EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Data Analysis Report

Rapid Data Analysis – Ceftriaxone and hepatic events

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands

Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000

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1. List of abbreviations

MAH	*Marketing Authorisation Holder*
EMA	*European Medicines Agency*
PRAC	*Pharmacovigilance Risk Assessment Committee*
RDA	*Rapid Data Analysis*

2. Amendments and updates

Amendment 1 on 17 November 2020:

The protocol was amended to specify that only the first hepatic outcome event after start of ceftriaxone and the time until the first hepatic outcome event is considered.

In addition, additional analysis considering also the incidence of events 60, 90, 180 and 365 days after treatment initiation was added as post-hoc analysis (section 6.11).

3. Milestones

(Timelines of the official signal procedure highlighted in grey)

Milestone	**Planned date**
Feasibility feedback with analysis proposal shared with Rapporteur	07 September 2020
Feedback from Rapporteur on proposed analysis	9 September 2020
Draft analysis protocol circulated to Rapporteur and PRAC Members for comments	18 September 2020
Comments from Rapporteur and PRAC Members on draft analysis plan by	02 October 2020
Updated analysis plan following comments circulated by EMA to Rapporteurs and PRAC Members by	16 October 2020
Analysis report by EMA circulated to Rapporteurs and PRAC Members by	18 November 2020
Registration in the EU PAS register (including study report)	*Pending approval from IQVIA - TBA*
Submission of data by the MAH	*11 November 2020*
Preliminary assessment report on additional data	*21 December 2020*
Deadline for comments	*04 January 2021*
Updated rapporteur assessment report	*07 January 2021*
Adoption of second PRAC recommendation	*14 January 2021*

4. Rationale and background

A signal on hepatitis associated with ceftriaxone has been identified.

MAHs have been asked to provide supplementary information by 11 November 2020.

To further support the evaluation of this signal at PRAC, an analysis using electronic medical records databases based on the German and French IMS® Disease Analyzer databases has been carried out by EMA.

This analysis aims to provide descriptive information on specific hepatic events occurring within 30 days of a prescription in patients using ceftriaxone, stratified by prior history of liver disease or other risk factors for hepatic events. Results are also be stratified by gender, age group, indication, and above or below the mean total dose prescribed on the date of the first prescription. No comparisons to other products will be performed due to the limitations of the data and the low sample size.

5. Research question and objectives

The hepatotoxicity after treatment initiation with ceftriaxone will be evaluated. The following research questions will be addressed:

- What is the incidence of potential hepatotoxic events within 30 days after treatment initiation of ceftriaxone in patients with and patients without a prior history of liver disease or other hepatic risk factors?
- What is the incidence of potential hepatotoxic events within 30 days after treatment initiation of ceftriaxone by gender, age group, indication, and dose?

6. Research Methods

6.1. Study Design

The study design is a descriptive incident cohort design without comparator. All patients with a minimum observation time of 365 days at the time of the first recorded prescription for ceftriaxone are included.

Patients are divided into subgroups based on a history of prior liver disease and other hepatic risk factors.

A history of prior liver disease is defined as ICD 10 codes K70 to K77 up to the date of ceftriaxone initiation.

A history of other hepatic risk factors is defined as a history of cancer (ICD 10 codes C00 to C97), HIV (ICD 10 codes B20 to B24), viral hepatitis (ICD 10 codes B15 to B19), or Budd-Chiari syndrome (ICD 10 code I82.0) up to the date of ceftriaxone initiation.

The three subgroups are:

- Patient without prior liver disease or other hepatic risk factors
- Patients with other hepatic risk factors, but no prior liver disease
- Patients with prior liver disease

Follow-up: Patients are followed until their first hepatic outcome event or up to a maximum of 30 days after each ceftriaxone prescription as long as the patient is observable in the database as determined by the date of their last visit.

The incidence rate of hepatic outcome events each of the subgroups is broken down by:

- o gender
- o age group (0-17, 18-49, 50-69 and ≥70 years)
- o indication (upper respiratory tract infection, lower respiratory tract infection, ear infection, urinary tract infection, genital infection, prostate infection, testicular infection, gastrointestinal infection, skin/soft tissue infection, bone infection, borrelia (Lyme disease), central nervous system infection, other infection)
- o dose (above or below the mean total dose prescribed on the date of the first ceftriaxone prescription)

6.2. Setting

The study population includes all patients in IMS® Disease Analyzer France and Germany with a ceftriaxone prescription and least 365 days of observation prior to their first ceftriaxone prescription.

Patients have been observed for hepatic outcome events for a maximum of 30 days after each ceftriaxone prescription.

Separate results are presented for:

- patients with prior liver disease
- patients with other hepatic risk factors but no prior liver disease
- patients without prior liver disease or other hepatic risk factors

Results are stratified by gender, age group at first ceftriaxone prescription (0-17 years, 18-49 years, 50-69 years and ≥70 years), indication at first ceftriaxone prescription (upper respiratory tract infection, lower respiratory tract infection, ear infection, urinary tract infection, genital infection, prostate infection, testicular infection, gastrointestinal infection, skin/soft tissue infection, bone infection, borrelia (Lyme disease), central nervous system infection, other infection), and total dose at first ceftriaxone prescription.

Different indications have been identified as per ICD-10 codes documented on the date of the first ceftriaxone prescription. A list of the different categories of indications in accordance with the ICD-10 codes can be found in Annex 2. Indications are not mutually exclusive, and it is therefore possible that the same patient can have more than one indication.

6.3. Variables

6.3.1. Exposure

- Exposure of interest: All prescriptions for ceftriaxone in the population of interest have been considered.

- Ceftriaxone is administered parenterally. The amount of ceftriaxone in each unit is 500 mg (IMS® Disease Analyzer France and IMS® Disease Analyzer Germany) 1 g (IMS® Disease Analyzer France and IMS® Disease Analyzer Germany) and 2 g (IMS® Disease Analyzer Germany). A list of available ceftriaxone products is included in Annex 1.
- Patients have been observed for up to 30 days after each ceftriaxone prescription.

6.3.2. Outcome(s)

Hepatic outcomes: A hepatotoxic event is defined as any of the following:

- toxic liver disease (ICD 10 code K71)
- hepatic failure not elsewhere classified (ICD 10 code K72)
- nonspecific reactive hepatitis (ICD 10 code K75.2)
- granulomatous hepatitis not elsewhere classified (ICD 10 code K75.3)
- unspecified and other specified inflammatory liver disease (ICD 10 codes K75.8-K75.9)
- unspecified and other specified diseases of liver (ICD 10 codes K76.8-K76.9)

6.4. Data sources

Version March 2020 of IMS® Disease Analyzer France that contains data until 31 March 2020, and version June 2020 of IMS® Disease Analyzer Germany that contains data until 30 June 2020 were used for analysis.

IMS® Disease Analyzer Germany collects computerised information from specialised and general primary care practices throughout Germany since 1982. Around 3% of GP practices are included in IMS® Disease Analyzer Germany. Data from IMS® Disease Analyzer Germany have been shown to be representative of German healthcare statistics [1, 2].

IMS® Disease Analyzer France collects anonymised patient medical records since 1997 through a representative panel of GPs. The physician sample represents approximately 2 % of physicians, and is weighted by age and gender of the physician, doctor region and the SNIR of the physician (National Official Indicator of the GP volume of activity in terms of visits and consultations) [3]. The age distribution of patients has been shown to be similar to France social security data (SNIIRAM) [3].

In both the IMS® Disease Analyzer Germany and France databases diagnoses are coded using WHO ICD 10 codes, and prescriptions are coded using EphMRA ATC codes and substance names.

6.5. Study size

Based on feasibility checks, the estimated number of patients treated with ceftriaxone in General Practices in IMS Germany is 3460 with 6039 prescriptions filed. A low event rate of 6 hepatic events in patients without prior history of hepatic events was found upon feasibility checks in the IMS® Disease Analyzer Germany database.

The estimated number of patients with available data in IMS® Disease Analyzer France treated with ceftriaxone is estimated at 20,315 patients that received 29,088 prescriptions. Among them, a low event rate of less than 20 hepatic events in patients without prior hepatic events was found.

6.6. Data management

Analyses will be conducted using SAS Enterprise Guide v 7.15.

The analyses will follow the objectives and will be run in the databases indicated.

Indications and age groups were established on the date of the first ceftriaxone prescription.

6.7. Data analysis

- All of the analyses in the study were performed by the authors based on data available in IMS® Disease Analyzer Germany and IMS® Disease Analyzer France
- A descriptive analysis has been performed. The incidence rate of hepatic outcome events during a maximum of 30 days of follow-up after each ceftriaxone prescription has been calculated per 1000 person-years of follow-up in each subgroup and stratum. Only the first hepatic outcome event after start of ceftriaxone and the time until the first hepatic outcome event is considered.
- The analysis is based on complete data. No imputations have been performed in case of any missing data for age or gender.
- Separate results are presented for:
    - patients with prior liver disease
    - patients with other hepatic risk factors but no prior liver disease
    - patients without prior liver disease or other hepatic risk factors
- Results are also stratified by gender, age group at first ceftriaxone prescription (0-17 years, 18-49 years, 50-69 years and ≥70 years), indication at first ceftriaxone prescription (upper respiratory tract infection, lower respiratory tract infection, ear infection, urinary tract infection, genital infection, prostate infection, testicular infection, gastrointestinal infection, skin/soft tissue infection, bone infection, borrelia (Lyme disease), central nervous system infection, other infection), and total dose at first ceftriaxone prescription.
- The total dose has been calculated from the total amount in grams available in each unit of the product, the number of units available in the product, and the number of packages of the product prescribed. For patients with more than one ceftriaxone product on the first prescription date, the total dose is the sum of the individual doses for each product.
- In IMS® Disease Analyzer Germany results are separated by speciality.
- The mean total dose of ceftriaxone on the first prescription date in each of the databases is the basis for dividing patients into dose groups (above and below the mean total dose).

Note for data analysis using IMS® Disease Analyzer France: Provisions on data protection do not allow to provide single event numbers in case of low number of patients involved (n<20), but analysis could be executed to calculate incidence rates that can be provided without providing details on the exact number of patients contributing to the incidence rate.

6.8. Quality control

The code used for execution of the study will be saved.

6.9. Limitations of the research methods

It is anticipated that recording of hepatic events in the databases might be incomplete as the diagnosis of liver disease can be made in hospital or other specialised care settings and may not be recorded by the prescribing physician. In addition, only diagnosis codes can be used to ascertain events as no clinical causality assessment by the treating physician is available for the association between the drug treatment and the coded event.

Initial feasibility analyses indicate low event rates and therefore any results might be based on small event number with associated uncertainties.

In Germany the patient has free physician choice: in IMS® Disease Analyzer Germany patients can only be followed for as long as they continue to visit the same physician as patients are not identifiable across physician practices for confidentiality reasons. Furthermore, as the patient can visit several physicians concurrently, collected data may be incomplete. Data for the patient may also be incomplete in IMS® Disease Analyzer France as the patient is not required to register with a single physician and like IMS® Disease Analyzer Germany patients are not identifiable across physician practices.

6.10. Other aspects

n.a.

6.11. Additional sensitivity analyses carried out post-hoc

Sensitivity analysis has been performed considering longer follow-up of patients of 60 days, 90 days, 180 days and 365 days. This has been done for all ceftriaxone prescriptions and as a separate analysis also for the first ceftriaxone prescription.

7. Results

7.1. IMS® Disease Analyzer France

The number of patients that have received ceftriaxone and the number of patients with a hepatic outcome following treatment with ceftriaxone are not provided for confidentiality reasons (please see section 6.7). Due to low patient counts, only percentages are provided.

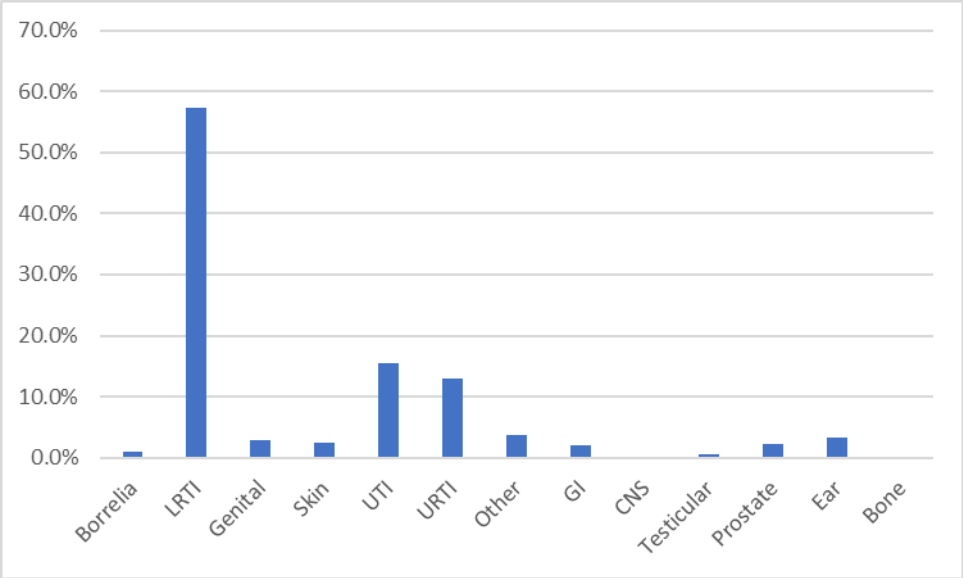
Age group and gender

There was a greater proportion of female compared to male patients that had received ceftriaxone, 58.3% vs. 41.7%. The highest proportion of ceftriaxone patients was seen in the age group ≥70 years (35.0%), decreasing to 33.8% in the age group 50-69 years, 25.0% in the age group 18-49 years and 6.0% in the age group 0-17 years.

Antibiotic treatment indications

Antibiotic treatment indications on the date of first initiation of treatment were identified in 70.9% of patients. The distribution of treatment indications, where known, is shown in Figure 1. In IMS® Disease Analyzer France ceftriaxone was mainly prescribed for respiratory tract infection and urinary tract infection.

Figure 1 Same-day infections recorded at first initiation of treatment with ceftriaxone



Borrelia = spirochaetal infections (including Lyme disease), LRTI = lower respiratory tract infection, Genital = genital infection, Skin = skin infection, UTI = urinary tract infection, URTI = upper respiratory tract infection, Other = other infection (please see list in Annex 2), GI = gastrointestinal infection, CNS = central nervous system infection, Testicular = testicular infection, Prostate = prostate infection, Ear = ear infection, Bone = bone infection.

Risk factors prior to ceftriaxone treatment initiation

Most patients had no recorded risk factor prior to ceftriaxone treatment initiation in IMS® Disease Analyzer France, see Table 1. Compared to females, males had a higher proportion of patients with a history of other risk factors. The proportion of patients with a history of other risk factors also increased with increasing age. The proportion of patients with a prior history of liver events was lowest in the youngest age group and highest in patients 50-69 years of age.

Table 1 The presence of risk factors prior to first treatment initiation with ceftriaxone by gender and age group

	%. of patients with no prior risk factor	% of patients with prior liver event (%)	% of patients with other risk factor but no prior liver event
All patients	94.6	1.2	4.2
Female	95.4	1.2	3.4
Male	93.4	1.2	5.5
0-17 years	99.6	0.2	0.1
18-49 years	97.9	1.3	0.9

	%. of patients with no prior risk factor	% of patients with prior liver event (%)	% of patients with other risk factor but no prior liver event
50-69 years	93.8	1.6	4.6
≥70 years	92.0	1.3	6.7

Hepatic outcome

Fewer than 20 patients had a hepatic outcome event within 30 days of a ceftriaxone prescription. The incidence rate of hepatic events occurring within 30 days of a ceftriaxone prescription, expressed as the number of hepatic outcome events per 1000 years of follow-up, by gender, age group and presence of risk factors prior to ceftriaxone treatment initiation, is shown in Table 2. The incidence rate by indication for treatment, for indications identified at start of ceftriaxone in at least 50 patients is shown in Table 3. The incidence rate stratified by a dose above or below the mean dose is shown in Table 4. The mean dose was 1.43 grams (standard deviation 1.38 grams). Patients with a dose of 2 or more grams were included in the high-dose category and patients with a dose below 2 grams were included in the low-dose category.

Although incidence rates were numerically higher in patients with prior liver events, there were no significant differences between patients with and patients without hepatic risk factors by gender or age group as all confidence intervals for incidence rates were overlapping.

However, patients starting ceftriaxone treatment for urinary tract infection had a higher incidence of hepatic outcome events compared to patients starting treatment for lower respiratory tract infection. Hepatic outcome events were only observed in patients starting ceftriaxone treatment for upper or lower respiratory tract infection and urinary tract infection, which were the most identified indications for ceftriaxone in IMS® Disease Analyzer France.

The incidence of hepatic outcome events did not differ by total prescribed dose of ceftriaxone on the first prescription date.

Sensitivity analysis considering longer follow-up periods showed decreasing incidence rates with increasing follow-up time, please see Figure 2. Results by existence or not of hepatic risk factors show that calculated incidence rates were only decreasing in patients with no history of hepatic risk factors. Confidence intervals are wide and cover similar ranges of incidence estimates, but observed rates tended to be higher during the 30-day follow-up period compared to a follow-up period of 365 days in patients with no hepatic risk factors. Results were similar when only the first ceftriaxone prescription was considered.

Table 2 Incidence rate[1] (95% CI) of hepatic outcome events within 1-30 days after a ceftriaxone prescription by gender, age group and presence of risk factors prior to first treatment initiation with ceftriaxone

	All patients	Patients with no prior risk factor	Patients with prior liver event	Patients with other risk factor but no prior liver event
Total	7.8 (3.9-14.0)	6.8 (3.1-12.9)	56.8 (1.4-317)	15.9 (0.4-88.7)
Females	7.3 (2.7-15.8)	7.7 (2.8-16.7)	0.0 (0.0-332)	0.0 (0.0-126)
Males	8.6 (2.8-20.1)	5.6 (1.1-16.2)	154 (3.9-860)	29.8 (0.8-166)
0-17 y	0.0 (0.0-46.1)	0.0 (0.0-46.2)	0.0 (0.0-44882)	0.0 (0.0-44882)
18-49 y	11.7 (3.2-29.9)	11.9 (3.3-30.6)	0.0 (0.0-1364)	0.0 (0.0-870)
50-69 y	8.0 (2.2-20.6)	8.6 (2.3-22.1)	0.0 (0.0-443)	0.0 (0.0-150)
≥70 y	6.2 (1.3-18.2)	2.3 (0.1-12.6)	154 (3.9-861)	29.6 (0.7-165)

CI = confidence interval, y = years.
[1] Per thousand person-years.

Table 3 Incidence rate[1] (95% CI) of hepatic outcome events within 1-30 days after a ceftriaxone prescription by treatment indication at first initiation of treatment

	All patients	Patients with no prior risk factor	Patients with prior liver event	Patients with other risk factor but no prior liver event
LRTI	1.6 (0.0-9.2)	0.0 (0.0-6.5)	0.0 (0.0-396)	32.6 (0.8-182)
UTI	43.4 (15.9-94.5)	38.9 (12.6-90.8)	621 (15.7-3459)	0.0 (0.0-459)
URTI	14.0 (1.7-50.5)	7.2 (0.2-40.4)	0.0 (0.0-4444)	239 (6.0-1329)
Other	0.0 (0.0-108)	0.0 (0.0-119)	0.0 (0.0-11220)	0.0 (0.0-1359)
Ear	0.0 (0.0-124)	0.0 (0.0-126)	0.0 (0.0-8976)	0.0 (0.0-44882)
Genital	0.0 (0.0-153)	0.0 (0.0-157)	0.0 (0.0-22441)	0.0 (0.0-7480)
Skin	0.0 (0.0-151)	0.0 (0.0-157)	0.0 (0.0-38470)	0.0 (0.0-4234)
Prostate	0.0 (0.0-196)	0.0 (0.0-208)	0.0 (0.0-11220)	0.0 (0.0-5100)
GI	0.0 (0.0-192)	0.0 (0.0-202)	0.0 (0.0-6412)	0.0 (0.0-11220)
Borrelia	0.0 (0.0-375)	0.0 (0.0-383)	0.0 (0.0-26401)	0.0 (0.0-44882)
Testicular	0.0 (0.0-777)	0.0 (0.0-805)	0.0 (0.0-44882)	0.0 (0.0-44882)

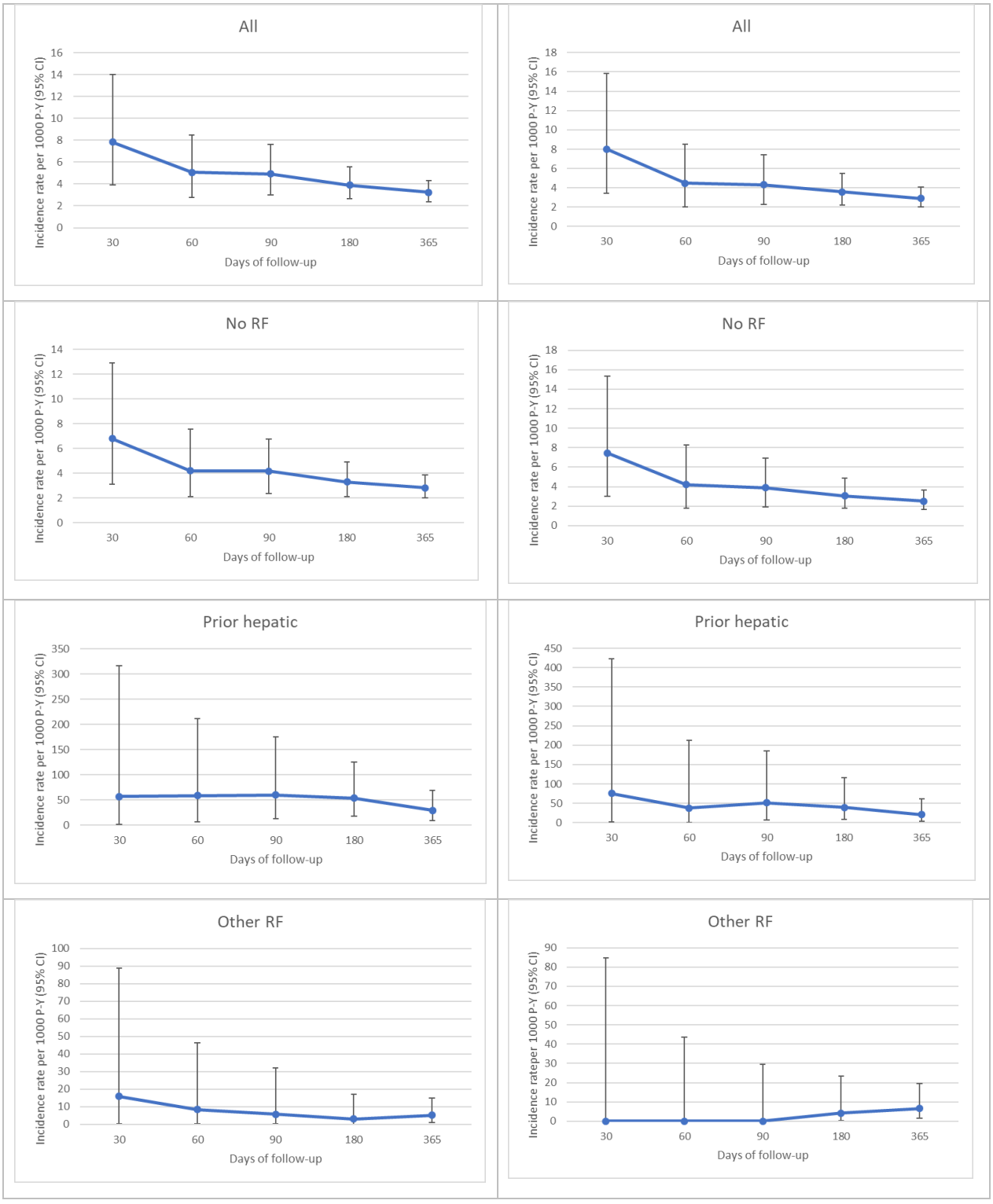
CI = confidence interval, LRTI = lower respiratory tract infection, UTI = urinary tract infection, URTI = upper respiratory tract infection, Other = other infection (please see list in Annex 2), Ear = ear infection, Genital = genital infection, Skin = skin infection, Prostate = prostate infection, GI = gastrointestinal infection, Borrelia = spirochaetal infections (including Lyme disease), Testicular = testicular infection.
[1] Per thousand person-years.

Table 4 Incidence rate[1] (95% CI) of hepatic outcome events within 1-30 days after a ceftriaxone prescription by total ceftriaxone dose on the first prescription date (<2 gram, ≥2 gram)

	All patients	Patients with no prior risk factor	Patients with prior liver event	Patients with other risk factor but no prior liver event
Dose <2 g	10.0 (4.3-19.6)	9.2 (3.7-18.9)	103 (2.6-575)	0.0 (0.0-117)
Dose ≥2 g	5.0 (1.0-14.6)	3.6 (0.4-12.9)	0.0 (0.0-467)	32.0 (0.8-178)

CI = confidence interval, g = grams, y = years.
[1] Per thousand person-years.

Figure 2 Incidence rates of hepatic events per 1000 patient-years of follow-up for increasing number of days of follow-up (All = all patients, No RF = patients with no hepatic risk factors, Prior hepatic = patients with prior hepatic events, Other RF = patients with other prior risk factors). Left figures = all ceftriaxone prescriptions, Right figures = first ceftriaxone prescription



7.2. IMS® Disease Analyzer Germany

Age group and gender

A total of 3264 patients had at least 365 days of observation at the time of the first ceftriaxone prescription. The percentage of ceftriaxone patients by speciality is shown in Figure 2. The distribution of gender across specialities is shown in Table 5 and the distribution of age group at first initiation of treatment across specialities is shown in Table 6. As expected, patients in gynaecologist practices are predominantly female and patients in urologist practices are predominantly male. Otherwise, except for psychiatry practices and ear- nose and throat (ENT) practices, the percentage of male patients is numerically higher. Except for paediatric practices most patients are identified in the age groups 18-49 and 50-69 years.

Figure 3 Percentage of ceftriaxone patients by speciality

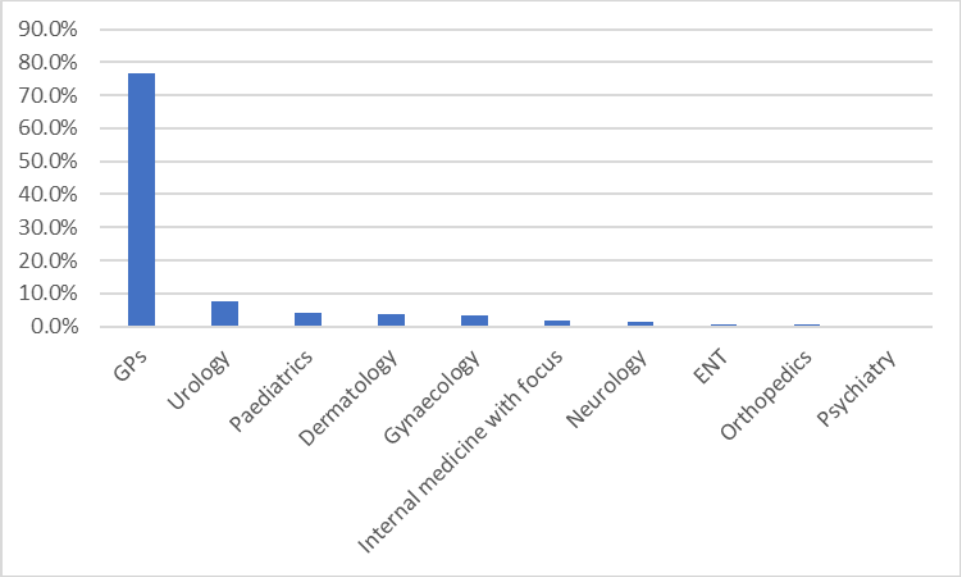


Table 5 Gender of ceftriaxone patients by speciality

Type of practice	All patients	Female (%)	Male (%)
All specialities	3264	1373 (42.1)	1884 (57.7)
GPs	2504	1086 (43.4)	1412 (56.4)
Urology	243	15 (6.2)	227 (93.4)
Paediatrics	134	53 (39.6)	81 (60.4)
Dermatology	119	38 (31.9)	81 (68.1)
Gynaecology	112	109 (97.3)	3 (2.7)
Internal medicine with focus	63	30 (47.6)	33 (52.4)
Neurology	50	24 (48.0)	26 (52.0)
ENT	20	10 (50.0)	10 (50.0)
Orthopedics	17	6 (35.3)	11 (64.7)
Psychiatry	2	2 (100.0)	0 (0.0)

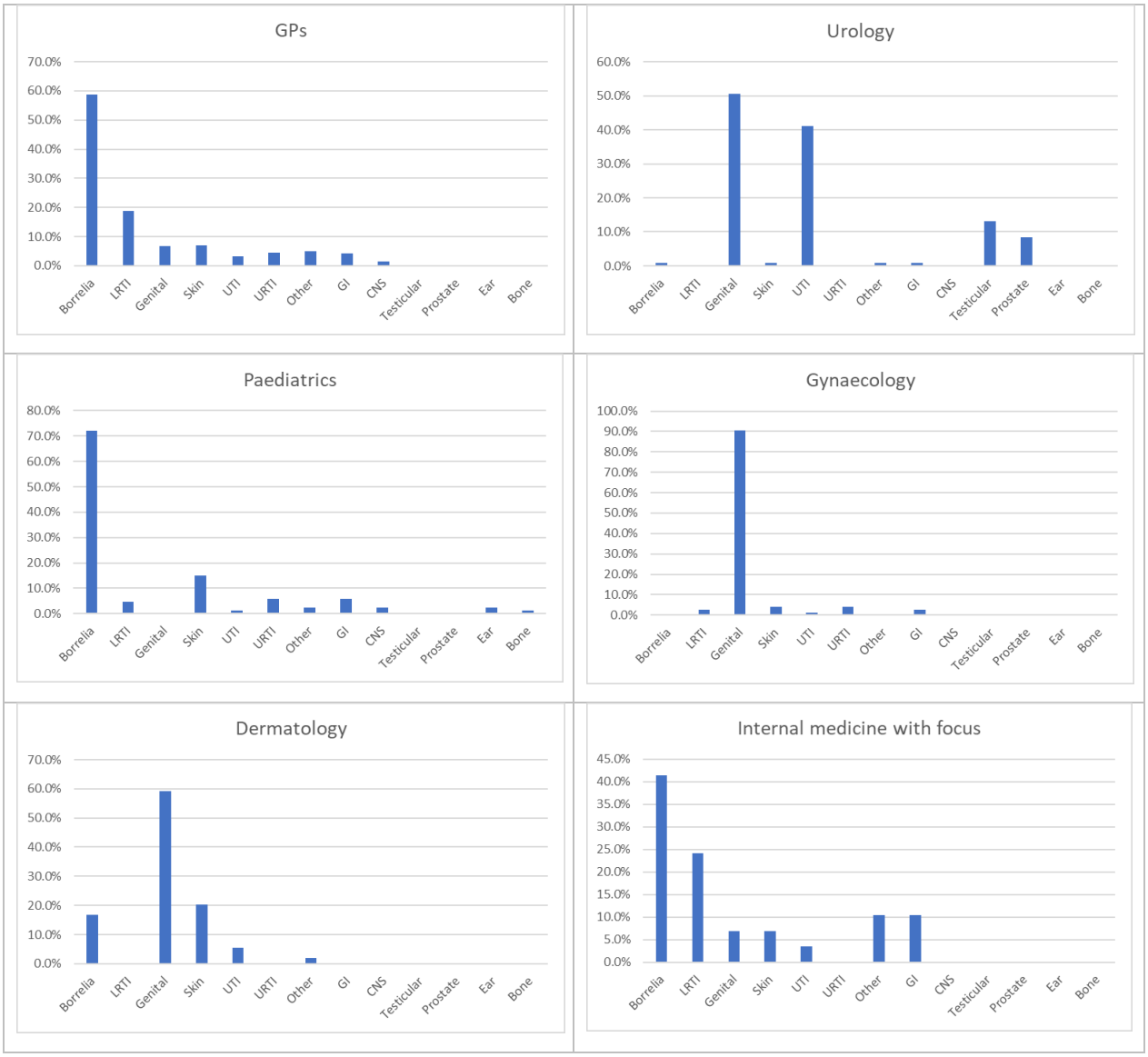
Table 6 Age groups of ceftriaxone patients at first initiation of treatment by speciality

Speciality	All patients	0-17 y (%)	18-49 y (%)	50-69 y (%)	≥ 70 y (%)
All specialities	3264	220 (6.7)	1076 (33.0)	1161 (35.6)	721 (22.1)
GPs	2504	78 (3.1)	780 (31.2)	942 (37.6)	635 (25.4)
Urology	243	1 (0.4)	110 (45.3)	83 (34.2)	41 (16.9)
Paediatrics	134	126 (94.0)	2 (1.5)	1 (0.7)	0 (0.0)
Dermatology	119	2 (1.7)	43 (36.1)	50 (42.0)	23 (19.3)
Gynaecology	112	6 (5.4)	91 (81.3)	15 (13.4)	0 (0.0)
Internal medicine with focus	63	2 (3.2)	13 (20.6)	32 (50.9)	14 (22.2)
Neurology	50	3 (6.0)	21 (42.0)	24 (48.0)	2 (4.0)
ENT	20	0 (0.0)	11 (55.0)	6 (30.0)	2 (10.0)
Orthopedics	17	2 (11.8)	4 (23.5)	7 (41.2)	4 (23.5)
Psychiatry	2	0 (0.0)	1 (50.0)	1 (50.0)	0 (0.0)

Antibiotic treatment indications

Antibiotic treatment indications on the date of first initiation of treatment were identified in 1930 patients (59.1%). A same-day treatment indication was identified in 60% or more of patients in gynaecologist practices (67.0%, n=75), paediatric practices (64.2%, n=86), GP practices (61.5%, n=1540) and ENT practices (60.0%, n=12). In the remaining practices fewer than 50% of patients had an identified same-day treatment indication: 46.0% (Internal medicine with focus, n=29), 45.4% (Dermatology, n=54), 44.0% (Urology, n=107), 41.2% (Orthopedics, n=7), 40.0% (Neurology, n=20) and 0.0% (Psychiatry). Treatment indications vary by speciality, please see Figure 3, which includes those specialities where more than 20 patients have a recorded same-day treatment indication. Spirochaetes (borrelia) is the most frequently identified infection in GP practices, paediatric practices and Internal medicine with focus practices, whereas genital infection is the most frequently identified infection in urologist practices, gynaecology practices and dermatology practices.

Figure 4 Same-day infections recorded at first initiation of treatment with ceftriaxone in practices where a same-day infection was recorded in >20 patients



Borrelia = spirochaetal infections (including Lyme disease), LRTI = lower respiratory tract infection, Genital = genital infection, Skin = skin infection, UTI = urinary tract infection, URTI = upper respiratory tract infection, Other = other infection (please see list in Annex 2), GI = gastrointestinal infection, CNS = central nervous system infection, Testicular = testicular infection, Prostate = prostate infection, Ear = ear infection, Bone = bone infection.

Risk factors prior to ceftriaxone treatment initiation

The presence of risk factors prior to treatment initiation by type of practice is shown in Table 7 below. No prior risk factor is identified in most patients. A prior liver event is more frequently recorded in GP practices compared to the other specialities.

The presence of risk factors prior to treatment initiation by gender and age group is shown in Table 8. The frequency of risk factors was slightly higher in male compared to female patients and increased with increasing age. A prior hepatic event was, however, most frequent in the age group 50 to 69 years.

Table 7 The presence of risk factors prior to first treatment initiation with ceftriaxone by speciality

Speciality	No. with no prior risk factor	%	No. with prior liver event	%	No. with other risk factor but no prior liver event	%
All specialities	2525	77.4%	330	10.1%	409	12.5%
GPs	1857	74.2%	323	12.9%	324	12.9%
Urology	198	81.5%	1	0.4%	44	18.1%
Paediatrics	132	98.5%	0	0.0%	2	1.5%
Dermatology	100	84.0%	0	0.0%	19	16.0%
Gynaecology	106	94.6%	1	0.9%	5	4.5%
Internal medicine with focus	52	82.5%	4	6.3%	7	11.1%
Neurology	43	86.0%	1	2.0%	6	12.0%
ENT	19	95.0%	0	0.0%	1	5.0%
Orthopedics	17	100.0%	0	0.0%	0	0.0%
Psychiatry	1	50.0%	0	0.0%	1	50.0%

Table 8 The presence of risk factors prior to first treatment initiation with ceftriaxone by gender and age group

	Total no. of patients	No. of patients with no prior risk factor (%)	No. of patients with prior liver event (%)	No. with other risk factor but no prior liver event (%)
All patients	3264	2525 (77.4)	330 (10.1)	409 (12.5)
Female	1373	1100 (80.1)	125 (9.1)	148 (10.8)
Male	1884	1418 (75.3)	205 (10.9)	261 (13.9)
0-17 years	220	211 (95.9)	3 (1.4)	6 (2.7)
18-49 years	1076	927 (86.2)	70 (6.5)	79 (7.3)
50-69 years	1161	845 (72.8)	161 (13.9)	155 (13.4)
≥70 years	721	469 (65.0)	91 (12.6)	161 (22.3)

Hepatic outcome

Patients with a hepatic outcome within 30 days after a ceftriaxone prescription were only recorded in GP practices. For this reason, only GP practices have been included in the calculation of the incidence of a hepatic outcome event. A total of 18 patients had a first hepatic outcome event after ceftriaxone treatment initiation and within 30 days of a ceftriaxone prescription. The incidence rate of hepatic events occurring within 30 days of a ceftriaxone prescription, expressed as the number of hepatic outcome events per 1000 years of follow-up, by gender, age group and presence of risk factors prior to ceftriaxone treatment initiation, is shown in Table 9. The incidence rate by indication for treatment, for indications identified at start of ceftriaxone in at least 50 patients is shown in Table 10. The incidence rate stratified by a dose above or below the mean dose is shown in Table 11. The mean dose was 12.28 grams (standard deviation 9.66 grams). Patients with a dose of 13 or more grams were included in the high-dose category and patients with a dose below 13 grams were included in the low-dose category.

Compared to patients with no prior risk factor, patients with a history of liver events had a higher incidence rate of hepatic outcome events, whereas the incidence rate in patients with other risk factors did not differ significantly from patients with no history of risk factors or from patients with a history of liver events. Results were also overlapping between female and male patients as well as between different age groups, treatment indications, and doses, but it should be noted that individual groups included in these comparisons were small resulting in wide confidence limits around estimated incidence rates.

Sensitivity analysis considering longer follow-up periods showed decreasing incidence rates with increasing follow-up time, please see Figure 5. Results by existence or not of hepatic risk factors show that estimated incidence rates were only decreasing in patients with no history of hepatic risk factors. Confidence intervals were covering the same range of point estimates, but estimated point estimates for the rates were higher during the 30-day follow-up period compared to a follow-up period of 365 days in patients with no hepatic risk factors. Results were similar when only the first ceftriaxone prescription was considered.

Table 9 Incidence of hepatic outcome events within 1-30 days after a ceftriaxone prescription by gender, age group and presence of risk factors prior to first treatment initiation with ceftriaxone in GP practices[1]

Patients in GP practices with hepatic outcomes	All patients	Patients with no prior risk factor	Patients with prior liver event	Patients with other risk factor but no prior liver event
Total HO (n)	18	7	8	3
IR (95% CI) [1]	70.6 (41.8-112)	37.0 (14.9-76.3)	247 (107-488)	89.3 (18.4-261)
Female HO (n)	7	3	2	2
IR (95% CI) [1]	63.1 (25.4-130)	35.4 (7.3-103)	158 (19.1-570)	148 (18.0-536)
Male HO (n)	11	4	6	1
IR (95% CI) [1]	76.7 (38.3-137)	38.6 (10.5-98.9)	305 (112-665)	49.7 (1.3-277)
HO 0-17 y (n)	0	0	0	0
IR (95% CI) [1]	0.0 (0.0-558)	0.0 (0.0-601)	0.0 (0.0-14961)	0.0 (0.0-16831)
HO 18-49 y (n)	3	2	1	0
IR (95% CI) [1]	38.8 (8.0-113)	30.9 (3.7-111)	152 (3.8-845)	0.0 (0.0-626)
HO 50-69 y (n)	7	3	3	1
IR (95% CI) [1]	69.2 (27.8-143)	41.8 (8.6-122)	190 (39.1-554)	73.7 (1.9-410)
HO ≥70 y (n)	8	2	4	2
IR (95% CI) [1]	124 (53.4-244)	47.7 (5.8-172)	427 (116-1092)	149 (18.0-538)

CI = confidence interval, HO = hepatic outcome patients, IR = incidence rate, n = number, y = years.
[1] Per thousand person-years.

Table 10 Incidence of hepatic outcome events within 1-30 days after a ceftriaxone prescription by treatment indication at first initiation of treatment[1]

Patients in GP practices with hepatic outcomes by treatment indication	All patients	Patients with no prior risk factor	Patients with prior liver event	Patients with other risk factor but no prior liver event
HO Borrelia (n)	5	3	0	2
IR (95% CI) [1]	53.4 (17.3-125)	40.6 (8.4-119)	0.0 (0.0-301)	269 (32.6-973)
HO LRTI (n)	0	0	0	0
IR (95% CI) [1]	0.0 (0.0-130)	0.0 (0.0-183)	0.0 (0.0-1163)	0.0 (0.0-715)
HO Genital (n)	1	0	1	0
IR (95% CI) [1]	107 (2.7-594)	0.0 (0.0-830)	749 (19.0-4176)	0.0 (0.0-1024)
HO Skin (n)	1	1	0	0
IR (95% CI) [1]	92.0 (2.3-512)	122 (3.1-677)	0.0 (0.0-3562)	0.0 (0.0-2290)
HO UTI (n)	0	0	0	0
IR (95% CI) [1]	0.0 (0.0-671)	0.0 (0.0-954)	0.0 (0.0-5343)	0.0 (0.0-3914)
HO URTI (n)	0	0	0	0
IR (95% CI) [1]	0.0 (0.0-522)	0.0 (0.0-605)	0.0 (0.0-14961)	0.0 (0.0-5159)
HO Other (n)	0	0	0	0
IR (95% CI) [1]	0.0 (0.0-494)	0.0 (0.0-714)	0.0 (0.0-3067)	0.0 (0.0-3366)
HO GI (n)	2	1	1	0
IR (95% CI) [1]	232 (28.1-839)	221 (5.6-1233)	412 (10.4-2298)	0.0 (0.0-2207)

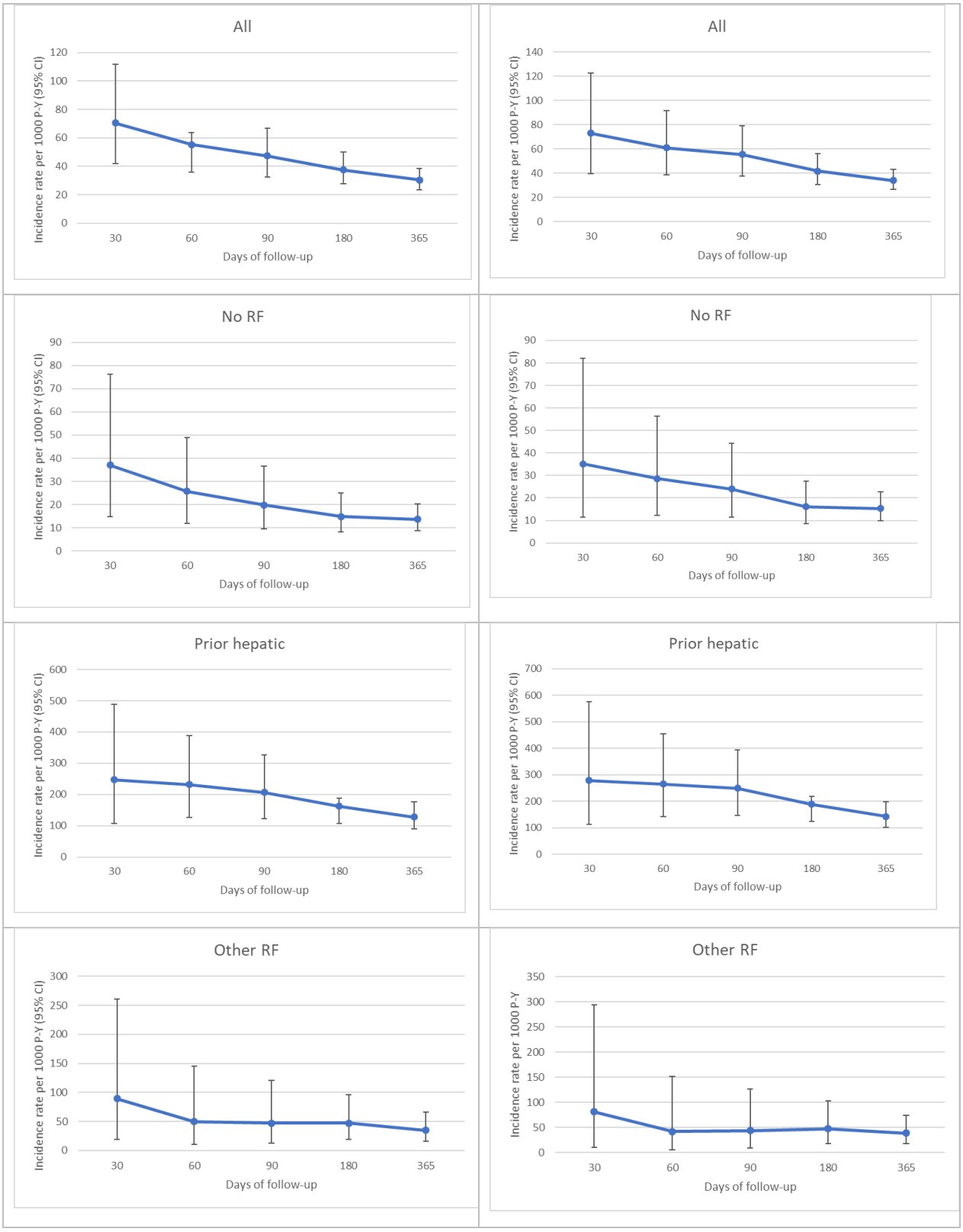
CI = confidence interval, HO = hepatic outcome patients, IR = incidence rate, n = patients.
Borrelia = spirochaetal infections (including Lyme disease), LRTI = lower respiratory tract infection, Genital = genital infection, Skin = skin infection, UTI = urinary tract infection, URTI = upper respiratory tract infection, Other = other infection (please see list), GI = gastrointestinal infection, CNS = central nervous system infection, Testicular = testicular infection, Prostate = prostate infection, Ear = ear infection, Bone = bone infection.
[1] Per thousand person-years.

Table 11 Incidence rate[1] (95% CI) of hepatic outcome events within 1-30 days after a ceftriaxone prescription by total ceftriaxone dose on the first prescription date (<13 gram, ≥13 gram)

Patients in GP practices with hepatic outcomes	All patients	Patients with no prior risk factor	Patients with prior liver event	Patients with other risk factor but no prior liver event
HO Dose ≥13 grams (n)	13	6	5	2
IR (95% CI) [1]	86.1 (45.8-147)	52.3 (19.2-114)	278 (90.2-649)	98.6 (30.5-432)
HO Dose <13 grams (n)	5	1	3	1
IR (95% CI) [1]	48.0 (15.6-112)	13.4 (0.3-74.8)	209 (43.2-612)	48.9 (1.2-272)

CI = confidence interval, HO = hepatic outcome patients, IR = incidence rate, n = number.
[1] Per thousand person-years.

Figure 5 Incidence rates of hepatic events per 1000 patient-years of follow-up for increasing number of days of follow-up (All = all patients, No RF = patients with no hepatic risk factors, Prior hepatic = patients with prior hepatic events, Other RF = patients with other prior risk factors). Left figures = all ceftriaxone prescriptions, Right figures = first ceftriaxone prescription



8. Discussion of results

8.1. Key results

In IMS® Disease Analyzer France, ceftriaxone was mainly prescribed for respiratory tract infection and urinary tract infection whereas in GP practices in IMS® Disease Analyzer Germany it was mainly prescribed for borrelia infection and lower respiratory tract infection. This might influence the total dose prescribed, which is expected to be higher for borreliosis. In line with this, the dose in IMS® Disease Analyzer Germany was higher than in IMS® Disease Analyzer France, although it is also possible that the number of packs has been underestimated in IMS® Disease Analyzer France due to the possibility that refills might not be recorded.

A higher percentage of patients in IMS® Disease Analyzer France (94.6%) compared to GP patients in IMS® Disease Analyzer Germany (74.2%) had no prior history of liver events or other risk factors. This difference is also reflected in the incidence rates for hepatic outcomes, which were higher in IMS® Disease Analyzer Germany (70.6 events per 1000 person-years, 95% confidence interval 41.8-112 events per 1000 person-years) compared to IMS® Disease Analyzer France (7.8 events per 1000 person-years, 95% confidence interval 3.9-14.0 events per 1000 person-years). In IMS® Disease Analyzer France, based on patients with no prior risk factor, there was some evidence that patients treated for urinary tract infection had a higher incidence of hepatic outcomes compared to patients treated for lower respiratory tract infection, whereas in IMS® Disease Analyzer Germany no differences in incidence rates for hepatic outcomes could be identified between indications. However, a higher percentage of ceftriaxone patients in IMS® Disease Analyzer France compared to GP patients in IMS® Disease Analyzer Germany (70.9% vs. 61.5%) had a same-day indication recorded on the first ceftriaxone prescription date, and it can also be noted that only around half of patients with hepatic outcome events in IMS® Disease Analyzer Germany had same-day indication diagnosis recorded on the first ceftriaxone prescription date.

No significant differences in incidence rates for hepatic outcomes were observed between genders or age groups. IMS® Disease Analyzer France incidence rates for hepatic outcomes were also not significantly different between patients with and patients without risk factors for hepatic events, whereas in IMS® Disease Analyzer Germany patients with a prior history of liver events had a higher incidence rate of hepatic outcome events compared with patients with no prior risk factor.

There were also no significant differences in incidence rates for hepatic outcomes between higher and lower doses, which does not support a dose-dependent reaction, although the possibility that doses may not be accurately recorded in the database needs to be considered.

Published incidence rates of drug-induced liver injury in the West vary from around 2.3-2.4 to 14-19 per 100,000 person-years [4]. However, there are many causes of liver disease, and it is difficult to find published estimates for incident liver disease from any cause. According to British Liver Trust, 90% of liver disease in the UK is due to alcohol, obesity and viral hepatitis [5].

This study provides descriptive incidence rates for hepatic outcome events during 30 days of follow-up after the ceftriaxone prescription in patients with a first prescription for ceftriaxone by prior history of risk factors for liver disease. These incidence rates include all patients with the respective hepatic outcome events and are not restricted to cases with suspected drug-induced liver injury. The rates are higher than published incidence rates of drug-induced liver injury, but it is unknown whether they are higher than expected considering all possible aetiologies for the events. When patients are followed up for a longer time period than the initial 30 days after the ceftriaxone prescription, rates decrease in patients with no history of risk factors for hepatic events. It should, however, be taken into account that liver injury can be associated with infection, i.e. the indication for treatment with ceftriaxone, as

for example in Lyme disease [6-9], or in case of cholecystitis or cholangitis, or there can be an indirect association between the infection and an increased risk of liver injury.

A large proportion of patients in Germany received ceftriaxone for treatment of borrelia infection, which might itself as disease be a risk factor for experiencing hepatic events. Therefore, confounding by indication is likely to be present in this study. Confounding by indication may be present to a greater extent in Germany, where a higher proportion of prescriptions seem to be related to treatment of Borreliosis, as compared to France, where most patients were treated for respiratory tract infection and urinary tract infection. The incidence rate of hepatic events in patients with an indication of borrelia at the time of the first ceftriaxone prescription was similar compared to the overall incidence of hepatic events where borrelia was the main indication. Also, the recommended ceftriaxone dose is higher for borrelia compared to other indications, which might influence results, although incidence rates were not significantly higher in high-dose patients compared to low-dose patients.

The results pertaining to this study are based on low numbers of events and do not allow for a firm interpretation of results and it should be noted that derived confidence intervals are wide.

As expected, the incidence rate of hepatic events was highest in patients that already had a prior hepatic event.

A comparative study was not undertaken due to difficulty identifying a comparator that has similar indications and method of administration and due to a low number of hepatic outcome events for ceftriaxone that result in incidence rates with wide confidence intervals.

The provided results are purely descriptive and have not been adjusted for confounding factors, which needs to be taken into account when the results are interpreted.

Due to the limitations, the results cannot provide firm information about a possible causal relationship between exposure with ceftriaxone and hepatic outcomes.

8.2. Strengths

Patients were required to have an observation period of 365 days prior to their first ceftriaxone prescription. All patients therefore had a minimum of 365 days during which baseline risk factors could be identified. In the main analysis patients were only observed for up to 30 days after each ceftriaxone prescription. The study was therefore limited to active care-seeking patients in active practices, which increases the likelihood that the patient was still under the care of the prescribing physician during the entire follow-up period, increasing the likelihood of observing and recording any events that occur.

8.3. Limitations

It is anticipated that recording of hepatic events in the databases might be incomplete as the diagnosis of liver disease can be made in hospital or other specialised care settings and may not be recorded by the prescribing physician. In addition, only diagnosis codes can be used to ascertain events as no clinical causality assessment by the treating physician is available for the association between the drug treatment and the coded event. No separate information on laboratory data has been analysed in this study to confirm coded events for hepatic outcomes.

The results are based on low event counts with associated uncertainties.

In Germany the patient has free physician choice: in IMS® Disease Analyzer Germany patients can only be followed for as long as they continue to visit the same physician as patients are not identifiable

across physician practices for confidentiality reasons. Furthermore, as the patient can visit several physicians concurrently, collected data may be incomplete. Data for the patient may also be incomplete in IMS® Disease Analyzer France as the patient is not required to register with a single physician and like IMS® Disease Analyzer Germany patients are not identifiable across physician practices.

Results derived from Germany, indicate that prior hepatic events were recorded in a higher percentage of patients visiting a GP than other specialities. The lack of recorded hepatic events for patients treated in the non-GP setting in Germany might be related to under-ascertainment of risk factors as these might be rather recorded in the GP setting and not by treated specialists. Information on prior risk factors for patients not treated by GPs might therefore be incomplete and incidence rates have also only been calculated for patients visiting GPs in the German database.

8.4. Main Summary and Conclusions

Main Summary

This is a descriptive cohort study on the occurrence of hepatic events in incident ceftriaxone users from Germany and France based on electronic health records from IMS® Disease Analyzer Germany and IMS® Disease Analyzer France. Patients with a minimum observation time of 365 days prior to the first recorded prescription of ceftriaxone were included and followed up until their first hepatic outcome event as defined by selected ICD 10 codes for hepatotoxic events (K71, K72, K75.2, K75.3, K75.8-K75.9, K76.8-K76.9).

In the French database, the majority of patients received ceftriaxone for respiratory tract infections followed by urinary tract infections. A percentage of 1.2% of patients are recorded with prior liver events and 4.2% are recorded with other hepatic risk factors at the time of prescriptions. Overall, fewer than 20 patients had a hepatic outcome recorded within 30 days after prescription, resulting in an incidence of hepatic events in 7.8 (95% CI 3.9-14.0) per 1000 patient-years (PY) overall, 6.8 (95% CI 3.1-12.9) per 1000 PY in patients with no prior risk factors and 56.8 (1.4-317) per 1000 PY in patients with prior liver events.

In Germany, the majority of patients (2504 of a total of 3264) were treated by GPs. In these, the most frequently documented diagnosis was treatment for borreliosis. Most patients receiving ceftriaxone had no documented risk factors for hepatic events and 12.9% had a recorded prior liver event. For patients treated by a GP, a total of 18 patients had a recorded hepatic outcome within 30 days after ceftriaxone treatment initiation resulting in an incidence rate of 70.6 (95% CI 41.8-112) events per 1000 PY overall, 37.0 (95% CI 14.9-76.3) events per 1000 PY in patients with nor prior risk factors and 247 events (95% CI 107-488) per 1000 PY in patients with prior liver events.

Analysis of the incidence rates 30, 60, 90, 180 and 365 days after first prescription of ceftriaxone overall show slightly higher incidence rates in the first 30 days after prescription in both databases. No significant differences in incidence rates for hepatic outcomes were observed between genders or age groups or between higher and lower doses, although the doses might not have been recorded correctly. As expected, the incidence rate of hepatic events was highest in patients that already had a prior hepatic event.

All analyses are based on small event numbers and therefore need to be interpreted with caution. Derived confidence intervals are generally wide because of the low numbers of events. Confounding by

indication cannot be excluded, in particular for the setting of Germany, where the majority of prescriptions was recorded in the setting of borreliosis.

Conclusion

This descriptive cohort study showed that hepatic events are recorded after prescription of ceftriaxone in the ambulatory setting in Germany and France and that the incidence of recorded events tends to be higher in patients with prior hepatic events. Treatment patterns with ceftriaxone seem to be country-specific with the majority of recorded indications being related to respiratory tract infections in France and to borreliosis in Germany. Confounding by indication cannot be excluded, especially for treatment of borreliosis. Overall, this descriptive analysis is based on a very limited number of events and needs to be interpreted carefully.

9. References

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10. Annexes

- Annex 1.: list of ceftriaxone products
- Annex 2.: List of ICD 10 codes for different types of infection (antibiotic indications).

Annex 2 List of ceftriaxone products

IMS® Disease Analyzer France

Therapy number	Therapy name
FR11791	CEFTRIAXONE EGN PDR IM+LIDO 3.5ML 1000MG 1
FR11837	CEFTRIAXONE IREX PDR IM+LIDO 3.5ML 1000MG 1
FR11975	CEFTRIAXONE MYLAN PDR IM+LIDO 3.5ML 1000MG 1
FR11976	CEFTRIAXONE MYLAN PDR INJ+SOLV 10ML 1000MG 1
FR12030	CEFTRIAXONE TEVA PDR IM+LIDO 3.5ML 1000MG 1
FR12041	CEFTRIAXONE DCI PDR IM+LIDO 2ML 500MG 1
FR12042	CEFTRIAXONE DCI PDR IM+LIDO 3.5ML 1000MG 1
FR12043	CEFTRIAXONE DCI PDR IV+SOLV 5ML 500MG 1
FR12044	CEFTRIAXONE DCI PDR IV+SOLV 10ML 1000MG 1
FR12950	CEFTRIAXONE ARROW PDR IM+LIDO 3.5ML 1000MG 1
FR12952	CEFTRIAXONE ARROW PDR IM+LIDO 2ML 500MG 1
FR13026	CEFTRIAXONE AGUETT PDR IM+LIDO 3.5ML 1000MG 1
FR13027	CEFTRIAXONE AGUETT PDR IV+SOLV 10ML 1000MG 1
FR14213	CEFTRIAXONE RATIO. PDR IM+LIDO 3.5ML 1000MG 1
FR14537	CEFTRIAXONE BIOG. PDR IM+LIDO 3.5ML 1000MG 1
FR14538	CEFTRIAXONE BIOG. PDR IV+SOLV 10ML 1000MG 1
FR15750	TRIACEFAN PDR IM+LIDO 3.5ML 1000MG 1
FR19990	CEFTRIAXONE ACTAVI PDR IV+SOLV 10ML 1000MG 1
FR19991	CEFTRIAXONE ACTAVI PDR IM+LIDO 3.5ML 1000MG 1
FR25703	ROCEPHINE PDR IM+LIDO 2ML 500MG 1
FR25704	ROCEPHINE PDR IV+SOLV 5ML 500MG 1
FR25705	ROCEPHINE PDR IM+LIDO 3.5ML 1000MG 1
FR25706	ROCEPHINE PDR IV+SOLV 10ML 1000MG 1
FR30667	CEFTRIAXONE ALMUS PDR IM+LIDO 3.5ML 1000MG 1

IMS® Disease Analyzer Germany

Therapy number	Therapy name
GE10141188	CEFTRIAXON STRAGEN TROCK SUBST 500MG 10 (N3)
GE10150868	CEFTRIAXON FK2 INF FL 2G 7 (N2)
GE10216709	CEFTRIAXON-GRY TROCK SUBST 500MG (N1)
GE10235465	ROCEPHIN KHP>> INF OHNE LSG 2G (N1)
GE10302396	CEFTRIAXON FK2 INJ FL 1G 5 (N2)
GE10311974	CEFTRIAXON FK2 INF FL 2G 5 (N2)
GE10613030	CEFTRIAXON-SAAR DURCHSTECHFL 2G 7 (N2)
GE1064942	ROCEPHIN INF OHNE LSG 2G
GE10677544	CEFTRIAXON-SAAR INF TRO.SUB. 2G (N1)
GE10818075	CEFTRIAXON-SAAR INF TRO.SUB. 2G 10 (N3)
GE10880332	CEFTRIAXON-SAAR INF TRO.SUB. 2G 7 (N2)
GE10908270	CEFTRIAXON-RATIOPH TROCK SUBST .5G 10 (N3)
GE11093738	CEFTRIAXON ATV(DM+ INJ FL TROCK 1G 10 (N3)
GE11201143	ROCEPHIN E-M>> INF MIT LSG 2G 7 40ML (N2)
GE1127728	CEFTRIAXON AZU TROCK SUBST 2G (N1)
GE11328933	ROCEPHIN TRO.SUB.+LSG 500MG 5 (N2)
GE12760746	ROCEPHIN E-M>> INF MIT LSG 2G 40ML (N1)
GE1313140	CEFTRIAXON SANDOZ TROCK SUBST 1G (N1)
GE13253953	CEFTRIAXON-SAAR INF TRO.SUB. 1G 10 (N3)
GE13500767	ROCEPHIN E-M>> INF OHNE LSG 2G 7 (N2)
GE1351021	ROCEPHINE BRA>> INJ IV +LSG 1G 5 10ML (N2)
GE13524513	ROCEPHIN E-M>> INF OHNE LSG 2G (N1)
GE13997390	CEFTRIAXON-PHARMO. TRO.SUBS.KVA 1G 5
GE1422249	ROCEPHINE MTK>> INJ IV +LSG 1G 5 10ML (N2)
GE14234901	ROCEPHIN INF TRO.SUB. 2G (N1)
GE14234920	CEFTRIAXON EBERTH INF TR.S+LSG 2G 10 (N3)
GE14304454	CEFTRIAXON EBERTH INF TR.S+LSG 2G 7 (N2)
GE144051	ROCEPHIN E-M>> INF OHNE LSG 2G ALT (N1)
GE14468028	CEFTRIAXON EBERTH INF TR.S+LSG 2G (N1)
GE14611515	CEFTRIAXON EBERTH INF TROC.KVA 2G 10
GE1485616	ROCEPHIN E-M>> INF OHNE LSG 2G ALT 7 (N2)
GE14913969	CEFTRIAXON EBERTH INJ TRO.SUB. 1G 10 (N3)
GE1519894	ROCEPHIN E-M>> INJ IV +LSG 1G 5 10ML (N2)
GE15608459	CEFTRIAXON DEVATIS TROCK SUBST 1G 5 (N2)
GE15677091	CEFTRIAXON DEVATIS TROCK SUBST .5G 5 (N2)
GE15949381	CEFTRIAXON DEVATIS TROCK SUBST 1G 10 (N3)
GE16097940	CEFTRIAXON DEVATIS TROCK SUBST .5G 10 (N3)
GE16230760	CEFTRIAX.RAT.BBF>> INF TRO.SUB. 2G 10 (N3)
GE16404183	CEFTRIAXON PUREN INF TRO.SUB. 2G (N1)
GE16442171	CEFTRIAXON PUREN INF TRO.SUB. 2G 5 (N2)
GE16829487	CEFTRIAXON PUREN INF TRO.SUB. 2G 10 (N3)
GE169364	ROCEPHINE KHP>> INJ IV +LSG 1G 10ML (N1)
GE17109816	CEFTRIAXON EBERTH INF TRO.SUB. 2G 10 (N3)
GE17160051	ROCEPHINE EUP>> INF TRO.SUB. 2G (N1)
GE17241916	ROCEPHINE EUP>> INF TRO.SUB. 2G 7 (N2)
GE1953961	ROCEPHIN CC4>> INJ IV +LSG 1G 5 10ML (N2)
GE1956759	ROCEPHIN E-M>> INJ IV +LSG 1G 10ML (N1)
GE201133	ROCEPHIN INJ IV +LSG 500MG 5 5ML (N2)
GE2013713	CEFTRIAXON HEXAL INJ TROC-LSG 1G 5 (N2)
GE211993	ROCEPHINE MTK>> INJ IV +LSG 1G 10ML (N1)
GE214525	ROCEPHIN GRK>> INF OHNE LSG 2G ALT (N1)
GE2147501	CEFTRIAXON FK2 INF FL 2G 10 (N3)
GE2253710	ROCEPHIN CC4>> INF OHNE LSG 2G ALT (N1)
GE2255285	CEFTRIAXON-RATIOPH INF TRO.SUB. 2G ALT 10 (N3)

Therapy number	Therapy name
GE2255286	CEFTRIAXON CRM ALT INF TRO.SUB. 2G 5 (N2)
GE2271681	ROCEPHIN GRK>> INJ IM +LSG 1G 5 3.5ML (N2)
GE2300037	CEFTRIAXON CRM ALT INF TRO.SUB. 2G (N1)
GE234713	ROCEPHIN INF MIT LSG 2G 5 40ML
GE2366349	CEFOTRIX INF TRO.SUB. 2G 5 (N2)
GE2371313	CEFTRIAXON-RATIOPH TROCK SUBST .5G ALT 10 (N3)
GE2386357	CEFTRIAXON CRM ALT INJ TROC-LSG .5G (N1)
GE2439761	ROCEPHIN CC4>> INJ IM +LSG 1G 5 3.5ML (N2)
GE2605060	CEFOTRIX INF TRO.SUB. 2G 10 2G (N3)
GE263576	ROCEPHIN INF OHNE LSG 2G 5
GE2668001	CEFTRIAXON HEXAL INJ TROC-LSG .5G 5 (N2)
GE268497	ROCEPHIN INJ IV +LSG 1G 10ML (N1)
GE27322	ROCEPHIN INF MIT LSG 2G 40ML (N1)
GE2794703	CEFTRIAXON-RATIOPH TROCK SUBST 1G ALT 10 (N3)
GE2816789	CEFTRIAXON DM+(CRM INJ TROC-LSG 1G (N1)
GE287496	CEFTRIAXON HEXAL INF TRO.SUB. 2G 5 (N2)
GE298793	ROCEPHIN KHP>> INF OHNE LSG 2G ALT 7 (N2)
GE3270648	ROCEPHIN KHP>> INF OHNE LSG 2G ALT (N1)
GE3303096	CEFTRIAXON DM+ ALT INF TRO.SUB. 2G 10 (N3)
GE34839	ROCEPHIN INF MIT LSG 2G 7 40ML (N2)
GE3638322	CEFTRIAXON DM+(CRM INJ TROC-LSG .5G (N1)
GE3668992	CEFTRIAXON-SAAR INF TRO.SUB. 2G 10 50ML (N3)
GE3710218	CEFTRIAXON-SAAR DURCHSTECHFL 1G 10 (N3)
GE3753803	CEFTRIAXON HIKMA INF TR.S-LSG 2G 10 (N3)
GE375803	ROCEPHIN CC4>> INF OHNE LSG 2G ALT 7 (N2)
GE3909852	CEFTRIAXON-SAAR INF TRO.SUB. 2G 50ML (N1)
GE394034	ROCEPHIN GRK>> INJ IV +LSG 1G 5 10ML (N2)
GE39477	ROCEPHIN INF MIT LSG 1G (N1)
GE396924	ROCEPHINE KHP>> INJ IV +LSG 1G 5 10ML (N2)
GE4075552	CEFOTRIX INJ TROC-LSG 1G 5 (N2)
GE4123513	CEFTRIAXON DM+ ALT INF TRO.SUB. 2G (N1)
GE4512853	CEFTRIAXON DM+ ALT INF TRO.SUB. 2G 5 (N2)
GE46263	ROCEPHIN GRK>> INF OHNE LSG 2G ALT 7 (N2)
GE4900846	ROCEPHIN EUP>> INF OHNE LSG 2G 7 (N2)
GE500869	ROCEPHINE E-M>> INJ IM +LSG 1G 3.5ML (N1)
GE5024967	CEFOTRIX INJ TROC-LSG 1G 10 1G (N3)
GE507629	ROCEPHINE BRA>> INJ IV +LSG 1G 10ML (N1)
GE507632	ROCEPHINE E-M>> INJ IM +LSG 1G 5 3.5ML (N2)
GE512596	ROCEPHIN INJ IM +LSG 1G 3.5ML (N1)
GE5684833	ROCEPHIN EUP>> INF OHNE LSG 2G (N1)
GE5747663	CEFOTRIX INJ TROC-LSG .5G 5 (N2)
GE5814838	ROCEPHIN ORI>> INJ IV +LSG 1G 5 (N2)
GE5934838	CEFTRIAXON FK2 INJ FL 1G 10 (N3)
GE6016811	CEFTRIAXON-PHARMO. INF TRO.SUB. 2G 5 (N2)
GE6224677	CEFTRIAXON DM+(CRM INF TRO.SUB. 2G (N1)
GE6608627	ROCEPHIN KHP>> INF MIT LSG 2G 7 40ML (N2)
GE6658447	CEFTRIAXON-PHARMO. TROCK SUBST 1G 5 (N2)
GE667061	CEFTRIAXON SANDOZ TROCK SUBST 2G (N1)
GE6700436	ROCEPHIN KHP>> INF MIT LSG 2G 40ML (N1)
GE6719415	CEFTRIAXON-SAAR INF TRO.SUB. 2G 30 50ML
GE6947220	CEFTRIAXON-PHARMO. TROCK SUBST .5G 5 (N2)
GE7185725	CEFTRIAXON HEXAL INF TRO.SUB. 2G 10 (N3)
GE7317643	CEFTRIAXON ATV(DM+ INF TRO.SUB. 2G ALT 5 (N2)
GE7343235	CEFTRIAXON HEXAL INJ TROC-LSG 1G 10 (N3)
GE7395597	CEFTRIAXON DM+(CRM INJ TROC-LSG 1G 5 (N2)
GE7571828	CEFTRIAXON HIKMA INJ/INF TR.S 1G 10 (N3)
GE7656717	CEFTRIAXON ATV(DM+ INF TRO.SUB. 2G ALT (N1)

Therapy number	Therapy name
GE7803209	CEFTRIAXON STRAGEN INF TRO.SUB. 1G 10 (N3)
GE7905943	CEFTRIAXON STRAGEN INF TRO.SUB. 2G 10 (N3)
GE8025547	CEFOTRIX INF TRO.SUB. 2G 7 (N2)
GE8247113	CEFTRIAXON-SAAR DURCHST.I.M. 1G (N1)
GE8320180	ROCEPHIN EUP>> INF MIT LSG 2G 7 40ML (N2)
GE8490154	CEFTRIAXON ATV(DM+ INF TRO.SUB. 2G ALT 10 (N3)
GE8496127	CEFTRIAXON ATV(DM+ INF TRO.SUB. 2G 5 (N2)
GE8596372	CEFTRIAXON ATV(DM+ INJ TROC-LSG 1G 10 (N3)
GE8629580	ROCEPHIN EUP>> INF MIT LSG 2G 40ML (N1)
GE8639439	CEFTRIAXON HEXAL INJ TROC-LSG .5G 10 (N3)
GE8715642	CEFTRIAXON FK2 INJ FL .5G 10 (N3)
GE8787607	CEFTRIAXON-SAAR INF TRO.SUB. 2G 12
GE8888286	CEFTRIAXON-RATIOPH INF TRO.SUB. 2G 10 (N3)
GE89205	ROCEPHIN INJ IM +LSG 1G 5 3.5ML (N2)
GE89208	ROCEPHIN INJ IV +LSG 1G 5 10ML (N2)
GE9217815	CEFTRIAXON-RATIOPH TROCK SUBST 1G 10 (N3)
GE9275624	CEFTRIAXON-GRY TROCK SUBST 2000MG (N1)
GE9409224	CEFTRIAXON ATV(DM+ INF TRO.SUB. 2G (N1)
GE9441836	ROCEPHIN GRK>> INF OHNE LSG 2G 7 (N2)
GE9468790	ROCEPHIN GRK>> INF OHNE LSG 2G (N1)
GE9519214	CEFTRIAXON-SAAR INF TRO.SUB. 2G 8
GE9555907	CEFTRIAXON ATV(DM+ INF TRO.SUB. 2G 10 (N3)
GE9687503	ROCEPHIN AC9>> INF OHNE LSG 2G 7 (N2)
GE9782462	ROCEPHIN CC4>> INF OHNE LSG 2G 7 (N2)
GE9799540	ROCEPHIN KHP>> INF OHNE LSG 2G 7 (N2)
GE9808628	ROCEPHIN CC4>> INF OHNE LSG 2G (N1)
GE9865092	ROCEPHIN AC9>> INF OHNE LSG 2G (N1)

Annex 2 List of ICD 10 codes for different types of infection (antibiotic indications)

Urinary tract infection

N029	Recurrent and persistent hematuria with unspecified morphologic changes
N100	Acute pyelonephritis
N120	Tubulo-interstitial nephritis, not specified as acute or chronic
N133	Other and unspecified hydronephrosis
N136	Pyonephrosis
N159	Renal tubulo-interstitial disease, unspecified
N200	Calculus of kidney
N201	Calculus of ureter
N209	Urinary calculus, unspecified
N230	Unspecified renal colic
N289	Disorder of kidney and ureter, unspecified
N300	Acute cystitis
N301	Interstitial cystitis (chronic)
N302	Other chronic cystitis
N308	Other cystitis
N309	Cystitis, unspecified
N329	Bladder disorder, unspecified
N342	Other urethritis
N390	Urinary tract infection, site not specified
N398	Other specified disorders of urinary system
N399	Disorder of urinary system, unspecified
R300	Dysuria
R309	Painful micturition, unspecified
R310	Gross hematuria
R320	Unspecified urinary incontinence
R350	Frequency of micturition
R391	Other difficulties with micturition
R398	Other symptoms and signs involving the genitourinary system
R829	Other and unspecified abnormal findings in urine
T835	Infection and inflammatory reaction due to prosthetic device, implant and graft in urinary system

Lower respiratory tract infection

A162	Tuberculosis of lung, without mention of bacteriological or histological confirmation
A493	Mycoplasma infection, unspecified site
C349	Malignant neoplasm of unspecified part of bronchus or lung
E849	Cystic fibrosis, unspecified
J110	Influenza due to unidentified influenza virus with pneumonia
J111	Influenza due to unidentified influenza virus with other respiratory manifestations
J157	Pneumonia due to Mycoplasma pneumoniae
J158	Pneumonia due to other specified bacteria
J159	Unspecified bacterial pneumonia
J180	Bronchopneumonia, unspecified organism
J181	Lobar pneumonia, unspecified organism
J182	Hypostatic pneumonia, unspecified organism
J188	Other pneumonia, unspecified organism
J189	Pneumonia, unspecified organism
J202	Acute bronchitis due to streptococcus
J208	Acute bronchitis due to other specified organisms
J209	Acute bronchitis, unspecified
J218	Acute bronchiolitis due to other specified organisms
J219	Acute bronchiolitis, unspecified
J220	Unspecified acute lower respiratory infection
J400	Bronchitis, not specified as acute or chronic
J410	Simple chronic bronchitis
J411	Mucopurulent chronic bronchitis
J418	Mixed simple and mucopurulent chronic bronchitis
J420	Unspecified chronic bronchitis
J439	Emphysema, unspecified
J440	Chronic obstructive pulmonary disease with acute lower respiratory infection
J441	Chronic obstructive pulmonary disease with (acute) exacerbation
J448	Other specified chronic obstructive pulmonary disease
J449	Chronic obstructive pulmonary disease, unspecified
J450	Asthma
J459	Other and unspecified asthma
J460	Status asthmaticus
J470	Bronchiectasis with acute lower respiratory infection
J680	Bronchitis and pneumonitis due to chemicals, gases, fumes and vapors
J690	Pneumonitis due to food and vomit
J841	Other interstitial pulmonary diseases with fibrosis
J848	Other specified interstitial pulmonary diseases
J900	Pleural effusion, not elsewhere classified
J961	Chronic respiratory failure
J969	Respiratory failure, unspecified
J980	Diseases of bronchus, not elsewhere classified

J984	Other disorders of lung
J988	Other specified respiratory disorders
J989	Respiratory disorder, unspecified
R042	Hemoptysis
R050	Cough
R060	Dyspnea
R062	Wheezing
R068	Other abnormalities of breathing
R091	Pleurisy
R093	Abnormal sputum

Upper respiratory tract infection

J000	Acute nasopharyngitis [common cold]
J010	Acute maxillary sinusitis
J011	Acute frontal sinusitis
J012	Acute ethmoidal sinusitis
J014	Acute pansinusitis
J018	Other acute sinusitis
J019	Acute sinusitis, unspecified
J020	Streptococcal pharyngitis
J028	Acute pharyngitis due to other specified organisms
J029	Acute pharyngitis, unspecified
J030	Streptococcal tonsillitis
J038	Acute tonsillitis due to other specified organisms
J039	Acute tonsillitis, unspecified
J040	Acute laryngitis
J041	Acute tracheitis
J042	Acute laryngotracheitis
J060	Acute laryngopharyngitis
J068	Other acute upper respiratory infections of multiple sites
J069	Acute upper respiratory infection, unspecified
J310	Chronic rhinitis
J311	Chronic nasopharyngitis
J320	Chronic maxillary sinusitis
J321	Chronic frontal sinusitis
J322	Chronic ethmoidal sinusitis
J323	Chronic sphenoidal sinusitis
J324	Chronic pansinusitis
J328	Other chronic sinusitis
J329	Chronic sinusitis, unspecified
J348	Other specified disorders of nose and nasal sinuses
J360	Peritonsillar abscess
J392	Other diseases of pharynx
J398	Other specified diseases of upper respiratory tract
J399	Disease of upper respiratory tract, unspecified
R070	Pain in throat
J350	Chronic tonsillitis and adenoiditis

Gastrointestinal infection

A020	Salmonella enteritis
A029	Salmonella infection, unspecified
A045	Campylobacter enteritis
A046	Enteritis due to Yersinia enterocolitica
A048	Other specified bacterial intestinal infections
A049	Bacterial intestinal infection, unspecified
A059	Bacterial foodborne intoxication, unspecified
A090	Infectious gastroenteritis and colitis, unspecified
A099	Gastroenteritis and colitis of unspecified origin
K047	Periapical abscess without sinus
K112	Sialoadenitis
K259	Gastric ulcer, unspecified as acute or chronic, without hemorrhage or perforation
K269	Duodenal ulcer, unspecified as acute or chronic, without hemorrhage or perforation
K291	Other acute gastritis
K293	Chronic superficial gastritis
K294	Chronic atrophic gastritis
K295	Unspecified chronic gastritis
K296	Other gastritis
K297	Gastritis, unspecified
K299	Gastroduodenitis, unspecified
K318	Other specified diseases of stomach and duodenum
K319	Disease of stomach and duodenum, unspecified
K358	Other and unspecified acute appendicitis
K370	Unspecified appendicitis
K509	Crohn's disease, unspecified
K519	Ulcerative colitis, unspecified
K523	Indeterminate colitis
K567	Ileus, unspecified
K571	Diverticular disease of small intestine without perforation or abscess
K572	Diverticulitis of large intestine with perforation and abscess
K573	Diverticular disease of large intestine without perforation or abscess
K579	Diverticular disease of intestine, part unspecified, without perforation or abscess
K603	Anal fistula
K610	Anal abscess
K628	Other specified diseases of anus and rectum
K638	Other specified diseases of intestine
K639	Disease of intestine, unspecified
K659	Peritonitis, unspecified
K660	Peritoneal adhesions (postprocedural) (postinfection)
K703	Alcoholic cirrhosis of liver
K768	Other specified diseases of liver
K800	Calculus of gallbladder with acute cholecystitis
K801	Calculus of gallbladder with other cholecystitis

K810	Acute cholecystitis
K819	Cholecystitis, unspecified
K830	Cholangitis
K929	Disease of digestive system, unspecified

Prostate infection

N410	Acute prostatitis
N411	Chronic prostatitis
N418	Other inflammatory diseases of prostate
N419	Inflammatory disease of prostate, unspecified
N429	Disorder of prostate, unspecified

Genital infection

A539	Syphilis unspecified
A540	Gonococcal infection of lower genitourinary tract without periurethral or accessory gland abscess
A549	Gonococcal infection, unspecified
A546	Gonococcal infection of anus and rectum
A548	Other gonococcal infection
A560	Chlamydial infection of lower genitourinary tract
A640	Unspecified sexually transmitted disease
A748	Other chlamydial diseases
A749	Chlamydial infection, unspecified
N341	Nonspecific urethritis
N481	Balanitis
N499	Inflammatory disorder of unspecified male genital organ
N508	Other specified disorders of male genital organs
N700	Acute salpingitis and oophoritis
N709	Salpingitis and oophoritis, unspecified
N719	Inflammatory disease of uterus, unspecified
N720	Inflammatory disease of cervix uteri
N739	Female pelvic inflammatory disease, unspecified
N758	Other diseases of Bartholin's gland
N760	Acute vaginitis
N762	Acute vulvitis
R360	Urethral discharge without blood

Skin infection

A260	Cutaneous erysipeloid
L049	Acute lymphadenitis, unspecified
A460	Erysipelas
I832	Varicose veins of lower extremities with both ulcer and inflammation
I889	Nonspecific lymphadenitis, unspecified
I890	Lymphedema, not elsewhere classified
I891	Lymphangitis
L020	Cutaneous abscess, furuncle and carbuncle of face
L022	Cutaneous abscess, furuncle and carbuncle of trunk
L023	Cutaneous abscess, furuncle and carbuncle of buttock
L024	Cutaneous abscess, furuncle and carbuncle of limb
L029	Cutaneous abscess, furuncle and carbuncle, unspecified
L030	Cellulitis and acute lymphangitis of finger and toe
L031	Cellulitis and acute lymphangitis of other parts of limb
L039	Cellulitis and acute lymphangitis, unspecified
L080	Pyoderma
L089	Local infection of the skin and subcutaneous tissue, unspecified
L303	Infective dermatitis
L709	Acne, unspecified
L891	Pressure ulcer of back
L984	Non-pressure chronic ulcer of skin, not elsewhere classified
L989	Disorder of the skin and subcutaneous tissue, unspecified
N610	Mastitis without abscess
R020	Gangrene, not elsewhere classified
S610	Open wound of thumb without damage to nail
S913	Open wound of foot
T140	Superficial injury of unspecified body region
T141	Open wound of unspecified body region
T793	Post-traumatic wound infection, not elsewhere classified
J340	Abscess, furuncle and carbuncle of nose
A269	Erysipeloid, unspecified
L010	Impetigo
L700	Acne vulgaris
L719	Rosacea, unspecified
T813	Disruption of wound, not elsewhere classified

Bone infection

M009	Pyogenic arthritis, unspecified
M869	Osteomyelitis, unspecified

Ear infection

H603	Other infective otitis externa
H609	Unspecified otitis externa
H610	Chondritis and perichondritis of external ear
H650	Acute serous otitis media
H651	Other acute nonsuppurative otitis media
H659	Unspecified nonsuppurative otitis media
H660	Acute suppurative otitis media
H663	Other chronic suppurative otitis media
H664	Suppurative otitis media, unspecified
H669	Otitis media, unspecified
H680	Eustachian salpingitis
H698	Other specified disorders of Eustachian tube
H709	Mastoiditis unspecified
H920	Otalgia
H921	Otorrhea

Testicular infection

N459	Orchitis, epididymitis and epididymo-orchitis without abscess

Borrelia (including Lyme disease)

A692	Lyme disease
A681	Tick-borne relapsing fever
A689	Relapsing fever, unspecified
A698	Other spirochaetal infections

Antibiotic prophylaxis

Z29.2	Other prophylactic chemotherapy

Central Nervous System Infections

G039	Meningitis, unspecified
G049	Encephalitis, myelitis and encephalomyelitis, unspecified

Other infections

A282	Extraintestinal yersiniosis
A419	Septicaemia unspecified
A490	Staphylococcal infection, unspecified site
A491	Streptococcal infection, unspecified site
A492	Hemophilus influenzae infection, unspecified site
A498	Other bacterial infections of unspecified site
A499	Bacterial infection, unspecified
B962	Escherichia coli [E. coli] as the cause of diseases classified elsewhere
B968	Other specified bacterial agents as the cause of diseases classified elsewhere
B990	Other and unspecified infectious diseases
H000	Hordeolum (externum) (internum) of eyelid
I380	Endocarditis, valve unspecified
I514	Myocarditis, unspecified
I831	Varicose veins of lower extremities with inflammation
R508	Other specified fever
R509	Fever unspecified
T814	Infection following a procedure