2. *Gulmez SE, et al. Risk of hospital admission for liver injury in users of NSAIDs and nonoverdose paracetamol: Preliminary results from the EPIHAM study. Pharmacoepidemiol Drug Saf. 2018;27(11):1174-81.*

Declaration of Interest Statement

This study was supported by an unconditional public joint help from *Direction Générale de la Santé* (DGS), from *Mission recherche de la Direction de la Recherche, des Etudes, de l'Evaluation et des Statistiques* (MiRe-DREES) of *Caisse Nationale d'Assurance Maladie des Travailleurs Salariés* (CNAMTS*), Régime Social des Indépendants* (RSI) and *Caisse Nationale de Solidarité pour l'Autonomie* (CNSA*),* as part of the general call for projects by IReSP *(Appel à Projets, Institut de Recherche en Santé Publique)* in 2013. It was conducted by Bordeaux PharmacoEpi Platform. All authors, none declared other relationships to disclose for this study.

Background

- Acute Liver Injury (ALI) is a major source of drug-induced regulatory action, drug-induced hospital admissions and burden of care.
- To our knowledge, hepatotoxicity studies were based on identification of individual cases and concerned a few hundred cases.
- A previous field study (SALT) exhaustively explored the acute liver failure leading to liver transplantation in 7 countries. The EPIHAM study was conducted in order to identify drugs with less severe hepatotoxicity, still resulting in hospital admission using the French nationwide claims database.

Objectives

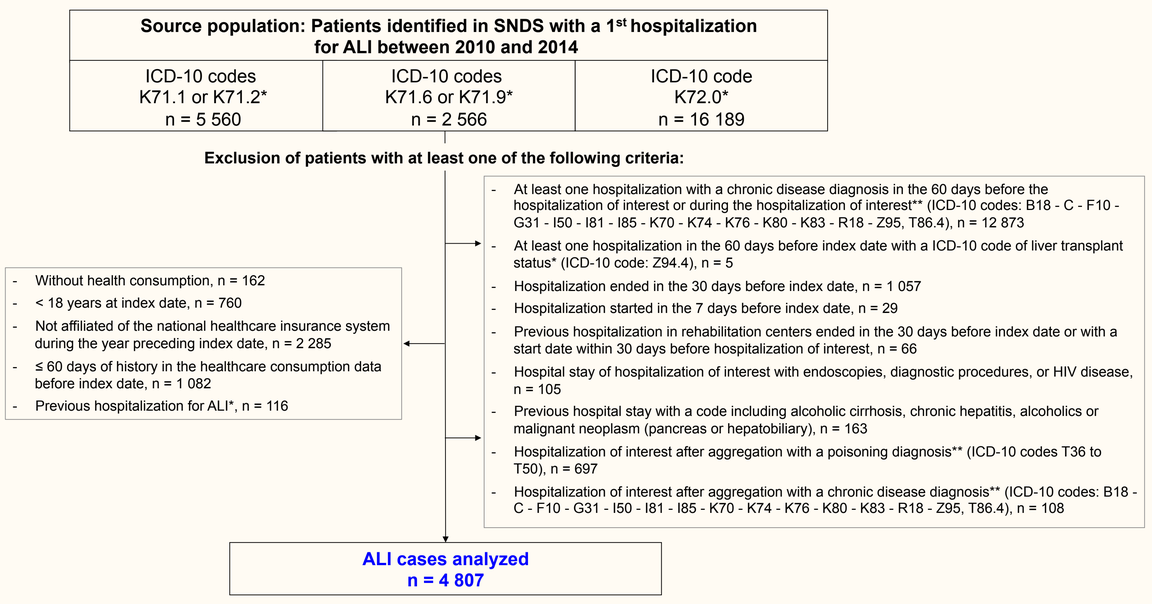
To quantify exposure to antibiotics (AB) or antimycobacterials (AMB) prior to hospital admission for ALI in the French National healthcare systems database SNDS.

Methods

- **Study design**
  - Case-population study of adults with a 1st hospitalization for ALI from 2010 to 2014.
  - Case-control study of adults exposed to interest drugs from 2010 to 2014.
- **Data source:** the SNDS French nationwide claims database which covers 99% of the French population and the EGB 1/97th permanent representative sample of SNDS.
- **Study population**
  - **Case** identified in SNDS among adult patients with a 1st hospital admission from 2010 to 2014 with main diagnosis of acute toxic liver injury (ICD-10 codes K71.1, K71.2, K71.6, K71.9) or hepatic failure (ICD-10 code K72.0) (Figure 1).
  - **Reference population** identified in EGB among adult patients affiliated at least one day for each year considered to the national healthcare insurance system for salaried workers (CNAMTS), extrapolated to the whole French population.
  - **Control** identified in EGB among adult patients affiliated to the CNAMTS and hospitalized between 2010 and 2014 for a reason other than ALI. Control were matched on age and gender using the same index date with a ratio of 5 controls / case identified (Figure 2).
- **Index date:** Date of first hospital admission for ALI.
- **Exposure**
  - **Case:** AB (ATC codes J01AA to J01MA) and AMB (J04) dispensing between 7 and 60 days preceding the date of 1st hospital admission for ALI (to avoid indication and protopathic bias).
  - **Reference population:** number of patients with at least one interest drug dispensed over the study period (2010-2014), extrapolated to the whole French population.
  - **Control:** AB (ATC codes J01AA to J01MA) and AMB (J04) dispensing in the same period as the identified cases.
- **Data analysis**
  - Incidence rate of ALI: number of exposed cases over the study period per million users (MP) or ten thousand patient-years (TPY) with 95% confidence intervals (case-population analysis).
  - Risk of ALI in exposed patients (Odds Ratio – OR, conditional logistic regression) compared to non-exposed patients (case-control analysis).

Results

Identification of ALI cases – Case-population analysis



** Main diagnosis; ** Main, associated or related diagnosis; *** Hospitalizations with a duration of 0 day or with a release "at home" were excluded from the aggregation*

Figure 1. Identification procedure of ALI cases in SNDS between 2010 and 2014

Identification of controls – Case-control analysis

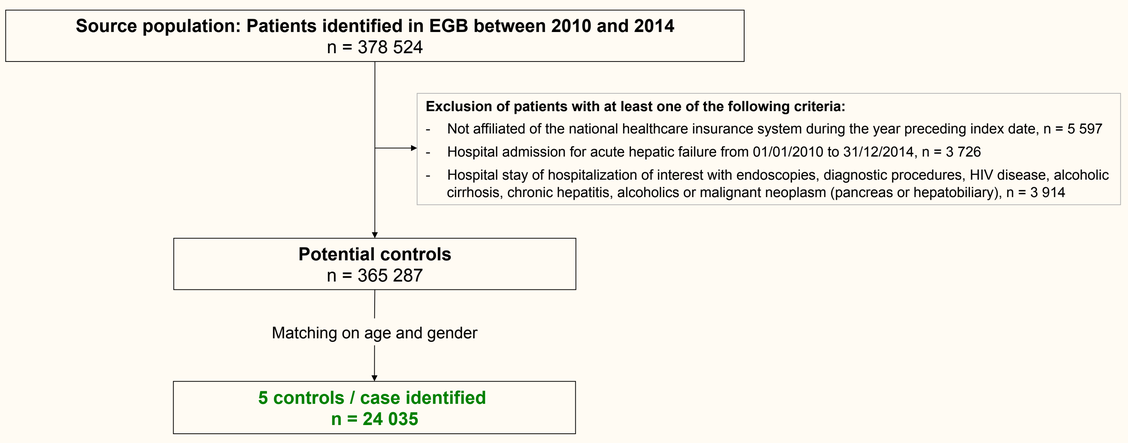


Figure 2. Identification procedure of controls in EGB between 2010 and 2014

Exposure of adult ALI cases

- 23% of cases were exposed to at least one AB. Exposure ranged from 293 cases for the association amoxicillin and beta-lactamase inhibitor to 5 cases for lymecycline (Table 1).
- Exposure to AMB (1.8%) ranged from 35 cases for the triple association rifampicin, pyrazinamide and isoniazid to 10 cases for pyrazinamide alone.

Incidence of hospitalization for ALI

- For AB, event rates per TPY ranged from 28.9 [21.8-37.5] for erythromycin to 0.4 [0.3-0.6] for doxycycline, and per MP from 186 [141-242] for erythromycin to 5 [3-6] for the association spiramycin and metronidazole.
- For AMB, event rates per TPY ranged from 108 [75-151] for the triple association rifampicin, pyrazinamide and isoniazid to 6 [4-10] for rifampicin alone, and per MP from 1729 [1204-2404] for the triple therapy to 158 [99-239] for rifampicin.

Table 1. AB and AMB exposure of adult ALI cases within 7 and 60 days preceding the index date and incidence of hospitalizations for ALI between 2010 and 2014

Drug dispensed within 7 and 60 days before index date	Case n = 4 807	Case / million patients [95% CI][1]	Case / ten thousand patients-year [95% CI][1]
J01 - Antibacterials for systemic use, n (%)	**1109 (23.1)**	**22.68 [20.24 ; 25.19]**	**1.34 [1.20 ; 1.50]**
J01CR02 - Amoxicillin and beta-lactamase inhibitor	293 (6.1)	15.37 [13.38 ; 17.52]	1.48 [1.28 ; 1.68]
J01CA04 - Amoxicillin	223 (4.6)	8.14 [7.01 ; 9.38]	0.88 [0.77 ; 1.02]
J01FG01 - Pristinamycin	68 (1.4)	8.26 [6.42 ; 10.48]	2.05 [1.61 ; 2.59]
J01DD13 - Cefpodoxime	67 (1.4)	7.41 [5.74 ; 9.41]	2.98 [2.30 ; 3.80]
J01FA09 - Clarithromycin	60 (1.2)	8.47 [6.47 ; 10.9]	1.94 [1.50 ; 2.52]
J01XX01 - Fosfomycin	58 (1.2)	10.99 [8.35 ; 14.21]	13.64 [10.37 ; 17.63]
J01FA01 - Erythromycin	56 (1.2)	186.09 [140.56 ; 241.65]	28.88 [21.83 ; 37.52]
J01EE01 - Sulfamethoxazole et trimethoprim	53 (1.1)	26.04 [19.51 ; 34.07]	4.58 [3.43 ; 5.99]
J01MA01 - Ofloxacin	53 (1.1)	11.89 [8.91 ; 15.56]	3.16 [2.37 ; 4.12]
J01MA02 - Ciprofloxacin	52 (1.1)	13.69 [10.23 ; 17.95]	3.49 [2.59 ; 4.56]
J01MA06 - Norfloxacin	50 (1.0)	12.28 [9.11 ; 16.19]	3.42 [2.56 ; 4.53]
J01RA04 - Spiramycin and metronidazole	44 (0.9)	4.67 [3.39 ; 6.27]	1.69 [1.24 ; 2.26]
J01DD08 - Cefixime	40 (0.8)	9.91 [7.08 ; 13.50]	2.66 [1.90 ; 3.61]
J01FA10 - Azithromycin	40 (0.8)	6.61 [4.72 ; 9.00]	2.69 [1.93 ; 3.65]
J01DD04 - Ceftriaxone	37 (0.8)	18.47 [13.00 ; 25.46]	11.17 [7.85 ; 15.40]
J01DC02 - Cefuroxime	32 (0.7)	7.65 [5.23 ; 10.80]	2.08 [1.42 ; 2.92]
J01XE01 - Nitrofurantoin	29 (0.6)	18.02 [12.07 ; 25.88]	3.57 [2.41 ; 5.15]
J01AA02 - Doxycycline	29 (0.6)	8.37 [5.60 ; 12.02]	0.44 [0.29 ; 0.62]
J01FA06 - Roxithromycin	22 (0.5)	5.62 [3.52 ; 8.51]	1.85 [1.17 ; 2.81]
J01MA12 - Levofloxacin	21 (0.4)	8.81 [5.45 ; 13.46]	2.22 [1.39 ; 3.39]
J01FA07 - Josamycin	18 (0.4)	10.54 [6.25 ; 16.66]	3.65 [2.15 ; 5.77]
J01FA02 - Spiramycin	14 (0.3)	9.78 [5.34 ; 16.41]	4.04 [2.19 ; 6.79]
J01MA07 - Lomefloxacin	14 (0.3)	8.20 [4.48 ; 13.76]	6.72 [3.69 ; 11.28]
J01CF02 - Cloxacillin	13 (0.3)	5.68 [3.02 ; 9.71]	1.60 [0.84 ; 2.74]
J01XC01 - Fusidic acid	10 (0.2)	11.04 [5.30 ; 20.30]	4.83 [2.34 ; 8.87]
J01DC07 - Cefotiam	10 (0.2)	9.27 [4.45 ; 17.05]	8.64 [4.16 ; 15.88]
J01FF01 - Clindamycin	10 (0.2)	31.39 [15.07 ; 57.73]	5.62 [2.70 ; 10.33]
J01MA14 - Moxifloxacin	8 (0.2)	7.91 [3.41 ; 15.58]	2.68 [1.17 ; 5.26]
J01FA15 - Telithromycin	7 (0.1)	9.89 [3.97 ; 20.38]	3.98 [1.61 ; 8.21]
J01DC04 - Cefaclor	5 (0.1)	6.39 [2.07 ; 14.91]	2.28 [0.73 ; 5.33]
J01AA04 - Lymecycline	5 (0.1)	5.40 [1.75 ; 12.61]	0.51 [0.18 ; 1.20]
J04 – Antimycobacterials, n (%)	**86 (1.8)**	**399.94 [319.91 ; 493.93]**	**9.09 [7.26 ; 11.24]**
J04AM05 - Rifampicin, pyrazinamide and isoniazid	35 (0.7)	1728.65 [1204.13 ; 2404.31]	108.40 [75.52 ; 150.75]
J04AM02 - Rifampicin and isoniazid	31 (0.6)	518.55 [352.28 ; 736.01]	19.08 [12.96 ; 27.08]
J04AK02 - Ethambutol	27 (0.6)	1212.50 [798.90 ; 1763.97]	46.47 [30.62 ; 67.60]
J04AB02 - Rifampicin	22 (0.5)	157.92 [98.99 ; 239.11]	6.50 [4.09 ; 9.86]
J04AC01 - Isoniazid	14 (0.3)	780.38 [426.42 ; 1309.36]	16.69 [9.13 ; 28.00]
J04AK01 - Pyrazinamide	10 (0.2)	1298.36 [623.21 ; 2387.69]	55.75 [26.75 ; 102.53]

[1] Taking into account the extrapolation of patient number for the reference population in the EGB database between 2010 and 2014

Risk of hospital admission for ALI

- For AB, OR ranged from 93.3 [29.2-298.2] for erythromycin to 1.1 [0.4-3.0] for lymecycline, with an OR of 3.5 [3.0-4.1] for the association amoxicillin and clavulanic acid, and 1.8 [1.5-2.1] for amoxicillin alone (Figure 3).
- For all AMB pooled, the OR was 71.7 [31.3-163.9]. Individual AMB were mostly not evaluable because there were no exposed controls. The estimated OR ranged from 175 for the triple therapy to 135 for ethambutol alone and 35 for isoniazid alone.

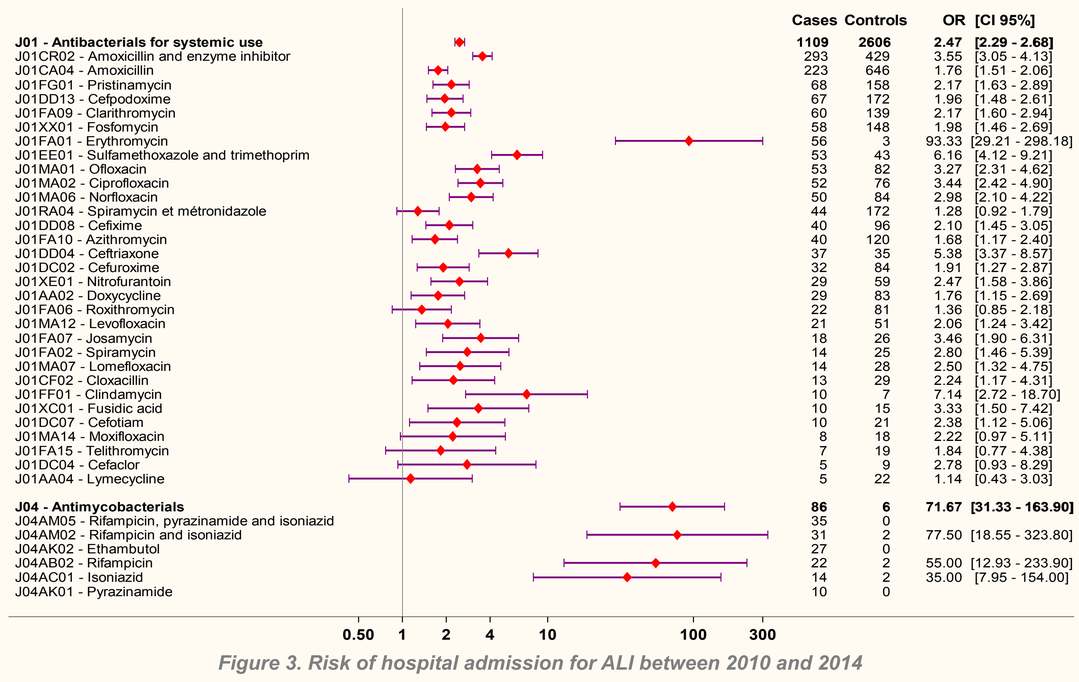


Figure 3. Risk of hospital admission for ALI between 2010 and 2014

Conclusion

- **The hospitalization risk for ALI was similar for most non AMB AB (OR around 2).**
- **The hospitalization risk for ALI was higher for AMB (estimated OR: 175 for rifampicin/ pyrazinamide/isoniazid, 135 for ethambutol).**
- **Erythromycin was also clearly associated with a higher risk of hospitalization for ALI (OR: 93.33).**

35th ICPE International Society for Pharmacoepidemiology
August 24-28, 2019, Philadelphia, PA, USA
[Abstract # 6566]