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Dyskalemia: a management problem for students

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Abstract

Background: Although dyskalemia is common, its management can be problematic for students and general practitioners, especially when it occurs in patients with heart and renal failure. The basic academic knowledge of general medicine students, who have often not yet encountered clinical situations of dyskalemia, remains unclear in this regard.

Objectives: The purpose of this study was to evaluate the knowledge and reflexive practices of general medicine students in regard to dyskalemia.

Methods: A cross-sectional survey, based on a self-questionnaire, of all of the students enrolled in general medicine studies at the Faculty of Medicine at the University of Nancy (France) at the end of their degree. The students were asked questions pertaining to specific

33 clinical situations. The answers were compared to the information provided in the medical
34 curriculum as well as to the relevant European guidelines.

35

36 **Results:** We collected 290 of the questionnaires (participation rate: 81.2%). The hyper- and
37 hypo-kalemia thresholds considered pathological (3.5-5.0 mmol/L) were known by 78% and
38 67% of the students, respectively. The perception of danger in case of severe hypokalemia
39 was underestimated by 62.7% of them. In most cases, the proposed management of
40 hyperkalemia in heart and renal failure did not comply with the relevant guidelines. The
41 students tended to favor permanent discontinuation of the administration of converting
42 enzyme inhibitors (ACE) and/or mineralocorticoid receptor antagonists (MRA) without
43 considering the need for their reintroduction (51.6%). Sodium polystyrene sulfate was
44 frequently seen as an appropriate first-line treatment for hyperkalemia (45%).

45 **Conclusions:** The knowledge and competence of general medicine students appear to be
46 lacking for hyperkalemia in heart and renal failure, and they are long way from full
47 compliance with the relevant European guidelines. Exposure to complex clinical situations as
48 part of the medical curriculum, therefore, seems essential to improve the way dyskalemia is
49 managed in France.

50

51

52 **Strengths and limitations of this study**

53

- 54 1) The main strength of this study lies with the use of an open-ended questionnaire,
55 which ensured that there were no leading questions and not suggest possible answers
56 to the situations described.
- 57 2) The second strength: The questionnaires were filled out in the presence of a friendly
58 and neutral team, without direct intervention but with immediate availability of
59 assistance if required (self-administered questionnaire).
- 60 3) The third strength: Methodological bias was minimized by providing resources to
61 organize the task of collecting, analyzing, and processing the information.
- 62 4) The first limitation: Sample selection bias cannot be fully ruled out, although we are
63 confident that we were able to ensure adequate representativity of the population of
64 students enrolled in French general medicine studies.
- 65 5) The second limitation: we cannot exclude that the respondents were the most
66 motivated students, however we had a high response rate of over 81%.

67

68

69 **1. Background**

70

71 Dyskalemia (hypokalemia and hyperkalemia) are potentially dangerous conditions (1,2). It is
72 mostly encountered in high-risk patients (e.g., with heart failure, renal failure, cardio-renal
73 syndrome, diabetes, hypertension) but also, occasionally and unexpectedly, people without
74 comorbidities (3). Management is not consensual according to the guidelines in place, and the
75 thresholds for hypokalemia and hyperkalemia are not universal (4).

76 Many studies of patients with heart failure have focused on the association between blockers
77 of the renin-angiotensin-aldosterone system (RAAS) and anti-aldosterone, as all may trigger
78 hyperkalemia and can be a source of problems, particularly for general practitioners (5-8). In
79 contrast, loop diuretics may lead to hypokalemia or dehydration, which can be difficult to
80 manage in the context of renal insufficiency (9).

81 It is not precisely known how general practitioners deal with dyskalemia, especially as there
82 is not a specific decision tree to guide them in this regard. While the way they go about this is
83 presumably based on their prior experiences and on interactions with other specialists, the
84 basic academic knowledge and skills of general medicine students who have not yet
85 encountered clinical situations of dyskalemia remains largely unknown.

86

87 **2. Methods**

88

89 2.1. Objectives

90

91 The main objective of this study was to evaluate the knowledge of French general medicine
92 students regarding dyskalemia.

93 The secondary objective was to evaluate how they manage clinical situations involving
94 dyskalemia.

95

96 2.2. Type of study

97

98 All of the students (from the first to the third year of study) at the end of their general medical
99 studies in Nancy, France, (N=357) were asked to answer a self-questionnaire, kind of like

100 Durieu et al, regarding the perception of adverse drug reactions (10) during their final exams
101 in June 2017. The questionnaire was in two parts: the first two questions focused on the
102 perception of dyskalemia and the next three questions were clinical situations with open
103 answers, to avoid influencing the answers. The questionnaire was constructed in such a way
104 that the study reflects a general medicine context, where more information is not available at
105 the start usually limited to the only information available in the medical report. The objective
106 was to evaluate the student's "reflex" management without suggesting a list of predefined
107 answers so as not to influence the student. The answer was open-ended.

108 The questionnaire was first tested with ten students to ensure that it was fully understood in
109 the first round and that the answers were stable in the second round, as well as to ensure the
110 validity of the questionnaire (11).

111 The results were analyzed by collecting the terms in verbatim form. Thus, "monitoring under
112 scope", "intravenous hydration", and "calcium gluconate" were classified under the term
113 "hospitalization/emergency" as these treatments are not available in the public health care
114 system; "taking vital signs" and "blood pressure measurement" were classified under
115 "assessment/clinical examination". The analysis and classification of the verbatim statements
116 were performed after comparing the independent analyses of two authors (S. L. and B. J.M.)
117 followed by arbitration.

118

119 The answers were then compared to the treatment stipulated in the medical curriculum (from
120 the University College of Nephrology Teachers) (12), and then to the treatment recommended
121 by the relevant European guidelines (12,13). The answers were stratified by the years of
122 study.

123

124 2.3. Statistical analysis

125

126 The analyses were performed using SAS® R9.4 software (SAS Institute, Cary, NC, USA).
127 The bilateral significance level was set at $p < 0.05$.

128

129 All of the students' answers, which were generally binary, were proportionally described in
130 the general population according to the year of study. Those regarding the hyperkalemia and
131 hypokalemia thresholds were categorized; their distribution was analyzed according to the
132 year of study.

133

134 The proportion of answers that were in keeping with the curriculum and the relevant
135 European recommendations/literature data/expert opinions were based on indicator variables.
136 These were created from the students' answers, as well as the information in the curriculum
137 and the European guidelines.

138 Each indicator variable was rated "1" if the student's answer was in keeping with the medical
139 curriculum or the guidelines, and "0" if the answer was non-compliant.

140

141 The results were compared according to the years of study using Fisher's exact test, and the
142 thresholds of dyskalemia according to the years of study were compared using a Chi^2 test of
143 homogeneity.

144

145 **3. Results**

146 The percentage of questionnaires returned was 81.2% (n=290/357). Three questionnaires were
147 partially completed and were not included (Figure 1).

148

149 3.1. Description of the population

150 The general medicine students who responded to the questionnaire were evenly distributed
151 among the three years of internship (33.8% in the first year, 35.9% in the second year, and
152 30.3% in the third year).

153

154 3.2. Overall results and by the years of study and compare with the relevant guidelines

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156 3.2.1. Limits of kalemia considered to be pathological

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The students considered a mean hyperkalemia of 5.1 mmol/L to be pathological. The minimum hyperkalemia value proposed by one student was 3.5 mmol/L and the maximum value was 6.5 mmol/L. The mean hypokalemia considered to be pathological by the students was 3.4 mmol/L (minimum 2.5 mmol/L and maximum 3.8 mmol/L). (table 1)

Year	n=287	Hyperkalemia threshold				Hypokalemia threshold			
		K<5	K=5	5<K≤5.5	K>5.5	K<3	3≤K<3.5	K=3.5	K>3.5
1 st	n=97	10 (18.2%)	72 (74%)	11 (11.3%)	4 (4.1%)	4 (4.1%)	16 (16.5%)	76 (78.4%)	1 (1%)
2 nd	n=103	6 (5.8%)	61 (59.2%)	34 (33%)	2 (1.9%)	3 (2.9%)	17 (16.5%)	82 (79.6%)	1 (1%)
3 rd	n=87	1 (1.1%)	59 (67.8%)	26 (29.9%)	1 (1.1%)	1 (1.1%)	20 (23%)	66 (79.5%)	0 (0%)
		<i>p=0.0005</i>				<i>p=0.85</i>			

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Table 1: Hyperkalemia and hypokalemia threshold (mmol/L) according to the years of study.

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There was a statistically significant difference in the hyperkalemia thresholds for the different years of study ($p=0.0005$). Nearly a quarter of the students rated the threshold for hypokalemia as being strictly below 3.5 mmol/L (21.3%, $n=61/287$) (Table 1).

The kalemia thresholds considered to be pathological according to the curriculum (11) and the relevant guidelines (13) were the same (hypokalemia = 3.5 mmol/L and hyperkalemia = 5.0 mmol/L). This hypokalemia threshold was indicated by 78% ($n=224/287$) of the students, while this hyperkalemia threshold was indicated by 66.9% ($n=192/287$) of the students, and 59.6% ($n=171/287$) of the students correctly identified both of these pathological thresholds.

3.2.2. Perception of danger

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 192

More than half of the general medicine students thought that severe hyperkalemia was more of a “concern” than severe hypokalemia (60.3% ($n=173/287$) vs. 26.5% ($n=76/287$)); for

193 10.8% (n=31/287) both types of kalemia were a concern, while for 2.4% (n=7/287) severe
194 dyskalemia was not a concern. The students' answers were similar across all internship years
195 (p=0.74).

196 There was no difference in terms of what the students had been taught regarding the danger
197 associated with hyperkalemia versus hypokalemia. The Expert Consensus of the European
198 Society of Cardiology has stated that hypokalemia maybe even more dangerous than
199 hyperkalemia (14) (only 26.5% (n=76/287) of the students shared this opinion).

200

201 3.2.3. Clinical cases and comparison with evidence by medicine

202 The students were presented with 3 hypothetical clinical situations:

203

204 1/ Isolated hypokalemia at 2.6 mmol/L (Figure 2)

205

206 Most of the students stated that they would perform an electrocardiogram (ECG) (79.8%,
207 n=229/287) and oral potassium supplementation (70.7%, n=203/287); while 16.7%
208 (n=48/287) would provide intravenous supplementation. Half of them (53.7%, n=154/287)
209 would request another kalemia test and 59.9% (n=172/287) would perform additional
210 biological tests. Only a quarter of the students (28.6%, n=82/287) would undertake oral
211 questioning and a clinical examination of the patient. They were generally not inclined to ask
212 for advice from a specialist (28.6%, n=82/287). The further along the student was with their
213 studies, the less likely they were to perform an electrocardiogram (ECG) in case of isolated
214 hypokalemia (p=0.0001). On the other hand, they would more often request additional
215 biological tests (p=0.004). The students in the second year were the most inclined to
216 supplement with potassium (p=0.029) and they were the least inclined to refer their patients to
217 the emergency department or to a hospital (p=0.025). There was not a statistical difference
218 between the internship year in terms of checking the kalemia a second time (p=0.33) or
219 performing an interview and a clinical examination (p=0.47).

220 More than 50% of the students provided answers that were in keeping with the medical
221 curriculum and with the data in the literature, except for the items "Interrogation/clinical
222 examination" (28.6%, n=82/287) and "Diet rich in potassium" (1.4%, n=4/287). The major
223 difference lies in the way the patient would be supplemented with potassium: 70.7%
224 (n=203/287) of the patients would be given an oral supplementation in accordance with the
225 data in the literature (15,16). Indeed, interrogation, clinical examination and further
226 investigations are essential to determine whether the patient should be hospitalized, and if so,

227 the route of administration will be intravenous. If there is good tolerance and no signs of
228 severity, the route of administration will be oral. There is no discrepancy between curriculum
229 and expert opinion.

230

231 2/ Isolated hyperkalemia at 5.7mmol/L (Figure 3)

232

233 Approximately three-quarters of the students indicated that they would first request another
234 kalemia test (75.3%, n=216/287). An ECG was favored by 59.9% (n=172/287), and slightly
235 less than half would prescribe an ion-exchange resin (44.9%, n=129/287) or additional
236 biological testing (47%, n=135/287). Very few would undertake oral questioning and a
237 clinical examination of the patient (15.7%, n=45/287) or ask for the opinion of a specialist
238 (20.6%, n=59/287). Students in the first year of internship were the most likely to favor
239 performing an ECG ($p < 0.0001$) and to treat the patient with Polystyrene Sulfonate
240 ($p = 0.0002$), while students in the second year were the least likely to recommend an ECG
241 ($p < 0.0001$) and to treat with Polystyrene Sulfonate ($p = 0.0002$). There was not a statistical
242 difference between the year of study with regard to checking the kalemia a second time **to**
243 **rule-out false hyperkalemia** ($p = 0.21$) or performing additional biological tests ($p = 0.098$).

244 In case of true hyperkalemia (excluding false hyperkalemia secondary to **hemolysis and/or**
245 delayed blood centrifugation), three items were different between the medical curriculum and
246 the expert opinions: the students agreed with the curriculum in terms of performing an ECG
247 (59.9%, n=172/287) but also with the experts' opinions in regard to not performing additional
248 biological examinations (53%, n=152/287) or prescribing Sodium Polystyrene Sulfonate
249 (55.1%, n=158/287), at this level of kalemia.

250

251 3/ Hyperkalemia of 6.0 mmol/L in a patient with heart and kidney failure (Figure 4)

252

253 The answers of the students regarding the management of this situation were very
254 heterogeneous: half of them would perform an ECG (51.2%, n=147/287, 51.6% of the
255 students would discontinue the MRA and/or ACE inhibitor (n=148/287), while a third would
256 reduce their dose (34.5%, n=99/287). More than a third of the students (39.7%, n=114/287)
257 stated that they would treat this hyperkalemia with an ion-exchange resin. Less than half of
258 the students (42.5%, n=122/287) indicated that they would ask for specialist advice. The
259 further along the general medicine student was with their studies, the more they favored
260 prescribing an ion-exchange resin ($p = 0.023$), and the more they would perform another check

261 of the kalemia ($p < 0.0001$) to rule-out a false hyperkalemia (due to the sampling process e.g.
262 at home, with delayed centrifugation leading to hemolysis) and additional biological
263 examinations ($p=0.024$). There was not a statistical difference between the years of study in
264 regard to whether they would perform an ECG ($p=0.42$) or transfer the patient to the
265 emergency department ($p=0.085$).

266 Several items were discordant between the medical curriculum and the guidelines: the
267 students' answers were in keeping with the European guidelines to not undertake additional
268 biological examinations (80.1%, $n=230/287$). On the other hand, only 3.8% ($n=11/287$)
269 followed the guidelines for "temporary" discontinuation of MRA and/or ACE, and more than
270 51.6% ($n=148/287$) recommended "permanent" discontinuation. Increasing the dosage of
271 Furosemide was considered appropriate by 20.6% ($n=59/287$).

272

273

274 **4. Discussion**

275

276 To our knowledge, this is the first study to evaluate the competence and the perception of
277 danger of graduating French general medicine students regarding dyskalemia.

278 - The knowledge regarding the management of dyskalemia was highly variable from one
279 student to the next and according to how close they were to completion of their medical
280 degree.

281 - The thresholds for dyskalemia were not well known and there was inadequate recognition of
282 the risk associated with hypokalemia.

283 - French medical students appear to favor the use of ion exchange resins. This is specific to
284 France and probably due to what is taught in the medical curriculum.

285 - In case of hyperkalemia in the context of heart and renal failure, management was mostly
286 focused on the renal risk, while ignoring the cardiovascular benefit.

287 - The students tended to be disinclined to examine patients in case of dyskalemia.

288 - The students tended to see little merit in engaging a specialist when faced with dyskalemia.

289 - The use of ECG decreased as the studies progressed, probably because the internship in the
290 GP's office has not yet been completed in the seventh-year initial formation.

291

292

293

294 4.1. Variability of the answers

295 We were surprised to discover that some students considered extreme and dangerous values to
296 be the pathological thresholds for kalemia: 2.5 mmol/L for hypokalemia and 6.5 mmol/L for
297 hyperkalemia.

298 The greatest diversity in the answers related to hyperkalemia with heart and renal failure, and
299 was dependent on the level of advancement in the specialty, especially in regard to the
300 prescription of Sodium Polystyrene Sulfonate (28.9% of students in the first year of internship
301 versus 47.1% in the third year) and performing a second kalemia test **to rule-out a false**
302 **hyperkalemia due to the sampling process** (19.6% in the first year versus 49.4% in the third
303 year). Four students even stated that they would stop all treatments (1.4%), which is generally
304 thought to be extremely dangerous for the patient.

305 In case of isolated hypokalemia, management varied also according to the years of study:
306 students in the second year of internship were the most likely to supplement by oral
307 administration and to not refer their patients to the emergency department, unlike the other
308 two years. In addition, there was a difference in the way the potassium would be
309 supplemented: 16.7% would do so intravenously versus 68.3% favoring oral administration.

310 In the case of isolated hyperkalemia, the approach of the seventh-year medical students was
311 essentially to perform an ECG, to treat with Sodium Polystyrene Sulfonate, and to recheck the
312 kalemia, whereas the approach of the ninth-year medical students was to initially only recheck
313 the kalemia. The thresholds considered pathological are different in each laboratory, and
314 students rely on these standards to manage hyperkalemia.

315

316 4.2 Inadequate recognition of the risk related to hypokalemia

317 The risk associated with hypokalemia is often underestimated by students. Indeed, mortality is
318 significantly increased below a threshold of 4.1 mmol/L in case of hypertension (1) or chronic
319 heart failure (17), and 3.9 mmol/L in case of acute heart failure after myocardial infarction
320 (18). Several studies have also shown that hypokalemia is associated with increased mortality
321 in heart failure (19), and that blood potassium levels below 4.0 mmol/L are associated with an
322 increased risk of all-cause mortality, mortality from cardiovascular disease and progressive
323 heart failure, and an increased rate of all-cause and cardiovascular hospitalizations (9,20).
324 Hypokalemia increases the risk of ventricular arrhythmia and cardiac arrest (2,21); a decrease
325 in blood potassium by 1 mmol/L increases the risk of ventricular arrhythmia by 28% (22). In
326 case of cardiac arrest, kalemia is thought to be significantly lower than in controls, and
327 survivors are often hypokalemic (23-25).

328 There is a U-shaped relationship between kalemia and all-cause mortality, and levels of
329 potassium that are considered "normal" are also associated with an increased risk of death. In
330 general, the more the potassium level deviates from normal, the higher the mortality (1).

331

332 4.3. Widespread use of ion-exchange resins

333 French general medicine students are taught to use Sodium Polystyrene Sulfonate (SPS),
334 which is an ion-exchange resin. This is in accordance with the practices of French doctors,
335 who use SPS much more frequently than their German, Italian, Spanish, and English
336 colleagues (26). However, there is no evidence regarding the efficacy of SPS in the
337 emergency treatment of hyperkalemia (27, 28). The optimal rate of correction for
338 hyperkalemia is unknown, and the relevance of an immediate decrease of kalemia in patients
339 without cardiac manifestations of hyperkalemia has not been demonstrated (29). Additionally,
340 this drug has not been rigorously evaluated in clinical trials to prove its efficacy and safety in
341 acute or chronic hyperkalemia (30). Since the counter-exchange ion is sodium, extreme
342 caution should be taken in patients with heart failure, as such patients cannot tolerate even a
343 small increase in sodium load (30). **It should be noted that SPS has marketing authorization**
344 **(MA) in France for medical services rendered that are considered important.** This drug was
345 indicated as a first-line treatment for hyperkalemic patients in the French medical curriculum
346 (12) at the time that the questionnaire was distributed (June 2017). This has been modified in
347 the new version of the curriculum released in 2018 by the University College of Nephrology
348 Teachers (version 8), which no longer considers SPS as a necessity but as an option in case of
349 hyperkalemia. **Of importance, none of the new-generation potassium binders is reimbursed in**
350 **France to date, therefore preventing from any related teaching process.**

351

352 4.4. Management of hyperkalemia in heart and renal failure

353 The management of hyperkalemia by French general medicine students differs quite
354 considerably from the European guidelines. They tend to discontinue ACE inhibitors and/or
355 MRAs without considering reintroducing them, which can adversely affect patients as the
356 morbi-mortality increases without the use of an optimal dose of these drugs (30-32). Trevisan
357 et al. have shown that after hyperkalemia, 47% of MRA treatments are halted, and they are
358 not reintroduced in 76% of cases (33). Discontinuation of RAAS inhibitor therapy is
359 associated with an increased risk of cardiovascular morbidity and mortality and total mortality
360 (14). The European guidelines in regard to heart failure tolerate a maximum hyperkalemia
361 threshold of 6.0 mmol/L. Above this limit, RAAS inhibitors should be discontinued for a

362 time, but not definitively; between 5.5 and 6.0 mmol/L, there can be brief discontinuation or
363 dose reduction (13,14). Thus, the European guidelines emphasize the need to try to
364 reintroduce RAAS inhibitors as soon as possible, when they have been temporarily halted or
365 the dosage decreased due to hyperkalemia, with close monitoring of kalemia and renal
366 function (13). Increasing the dosage of furosemide, considered as appropriate by 20% of the
367 students, is an acceptable solution in case of hyperkalemia, but it should however be avoided
368 in case of AKI and signs of dehydration.

369 The management is in accordance with what is taught in the Nephrology module of the
370 medical school curriculum in the chapter entitled "Potassium balance abnormalities" (12).
371 This is theory-based teaching that does not consider the complexity encountered in case of
372 comorbidities such as the association with heart failure, and which recommends, in the case of
373 moderate hyperkalemia, "eviction of hyperkalemic drugs", without their subsequent
374 reintroduction. The risk/benefit ratio of hyperkalemia is not emphasized in teaching, and
375 general medicine students tend to refer to "*Primum Non Nocere*", which is a concept that has
376 become obsolete.

377 On the other hand, in the chapter regarding how to treat chronic renal failure, the possibility
378 of "temporary" discontinuation of ACE inhibitors or ARA2 is discussed, without any
379 reference to anti-aldosterone drugs, which are not mentioned in the curriculum. However, this
380 information is too "diluted" to be taken in by the students, especially as it contradicts the
381 information in the chapter "Potassium balance abnormalities".

382 Medical students are faced with contradictions that are even more prejudicial, as there is no
383 clear consensus regarding the management of these patients with cardio-renal syndrome in
384 general practice. The fear of inducing serious secondary effects (hyperkalemia, deterioration
385 of renal function) has led some doctors to avoid RAAS inhibitors (6), without considering the
386 demonstrated benefit of these molecules on morbi-mortality in the event of heart failure (5,
387 34,35). Moreover, the use of RAAS inhibitors in France is low compared to Germany, Italy,
388 Spain, and the United Kingdom (26). For this reason, the use of new experimental potassium
389 chelating agents (patiromer or sodium zirconium cyclosilicate (ZS-9)) could be an option in
390 the near future to compensate for this under-prescription (36-40). These drugs have a
391 European MA but are not presently available in France.

392

393 4.5. Limited use of interrogation and clinical examination

394 Surprisingly, we found that the students were very rarely inclined to carry out an interrogation
395 and clinical examination of patients with dyskalemia, even though this is generally considered

396 to be essential during a medical consultation. In case of dyskalemia, it is crucial to identify
397 any dietary issues and clinical elements associated with dyskalemia and to provide advice
398 accordingly. Very few students introduce, and therefore explain to the patient, a potassium-
399 rich diet in case of hypokalemia, whereas it is recommended in association with
400 supplementation (41,42).

401

402 4.6. Limited use of specialists

403 The students indicated that they would rarely request specialist advice and rarely refer their
404 patients to hospitals or emergency departments in case of isolated dyskalemia. They are
405 inclined to manage these situations on their own, especially if they are advanced in their
406 studies. The use of specialists and hospitalization is also low among practicing GPs, ranging
407 from 5.8 to 6.6% according to the study (43-45).

408

409 4.7. Use of the ECG

410 For isolated dyskalemia discovered in general practice, students in the first year of internship
411 more often recommend performing an ECG than those in the following two years of study.
412 This may be a result of the internship with a general practitioner. Indeed, although the
413 availability of the required equipment in doctors' offices varies from 49% to 86% according to
414 the study, the frequency of their use is at least once a week for half of the doctors who have
415 an ECG device available (46,47). Moreover, an ECG is not a very sensitive indicator of the
416 severity of dyskalemia. Cardiac manifestations may be non-specific or absent at potassium
417 concentrations that are associated with a risk of mortality (29). In case of hyperkalemia, an
418 ECG is recommended above 6.0 mmol/L (29), whereas in case of hypokalemia, it is
419 recommended for all patients, irrespective of their potassium level (49).

420

421 4.8. Strengths and limitations of the study

422

423 The main strength of this study lies with the use of an open-ended questionnaire, which
424 ensured that there were no leading questions.

425 We limited the potential for bias by clearly explaining the objectives of the study and how the
426 questionnaire was to be filled out before completing it. The questionnaires were filled out in
427 the presence of a friendly and neutral team, without direct intervention but with immediate
428 availability of assistance if required (self-administered questionnaire).

429 Methodological bias was minimized by providing resources to organize the task of collecting,
430 analyzing, and processing the information. The questions asked were intended to be
431 straightforward, short, neutral, and without ambiguity.

432 Naturally, sample selection bias cannot be fully ruled out, although we are confident that we
433 were able to ensure adequate representativity of the population of students enrolled in French
434 general medicine studies.

435 The bias linked to the "experience" of the general medicine students could be assessed by the
436 last question, although this question contained ambiguities. In June 2017, the students who
437 had just started a new stage of internship on May 1st did not necessarily include this in their
438 answer. Indeed, "current or ongoing internships" was not specified. There was, therefore, a
439 loss of information.

440 The questionnaire is not without its limitations, but overall, we avoided many of the potential
441 biases by excluding any leading questions and by reducing the time needed to complete the
442 questionnaire. The questions were open-ended so as not to suggest possible answers to the
443 situations described.

444 In conclusion, the validity of the results clearly needs to take into account the limitations
445 mentioned above, but these do not significantly detract from the coherence and overall
446 meaning of the results.

447

448 **5. Conclusion**

449 The medical curriculum cannot always take into account the complex situations experienced
450 in clinical practice. Our study points out a lack of coherence between what is taught regarding
451 the management of dyskalemia and the guidelines regarding patients with heart and renal
452 failure. This often results in inadequate management and a reluctance to reintroduce drugs
453 prone to induce hyperkalemia (ACE/ARA2 and MRA) after an initial episode of
454 hyperkalemia. This at least in part explains why France has the lowest level of RAAS
455 inhibitor use in Europe (27), and why these drugs are often used at a suboptimal dosage in
456 heart failure. This is quite the opposite in case of chronic kidney insufficiency, for which
457 France has the highest level of RAAS inhibitor use in Europe (50).

458 It is essential for medical students to very early on be faced with complex situations in the
459 management of cardio-renal syndrome, due to the increasing prevalence of this syndrome
460 among older patients with diabetes, heart failure, and kidney disease.

461 Medico-administrative data such as the SNDS (Système National de Données de Santé) are
462 collected by the Primary Health Insurance in France, but the tools proposed to SNDS users
463 make their in-depth exploitation difficult. A view based on a generic model of care
464 trajectories could make it possible to identify situations in which the trajectory of care can
465 be improved (e.g., severe hypokalemia, severe hyperkalemia) and thus serve as a basis for
466 more pragmatic teaching, adapted to general practitioners. (51)

467 Indeed, the recent opening of access to the French nationwide health record database SNDS
468 is a great opportunity to carry out comprehensive health studies at the country level. Happe
469 and Drezen have proposed a toolbox to query and cope with the complexity of care
470 pathways of patients, because access is very difficult for nonexpert data scientists. This
471 toolbox is particularly suitable for understanding timeline representations of individual
472 patient healthcare trajectories in case of heart failure and cardiorenal syndrome. (52)

473 It would also be appropriate to standardize the guidelines and the curriculum in order to
474 provide pragmatic instruments to help with the management of dyskalemia in patients with
475 heart failure and kidney disease, either as a decision tree or a dedicated computer tool.

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480 **6. References**

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651
652 Lisa Senninger: Research design, data collection, data entry, writing.
653 Laure Abensur-Vuillaume: Proofreading, partial writing
654 Luc Frimat: Proofreading, partial writing
655 Nicolas Girerd: Proofreading, partial writing
656 Zohra Lamiral: statistical review
657 Patrick Rossignol: Proofreading, partial writing
658 Jean-Marc Boivin: Research design, Proofreading, partial writing

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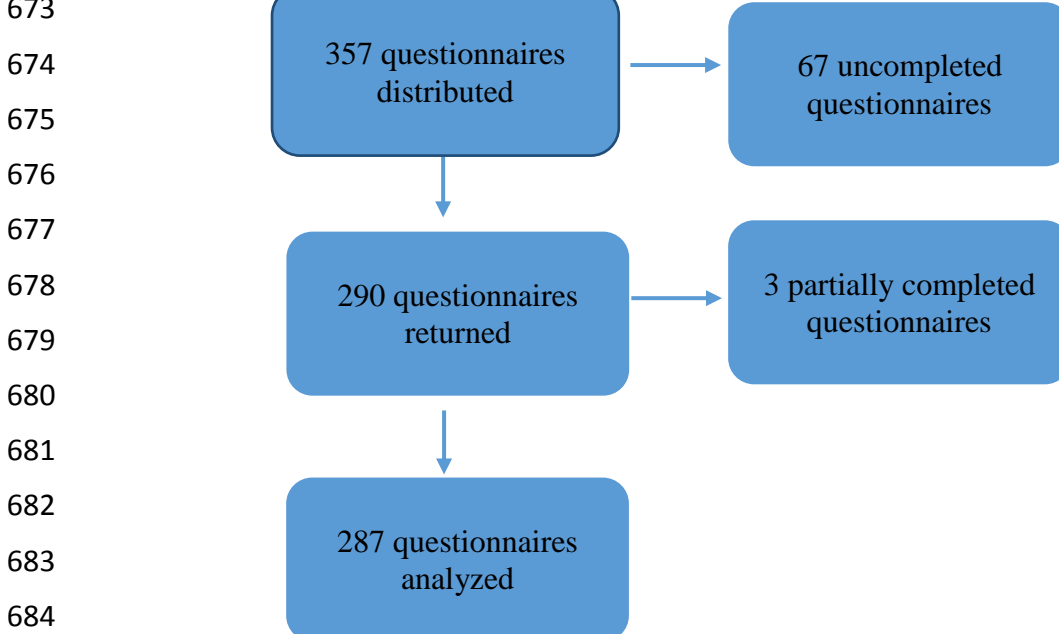
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667 d. Data sharing statement: All data are available on request to the corresponding author.

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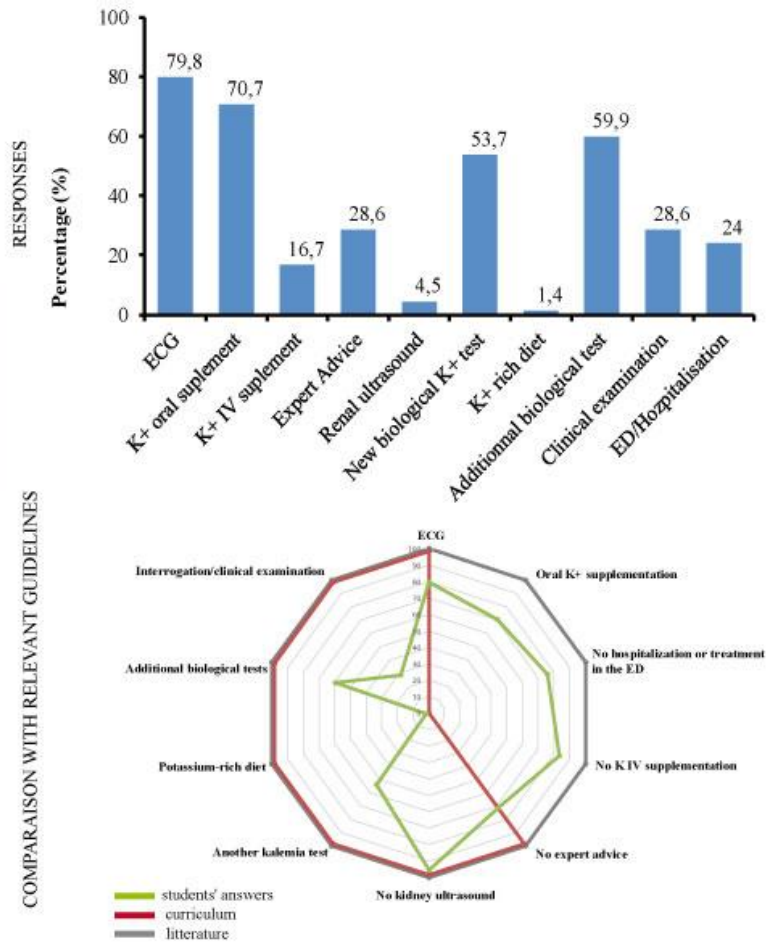
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686 **Figure 1: Flowchart of the participants**

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CLINICAL CASE

In an otherwise healthy patient (i.e. with no history of comorbidities) with not any treatment, you discover a kalemia of 2.6 mmol/L during a routine check-up. What is (are) your reaction(s) in terms of drug prescriptions, investigations, specialist advice?



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Figure 2: Hypokalemia of 2.6mmol/L in a patient who is not on any treatment: student's responses and comparison with literature and curriculum

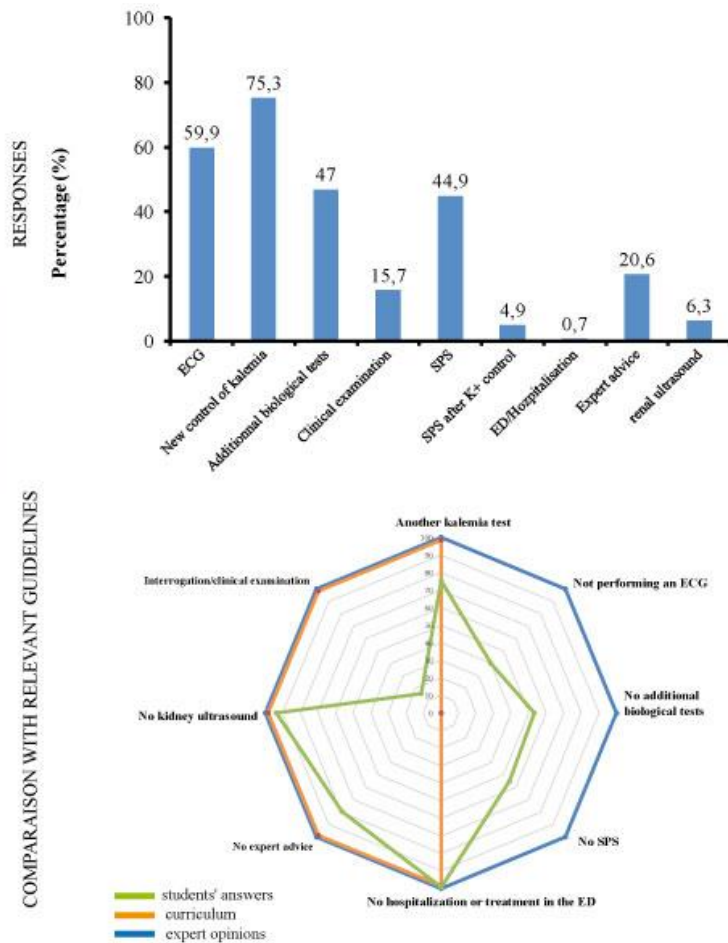
The radar chart is represented by student's answers in green, curriculum in red, and expert opinion in grey.

Legend: IV (intravenous), ED (emergency department).

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CLINICAL CASE

In an otherwise healthy patient (i.e. with no history of comorbidities) with not any treatment, you discover a blood potassium level of 5.7 mmol/L during a routine check-up. What is (are) your reaction(s) in terms of prescriptions, additional examinations, and specialist advice?



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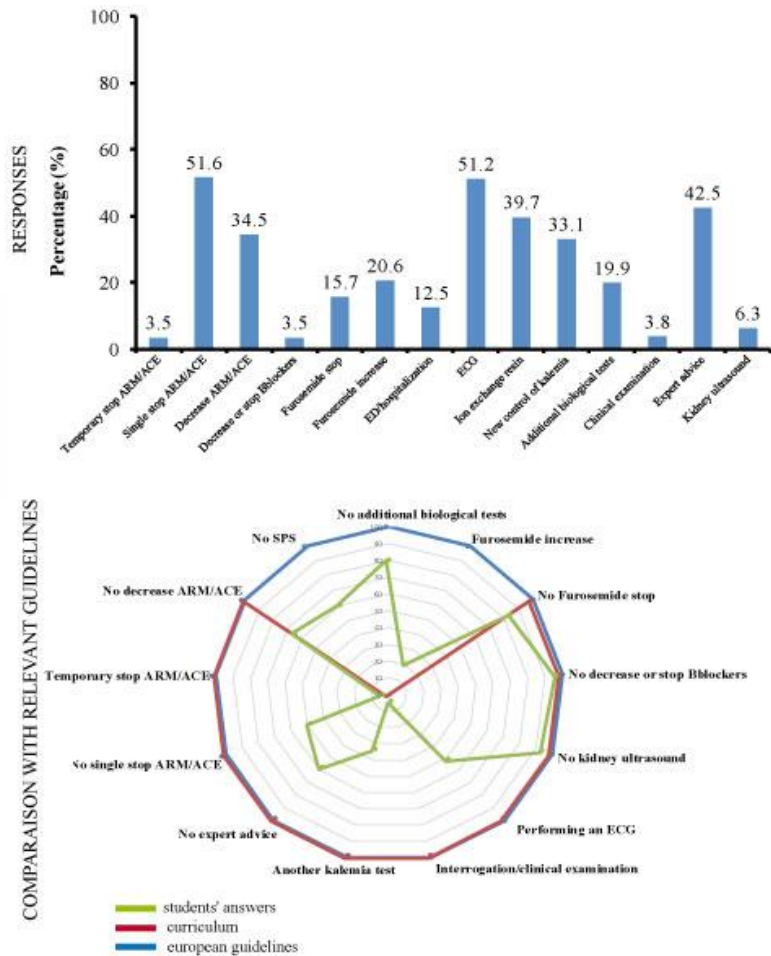
Figure 3: Hyperkalemia of 5.7mmol/L in a patient who is not on any treatment: student's responses and comparison with expert opinions and curriculum

The radar chart is represented by student's answers in green, curriculum in orange, and expert opinion in blue.

Legend: ARM (Angiotensin Receptor Agonist), ACE (Angiotensin-converting enzyme inhibitors), SPS (Sodium Polystyrene sulfates), ED (emergency department).

CLINICAL CASE

In a patient known to have severe HF and CKD, treated with Perindopril 10 mg, Aldactone 50 mg, Bisoprolol 10 mg, and Furosemide 20 mg, what is (are) your reaction(s) in terms of possible changes in medication (dose), drug prescriptions, additional tests, specialist advice, if the patient has a potassium level of 6.0 mmol/L with creatinine at 15 mg/L (GFR: 50 ml/min)?



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Figure 4: Hyperkalemia of 6.0mmol/L in a patient with heart and kidney failure, student's responses and comparison with European guidelines and curriculum
The radar chart is represented by student's answers in green, curriculum in red, and expert opinion in blue.
Legend: ARM (Angiotensin Receptor Agonist), ACE (Angiotensin-converting enzyme inhibitors), SPS (Sodium Polystyrene sulfate), ED (emergency department), GFR (Glomerular filtration rate), HF (Heart failure), CKD (Chronic kidney disease).

		Hyperkalemia threshold				Hypokalemia threshold			
Year	n=287	K<5 17 (5.9%)	K=5 192 (66.9%)	5 < K ≤ 5.5 71 (24.7%)	K > 5.5 7 (2.4%)	K < 3 8 (2.8%)	3 ≤ K < 3.5 53 (18.5%)	K=3.5 224 (78%)	K > 3.5 2 (0.7%)
1 st	n=97	10 (18.2%)	72 (74%)	11 (11.3%)	4 (4.1%)	4 (4.1%)	16 (16.5%)	76 (78.4%)	1 (1%)
2 nd	n=103	6 (5.8%)	61 (59.2%)	34 (33%)	2 (1.9%)	3 (2.9%)	17 (16.5%)	82 (79.6%)	1 (1%)
3 rd	n=87	1 (1.1%)	59 (67.8%)	26 (29.9%)	1 (1.1%)	1 (1.1%)	20 (23%)	66 (79.5%)	0 (0%)
		<i>p=0.0005</i>				<i>p=0.85</i>			

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742 **Table 1: Hyperkalemia and hypokalemia threshold (mmol/L) according to the years of**

743 **study.**

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