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Hepatotoxicity risk factors and acetaminophen dose adjustment, do prescribers give this issue adequate consideration? A French university hospital study

Astrid Bacle, Charlotte Pronier, Helene Gilardi, Elisabeth Polard, Sophie Potin, Lucie-Marie Scailteux

► To cite this version:

Astrid Bacle, Charlotte Pronier, Helene Gilardi, Elisabeth Polard, Sophie Potin, et al.. Hepatotoxicity risk factors and acetaminophen dose adjustment, do prescribers give this issue adequate consideration? A French university hospital study. *European Journal of Clinical Pharmacology*, In press, 10.1007/s00228-019-02674-5 . hal-02119177v1

HAL Id: hal-02119177

<https://univ-rennes.hal.science/hal-02119177v1>

Submitted on 5 Jul 2019 (v1), last revised 8 Jul 2019 (v2)

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1 **Hepatotoxicity risk factors and acetaminophen dose adjustment, do**
2 **prescribers give this issue adequate consideration? a French university**
3 **hospital study.**

4

5 Running title: **Hepatic risk factors and acetaminophen dose.**

6

7 Astrid BACLE^{1,2}, Charlotte PRONIER^{2,3}, H el ene GILARDI¹, Elisabeth POLARD^{4,5}, Sophie
8 POTIN^{1,2}, Lucie-Marie SCAILTEUX^{4,5}.

9

- 10 1. Pharmacy Department, CHU Rennes, France
11 2. Univ Rennes, Inserm, EHESP, Irset (Institut de recherche en sant e, environnement et travail) -
12 UMR_S 1085 , F-35000 Rennes, France
13 3. Virology Department, CHU Pontchaillou, Rennes, France
14 4. Pharmacovigilance and pharmacoepidemiology centre, Pharmacology Department, CHU Rennes,
15 France
16 5. Univ Rennes, REPERES ([Pharmacoepidemiology and Heath Services Research]) - EA 7449, F-
17 35000 Rennes, France

18

19 Corresponding author: Lucie-Marie SCAILTEUX

20 Pharmacovigilance and pharmacoepidemiology centre, CHU Rennes

21 2, rue Henri Le Guilloux – 35000 Rennes – France

22 Luciemarie.scailteux@chu-rennes.fr

23

24 Word count: 3516 words

25

26 Key words: hepatotoxicity, acetaminophen, dose adjustment, risk factor

27

28 **Abstract** (247/250 words)

29 *Background:* The hepatotoxicity of acetaminophen is recognized worldwide. Unfavourable prognoses
30 relating to overdose include liver transplantation and/or death. Several hepatotoxicity risk factors
31 (HRFs) should motivate the adjustment of acetaminophen daily intake (to < 4 g/day): advanced age,
32 weight < 50 kg, malnutrition, chronic alcoholism, chronic hepatitis B and C and HIV infection, severe
33 chronic renal failure, and hepatocellular insufficiency.

34 *Method:* Over a seven-day period in Rennes University Hospital in December 2017, using DxCare®
35 software, with an odds ratio estimation, we analysed all acetaminophen prescriptions, to assess to
36 what extent the presence of HRFs altered the prescribers' choice of acetaminophen dose (< 4 g/day
37 versus 4 g/day).

38 *Results:* Among 1842 patients, considering only the first acetaminophen prescription, 73.7 % were on
39 4 g/day. Almost half this population had at least 1 HRF. Whereas around 80 % of the prescriptions in
40 the < 4 g/day group were for patients with at least 1 HRF, only 53 % of the prescriptions in the
41 4 g/day group concerned patients without HRFs ($p < 0.001$). Age > 75 and low weight were associated
42 with the prescriber's choice of dose. Neither chronic alcoholism nor hepatocellular insufficiency
43 influenced the acetaminophen doses prescribed.

44 *Conclusion:* Considering the widespread use of acetaminophen and its favourable safety profile
45 compared to other analgesic drugs, it appears urgent to remind prescribers of the maximum daily
46 dose recommendations for acetaminophen for patients with HRFs, especially those with chronic
47 alcoholism and hepatocellular insufficiency.

48

49 **What is already known about this subject:**

- 50
- Acetaminophen is widely known to be a hepatotoxic drug.
 - 51 • Recommendations include a maximum daily dose of acetaminophen of < 4 g/day for patients
 - 52 with hepatotoxicity risk factors (chronic alcoholism, hepatocellular insufficiency, advanced
 - 53 age, anorexia...).
 - 54 • Studies have described up to 21 % of acetaminophen prescriptions without dose adjustment
 - 55 among patients with hepatotoxicity risk factors.

56

57 **What this study adds:**

- 58
- Age >75 and weight <50 kg are linked to prescriptions of < 4 g/day.
 - 59 • Chronic alcoholism, hepatocellular insufficiency, severe chronic renal failure, chronic viral
 - 60 infections and malnutrition have no influence on the choice of the dose.
 - 61 • Clinicians should systematically assess patient history, checking for any hepatotoxicity risk
 - 62 factors when prescribing acetaminophen.

63

64 **Introduction**

65 Acetaminophen, also known as “paracetamol”, is the most widely prescribed first-line analgesic
66 worldwide. Available as an over-the-counter drug in many countries such as France or the United
67 States, it appears as the most frequent medication involved in both intentional and unintentional
68 drug poisoning, according to the annual report by the American Association of Poison Control Center
69 Data System and the French Addiction Monitoring Network[1, 2].

70 In case of acetaminophen accumulation and overdose, the main expected adverse effect is acute
71 liver failure, including fulminant hepatitis, which can lead to liver transplantation and/or death[1, 3–
72 5]. The hepatotoxicity mechanism involves a CYP 450 (mainly 2E1) highly reactive converted
73 metabolite, namely N-acetyl p-benzoquinone imine (NAPQI). NAPQI is physiologically broken down
74 by glutathione in the liver and excreted in the urine. However, in case of acetaminophen overdose,
75 NAPQI production increases and exceeds the conjugation abilities of glutathione; as it binds to the
76 hepatocellular membrane proteins, it induces liver parenchymal cell death[6].

77 For a mean adult weight, clinical symptomatic acetaminophen hepatotoxicity is usually expected
78 after a single acetaminophen ingestion of around 10 grams per 24 hours or 150 mg/kg, with an initial
79 phase of cytolysis occurring in the first 24 to 48 hours. The hepatotoxicity is dose-dependent and can
80 be predicted by a nomogram[7]. Immediately after an acetaminophen overdose, N-acetylcysteine is
81 used to restore glutathione reserves which can limit hepatotoxicity[8] with recovery expected in 4-5
82 days where the prognosis is favourable[9]. Studies have shown that advanced age, chronic alcohol
83 consumption, as well as fasting/anorexia and poor nutritional status could be associated with
84 glutathione depletion; it is worth noting that chronic alcohol consumption has also been shown to be
85 a CYP 2E1 inducer leading to NAPQI increase[10–12]. Chronic renal failure as well as chronic liver
86 disease (hepatic failure, cirrhosis, viral hepatitis) are also considered to be acetaminophen
87 hepatotoxicity risk factors (HRFs)[13–16] and should lead to an adjustment of acetaminophen daily
88 intake. Meanwhile, case reports of hepatitis observed at therapeutic doses of 3 or 4 g/day have been
89 reported among patients with low weight, a history of chronic alcoholism, hepatic steatosis or recent
90 fasting[17–21]. Furthermore, certain randomised controlled trials have reported an increase (mostly
91 3 to 4 times the normal upper limit) in serum alanine aminotransferase activity (ALT) for a significant
92 proportion of ‘healthy’ patients exposed to acetaminophen at 4 g/day for several days, compared to
93 placebo[22, 23], although the clinical significance is uncertain.

94 Recommendations have been established for acetaminophen prescription, with a maximum daily
95 dose of 4 grams, and they include dose adjustment for patients with HRFs[24–26]. Dose adjustments
96 are detailed in most summary of product characteristics (SmPC) for acetaminophen-based

97 medications. A lack of accurate and harmonised information across SmPC is however observed. In
98 general terms, it is recommended to use the “lowest possible dose” for symptom relief and make
99 gradual adaptation of the dose to the pain. Regarding the maximum acetaminophen dose, some
100 SmPC mention that “it is generally not necessary to exceed 3 g per 24 hours”. Regarding dose
101 adjustments for special populations (liver failure, renal failure, dehydration, weight <50 kg...),
102 although it is formulated differently across SmPC, it is recommended to use the lowest possible
103 effective doses, and specifically to increase interval between two intakes (>8h) in severe chronic
104 renal failure. The maximum recommended doses in special population are given as an indication
105 (sometimes 2g/day or 3g/day) but are not necessarily related to clinical studies (no reference
106 provided in SmPC).”

107 Few studies have described acetaminophen prescription patterns in hospitals or assessed
108 compliance with recommendations relating to HRFs: in French and American cohorts, failure to
109 adjust doses in view of the presence of HRFs was observed in 1 % to 21 % of prescriptions[27–31]. It
110 can be noted that neither the type of hospital units (surgery, geriatrics...) nor pharmaceutical
111 validation studies have an influence on dose adjustment[27, 30].

112 This work was performed after the notification in our local Pharmacovigilance unit of cases of
113 acetaminophen toxicity at doses in the therapeutic range among patients with HRFs: the most
114 recent, with a fatal outcome, concerned a 72-year-old hospitalised man who developed cytolysis
115 with acute hepatic failure two days after the initiation of 4 g/day acetaminophen for acute pain. The
116 patient’s history included alcoholism and cachexia, in a context of hepatic steatosis, septic shock and
117 the discovery of metastatic colorectal cancer.

118 As we believe that some HRFs are more likely to induce dose adjustments than others, the aim of our
119 study was to assess to what extent the existence of HRFs (single or in combination) modify the
120 prescribers’ choice of acetaminophen dose (< 4 g/day versus 4 g/day).

121

122 **Materials and methods**

123 We conducted a retrospective monocentric cross-sectional study including all patients with an
124 acetaminophen prescription in Rennes University Hospital.

125 All data was collected in accordance with the French legislation on retrospective clinical studies, in
126 accordance with the precepts established by the Helsinki declaration.

127

128 • *Data sources*

129 The extraction of data concerning acetaminophen prescriptions (oral and intravenous) (Dxcare®
130 software version 7.5.20p049, Medasys®) was carried out over one week, from the 13th to the 19th
131 December 2017. Only patients aged over 18 years, i.e. born after 12/12/1999, were considered for
132 this analysis.

133

134 • *Exposure*

135 All medications containing acetaminophen were considered, prescribed on their own or in
136 combination with other drugs. We collected the names of the medications, the routes of
137 administration and the daily doses. Patients were categorised as having a maximum dose of 4 g/day
138 or less than 4 g/day. The patients for whom the dose was specified as “1 g ‘upon request’, maximum
139 4 times a day,” were considered as having the maximum 4 g/day dose.

140

141 • *Other variables*

142 Data was collected from the patients' electronic files: age at the time of the acetaminophen
143 prescription, gender, hospital unit, weight, body mass index, biological parameter values (serum
144 creatinine, serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline
145 phosphatase (PAL), gamma-glutamyl transpeptidase (GGT), direct bilirubin, total bilirubin,
146 prothrombin time (TP), international normalised ratio (INR), factor V, serum albumin and pre-
147 albumin), the presence of chronic viral hepatitis (B or C) and human immunodeficiency virus (HIV),
148 current chronic alcoholism, current intake of oral anticoagulants, current malnutrition, history of liver
149 or renal transplantation.

150

151

152 • *Risk factors predisposing to hepatotoxicity*

153 According to the SmPC and French recommendations on acetaminophen prescription [24–26], we
154 considered seven HRF categories that should lead to dose adjustment, defined as followed:

- 155 - age over 75 years, i.e. patients born before the 12th December 1942;
- 156 - low weight: under 50 kg;
- 157 - malnutrition defined by the presence of one or more of the following criteria: serum albumin
158 < 30 g / L, serum pre-albumin <150 mg / L, BMI < 18.5 for patients < 70 years old, BMI < 21
159 for patients ≥ 70 years old, the specific mention of “malnutrition” in the electronic file;
- 160 - chronic alcoholism: we selected patients whose electronic file records specified excessive
161 and chronic alcohol consumption;
- 162 - current chronic viral infections (hepatitis B, C and/or D) and/or HIV; patient status was
163 individually checked by a virologist (CP author). HIV patients with an undetectable viral load
164 were considered as presenting a risk factor; patients who had recovered from hepatitis C at
165 study entry were not considered as presenting a risk factor;
- 166 - severe chronic renal failure defined by a creatinine clearance value (estimated by the CKD-
167 EPI equation) of < 30 ml / min in the electronic file;
- 168 - hepatocellular insufficiency, biologically defined by one or more following abnormalities:
169 factor V < 70 %, prothrombin time decrease, INR > 1.5 for patients without anticoagulant
170 treatment or INR > 5 with anticoagulant treatment, ALT > 40 UI/L, AST > 40 UI/L. Other
171 biological parameters were considered only in case of association with other abnormalities:
172 serum albumin concentration < 35 g / L and/or the following clinical signs specified in the
173 electronic file: “jaundice”, “hepatic encephalopathy”, “cirrhosis”, “stellate angioma” or
174 “palmar erythrosis”, “alcoholic hepatitis”, “viral hepatitis”.

175

176 • *Statistical methods*

177 In case of several acetaminophen prescriptions for the same patient, only the first was considered for
178 the descriptive and statistical analyses in order to ensure the independence of the data and analyses.
179 We considered the first prescription as the initial prescriber’s intention to treat, as the second or
180 following prescriptions could be related to medical or pharmaceutical re-assessment.

181 Descriptive statistics characterised patients at the time of the 1st acetaminophen prescription.
182 Proportions were compared across levels of exposure using chi-square tests or Fisher’s exact test;
183 age was compared using the Student t test.

184 A logistic regression model considering all HRFs was used to estimate those that were significantly
185 related to the prescribers' choice of acetaminophen dose (< 4 g/day versus 4 g/day).

186 A descending step-by-step selection model was used, retaining only the variables (HRF) significantly
187 associated with acetaminophen dose adjustment (< 4 g/day) at a 5 % statistical threshold.

188 An odds ratio estimation was used to determine which HRFs were associated with dose adjustment
189 (< 4 g/day or 4 g/day) in the prescribers' prescriptions.

190 All analyses were conducted using the SAS statistical package (version 9.4; SAS Institute, Cary, NC,
191 USA).

192 Results

193 Over a seven-day period in December 2017, 2338 acetaminophen prescriptions were collected from
194 Rennes University Hospital. After excluding prescriptions for patients under 18 years, 2048
195 acetaminophen prescriptions concerning 1842 patients were included in this study. Retaining only
196 the first prescription for each patient, 1842 prescriptions were used for the analyses (see Figure 1).

197 The characteristics of the study population are displayed in table 1. Around 54 % were female. The
198 median age was 65 years (min 18 years – max 101 years) and 32.9 % were over 75 years old.

199 Among the 1842 prescriptions, 73.7 % were for 4 g/day (table 1); it can be noted that no prescription
200 exceeded the maximum 4-g daily dose. Females were more frequently in the < 4 g/day group than in
201 the 4 g/day group (60.1 % vs 51.3 %, $p < 0.001$). Regarding the hospital unit, in the < 4 g/day group,
202 prescribers mainly belonged to geriatric or other clinical units (respectively 44.6 % and 41.1 %); in the
203 4 g/day group, prescriptions mainly derived from surgery / anaesthesia / intensive care / palliative
204 units and other clinical units (respectively 57.1 % and 32.6 %).

205 Around 55 % of the overall population presented with at least one HRF. Among patients with only
206 one HRF ($n = 549$), the HRF was mainly age > 75 years, and secondarily hepatocellular insufficiency or
207 chronic alcoholism (appendix table 1). Whereas around 80 % of prescriptions in the < 4 g/day group
208 were for patients with at least 1 HFR, only 53 % of prescriptions in the 4 g/day group concerned
209 patients without any HFR ($p < 0.001$). Furthermore, some HRFs were significantly more frequent in
210 the < 4 g/day group (table 1) : age > 75, low weight, malnutrition and severe renal failure.

211 Concerning the statistical analysis, only prescriptions without missing data on the HRF category were
212 used ($n = 1103$), including 363 patients in the < 4 g/day group and 740 in the 4 g/day group. The
213 logistic regression showed that age > 75 and low weight were significantly associated with the
214 prescriber's choice of dose (table 2). The descending step-by-step model confirmed that only age >
215 75 and low weight remained significantly associated with the < 4 g/day dose (data not shown). We
216 observed similar results in a sensitivity analysis using age > 75 and weight as continuous variables
217 (data not shown).

218 It can be noted that among patients > 75 years ($n = 606$), who accounted for one-third of the overall
219 population, all had 1 ($n = 315$) or 2 ($n = 291$) HRFs. Despite this, around 50 % ($n = 302$) had no dose
220 adjustment.

221 As regards the administration route, 63 (3,4 %) concerned intravenous use, most of whom (86 %;
222 $n=54$) had a 4 g/day dose. In those patients, at least one HRF was recorded in 34 patients. As regards
223 the 9 patients in the < 4 g/day group, 1 had no HRF, 2 had only one HRF (age > 75 in both cases) and

224 7 had at least 2 HRF. More in depth, Paracetamol B Braun 1g/100 ml[®] (adult formulation) was used in
225 all cases. Its SmPC recommends a dose adjustment considering weight category (between 33 and 50
226 kg or > 50 kg) and whether HRF are present (chronic alcoholism, hepatocellular insufficiency, chronic
227 malnutrition, and dehydration for which maximal dose is 3 g/day).

228

229

230 **Discussion**

231 In our seven-day study focusing on acetaminophen prescriptions in Rennes University Hospital,
232 around three quarters of prescriptions were full-dose (4 g/day); in this group, 47 % of prescriptions
233 were for patients with at least one HRF: these can be considered as non-compliant prescriptions, and
234 the proportion is greater than in previous studies showing up to 21 % of non-compliant
235 acetaminophen prescriptions in hospital[27–31]. The lower non-compliant prescriptions could be
236 related to the fact that age > 75 years is not considered as a HRF in SmPC and no dose adjustment is
237 recommended. As mentioned by Pacé et al., medicine and geriatric units seem to be more aware of
238 the HRFs of acetaminophen[31]: in our study the number of prescriptions for < 4 g/day in these units
239 amounted to around 85 % of the prescriptions.

240 For the HRFs studied, we showed that age > 75 years and low weight influenced the prescribers'
241 choice of dose. The impact of advanced age here could be linked to age in our cohort since the
242 median age was 65.0 years and one third of the patients were over 75 years old. Another explanation
243 linked to age is the fact that, in Rennes University Hospital, prescribers are particularly aware of
244 dosage adjustment for elderly patients thanks to careful monitoring by the pharmacists. Surprisingly,
245 neither chronic alcoholism nor hepatocellular insufficiency were associated with dose adjustment.
246 Although acetaminophen is a highly hepatotoxic drug and its metabolism involves the liver,
247 prescribers appear not to consider these HRFs in their choice of dose. Hepatic tests after
248 acetaminophen initiation were not performed in our study, so we could not check for clinical or
249 biological signs of hepatotoxicity among patients with these HRFs. Pace et al. also observed a high
250 rate of non-compliance with recommendations (> 68 %) for patients with chronic alcoholism or
251 hepatocellular insufficiency[31], suggesting that prescribers need to be made aware of dose
252 adjustments in these patient groups. Unlike our study where low weight was a dose-adjustment
253 variable in acetaminophen prescriptions by clinicians, this factor was explored in heterogeneous
254 manner in other studies and was related to non-compliance[29, 31].

255 None of the prescriptions exceeded the 4-g per day, which is no doubt linked to the use of software
256 (DxCare®) limiting acetaminophen daily doses; a warning is also displayed when several drugs
257 containing acetaminophen are coprescribed.

258 Some HRF as well as their definition can be discussed. In a literature review, Caparrotta et al. found
259 no good quality evidence to establish that factors were HRF[11]. They notably pointed that the safe
260 oral acetaminophen dose in patients < 50 kg had not been established. In our study, chronic
261 alcoholism status has only been identified through a subjective HRF reading (potentially
262 underestimated) without re-assessment by an independent committee. No additional information

263 was collected (severity, care...). Age, especially advanced age is described as HRF whereas literature
264 data are inconsistent (PK, case series, population-based studies)[11, 12]. As evoked by Caparrotta et
265 al. there is a lack of good quality clinical evidence that older people have a clinically significant
266 difference in acetaminophen metabolism or are at increased risk of toxicity at (supra)therapeutic
267 dose. Age cut-off also varied across studies[12, 32–34]. Moreover, neither French SmPC nor
268 recommendations provide an age cut-off. Considering that “old age” definition is complex,
269 potentially subjective (physical, psychological conditions), and is not only related to years, we
270 arbitrarily chose 75 years-old as cut-off in our study. In addition to biological criteria, hepatocellular
271 insufficiency definition also included a HRF reading seeking specific terms (cirrhosis, hepatic
272 encephalopathy) without secondary objective re-assessment. All these limitations could have
273 induced misclassification bias of HRF.

274 The main strength of our work lies in the data collection that took place within a week and involved
275 all adult patients’ electronic files in all Rennes University Hospital units. Among the weaknesses, we
276 recognize that our results concern only one hospital and may not be representative of French
277 hospital prescribers. But the objective of our study was not to compare with practices in other
278 hospitals but rather to highlight the fact that HRFs are not always considered by prescribers, even in
279 university hospitals, when prescribing acetaminophen. Nor did we consider the indication for
280 acetaminophen, treatment duration or the potential need for opioid treatments, which could have
281 impacted dose adjustment. Considering a safety approach, we deliberately focused our study on the
282 first acetaminophen dose prescribed, irrespective of its indication, as representing intention-to-treat.
283 Furthermore, our statistical analysis did not include all the 1842 prescriptions in the overall
284 population as a result of missing data for some HRFs: around 33 % of patients had missing data for
285 the hepatocellular insufficiency variable, and 10 % for malnutrition status. It can be noted that some
286 HRFs could have been under-estimated, especially alcoholism which is often concealed by patients
287 when questioned on the subject. We did not assess either whether the 4g/day dose for patients with
288 one or more HRF had clinical significance for liver function, nor did we consider the type of HRF;
289 indeed, hepatic cytolysis is more likely among patients with cirrhosis than among elderly patients
290 without other liver diseases. We did not consider co-medication and especially drug-drug interaction,
291 nor other clinical conditions (sepsis, heart failure[35, 36]) that affect the hepatic enzymes. In
292 acetaminophen SmPCs, drug interaction section mentioned a precaution of use when associated with
293 other hepatotoxic drugs or CYP 450 drug enzyme inducers. However, on the basis of the French drug-
294 drug interaction referential provided by the French Health Authorities (French National Agency for
295 Medicines and Health Products Safety [ANSM])[37], no clinically significant interaction with
296 paracetamol was highlighted, even with drugs impacting CYP 2E1 (doxycycline, isoniazide).

297 We should bear in mind that although acetaminophen is the most widely recognized drug in inducing
298 liver damage[38, 39], its use is commonplace, mainly as a result of a good reputation with regard to
299 safety compared to other analgesic drugs (non-steroid anti-inflammatory drugs for example). In
300 order to limit the risk of poisoning and suicide using acetaminophen, France was the first country in
301 Europe in the 1980s to limit packaging to a maximum dose of 8 grams of acetaminophen. In the
302 2000s, the Federal Drug Agency in the United States and the United Kingdom Health Authorities also
303 restricted the acetaminophen pack size[40, 41]; the FDA also limited the acetaminophen dosage unit
304 to 325 mg in 2011[42, 43]. Despite this, acetaminophen remains the first drug involved in overdose
305 (intentional or otherwise)[1, 2]. In 2017, W. Lee described the controversy surrounding
306 acetaminophen use in pain management[9]: he pointed out that worldwide regulatory efforts had
307 been ineffective in reducing the cost in money and lives resulting from its hepatotoxicity. In France,
308 however, the French Pharmacovigilance network regularly collects case reports of acute
309 acetaminophen poisoning. A recent fatal case in December 2017, which was highly publicized across
310 France, led the Health Authorities to reinforce the data available on acetaminophen-based drugs: the
311 objective was to raise awareness among patients and prescribers about liver damage. A public
312 consultation was thus initiated on August 20th, 2018, ending on September 30th, 2018 for the
313 definition of the best warning message to put on drug packaging[44]; but the results have not yet
314 been issued. With the exception of hepatocellular insufficiency, there is a lack of information on dose
315 adjustment, special warnings or contraindications in case of other HRFs with some acetaminophen-
316 based medications (e.g. Paracetamol Teva 1g, tablets; Paracetamol EG 500 mg/30 mg[®], effervescent
317 scored tablets; Paracetamol Zydus 500 mg, gelules[®]...[45–47]). It is worth noting that maximum
318 dose could vary from one SmPC to another: for instance, in case of HRF, 2g/day is mentioned in
319 Paracetamol AHCL 1g, effervescent tablet[48] compared to 3g/day in Doliprane 1 g, tablets[49]. In
320 general terms, lack of SmPC harmonisation, especially regarding the appropriate maximal dose to be
321 used in case of HRF is a limitation for clinicians' prescriptions compliance. ANSM planned a
322 harmonisation of the warnings included in the SmPC for acetaminophen-based drugs in 2019.

323 Considering pharmacovigilance cases report of acetaminophen toxicity in patients with HRF treated
324 with (sub)therapeutic ≤ 4 g/day dose and the results of the current study, in Rennes University
325 Hospital, several improvement measures are planned: awareness raising at the residents' welcome
326 seminars twice a year, poster campaign in clinical departments, configuration of software as regards
327 prescription schemes, awareness raising of pharmacist responsible of prescriptions' pharmaceutical
328 validation.

329

330 **Conclusion**

331 This work shows that in Rennes University Hospital, HRFs are not systematically considered by
332 clinicians when acetaminophen is prescribed. Age > 75 years and low weight had a greater impact on
333 acetaminophen prescription than alcoholism, malnutrition, chronic viral hepatitis, severe renal
334 failure or hepatocellular insufficiency. Considering the widespread use of acetaminophen, it appears
335 important to remind healthcare professionals and patients of the hepatotoxicity risk resulting from
336 misuse, especially in presence of HRF.

337

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442 **Authors contribution:**

443 LMS and AB had full access to all of the data in the study and take responsibility for the integrity of
444 the data and the accuracy of the data analysis. SP, EP, LMS and AB were part of the study concept
445 and design. All authors were a part in the acquisition, analysis or interpretation of data. Drafting of
446 the manuscript was done by LMS. All authors took part in the critical revision of the manuscript for
447 important intellectual content. LMS was a part in the statistical analysis. Administrative, technical or
448 material support was provided by Rennes Hospital University.

449

450 **Conflict of interest:**

451 None.

452

453 **Funding / support:**

454 None.

455

456 **Additional contribution:**

457 We thank Jean-Paul Sinteff (Medical Information Departement, CHU Rennes) for the DxCare[®]
458 software data extraction, and Adrien Turban, Anne-Sophie Michel, Justine Geffroy and Stephanie
459 Ollivier for their help in the data collection.

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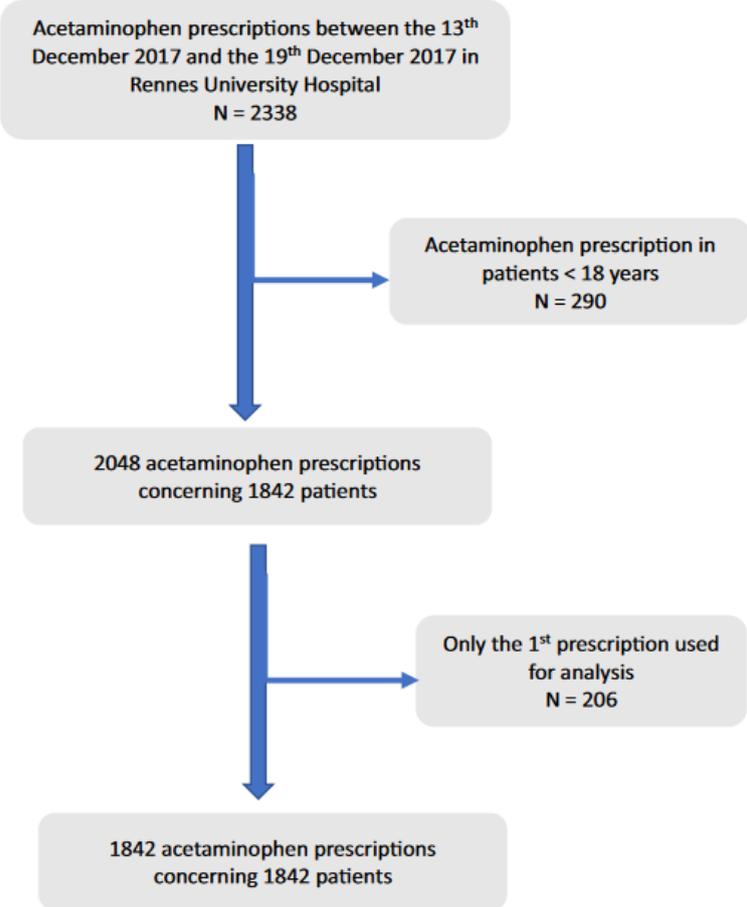
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471 **Fig. 1** Flowchart

Table 1 Population characteristics

	Overall	< 4g/day	4g/day	p-value
number of prescription (%)	1842 (100)	484 (26.3)	1358 (73.7)	
Age in year, mean (SD) (min - max)	61.6 (20.8) (18 - 101)	74.8 (17.2) (18 - 97)	57.0 (20.0) (18 - 101)	<0.001
Female Sex	987 (53.6)	291 (60.1)	696 (51.3)	<0.001
Weight (kg), mean (SD) (missing value, n = 166)	70.5 (17.4) (min 25.5 - max 164.0)	66.2 (18.8) (min 25.5 - max 134.6)	72.1 (16.6) (min 34.0 - max 164.0)	
BMI, mean (SD) (missing value, n = 1269)	25.2 (5.6) (min 12.0 - max 55.8)	25.1 (6.1) (min 12.0 - max 55.8)	25.3 (5.1) (min 14.7 - max 46.7)	
Hospitalisation Department				<0.001
Surgery, anaesthesia, intensive care or palliative departments	835 (45.3)	59 (12.2)	776 (57.1)	
Emergency department	74 (4.0)	10 (2.1)	64 (4.7)	
Geriatric department	291 (15.8)	216 (44.6)	75 (5.5)	
Other clinical departments	642 (34.9)	199 (41.1)	443 (32.6)	
Number of hepatotoxicity risk factor				<0.001
0	819 (44.5)	99 (20.5)	720 (53.0)	
1	549 (29.8)	173 (35.7)	376 (27.7)	
≥ 2	474 (25.7)	212 (43.8)	262 (19.3)	
Description by type of hepatotoxicity risk factor				
age > 75	606 (32.9)	304 (62.8)	302 (22.2)	<0.001
low weight (missing value, n = 168)	171 (9.3)	93 (20.5)	78 (6.4)	<0.001
malnutrition (missing value, n = 207)	363 (22.2)	138 (31.3)	225 (18.8)	<0.001
chronic alcoholism	157 (8.5)	43 (8.9)	114 (8.4)	0.74
chronic viral hepatitis	53 (2.9)	15 (3.1)	38 (2.8)	0.73
chronic severe renal failure (missing value, n = 413)	113 (7.9)	48 (10.6)	65 (6.7)	0.01
hepatocellular insufficiency (missing value, n = 501)	272 (20.3)	74 (18.1)	198 (21.2)	0.19

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Appendix Table 1. Repartition of patients with only one hepatotoxicity risk factor (n= 549) by type of risk factor.

Hepatotoxicity risk factor (HRF)	n	%
Age > 75	315	57.4
Low weight	21	3.8
Malnutrition	47	8.6
Chronic alcoholism	55	10.0
Chronic viral hepatitis or HIV	19	3.5
Chronic severe renal failure	25	4.6
Hepatocellular insufficiency	67	12.2

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