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► **To cite this version:**

Cyril Mousseaux, Romain Arrestier, Khalil Chaibi, Antoine Braconnier, Aldjia Hocine, et al.. Management of severe hypercalcaemia: results of the French-speaking physicians' practice survey. *Nephrology Dialysis Transplantation*, 2023, 38 (6), pp.1571-1573. 10.1093/ndt/gfad018 . hal-04400886

HAL Id: hal-04400886

<https://amu.hal.science/hal-04400886>

Submitted on 5 Feb 2024

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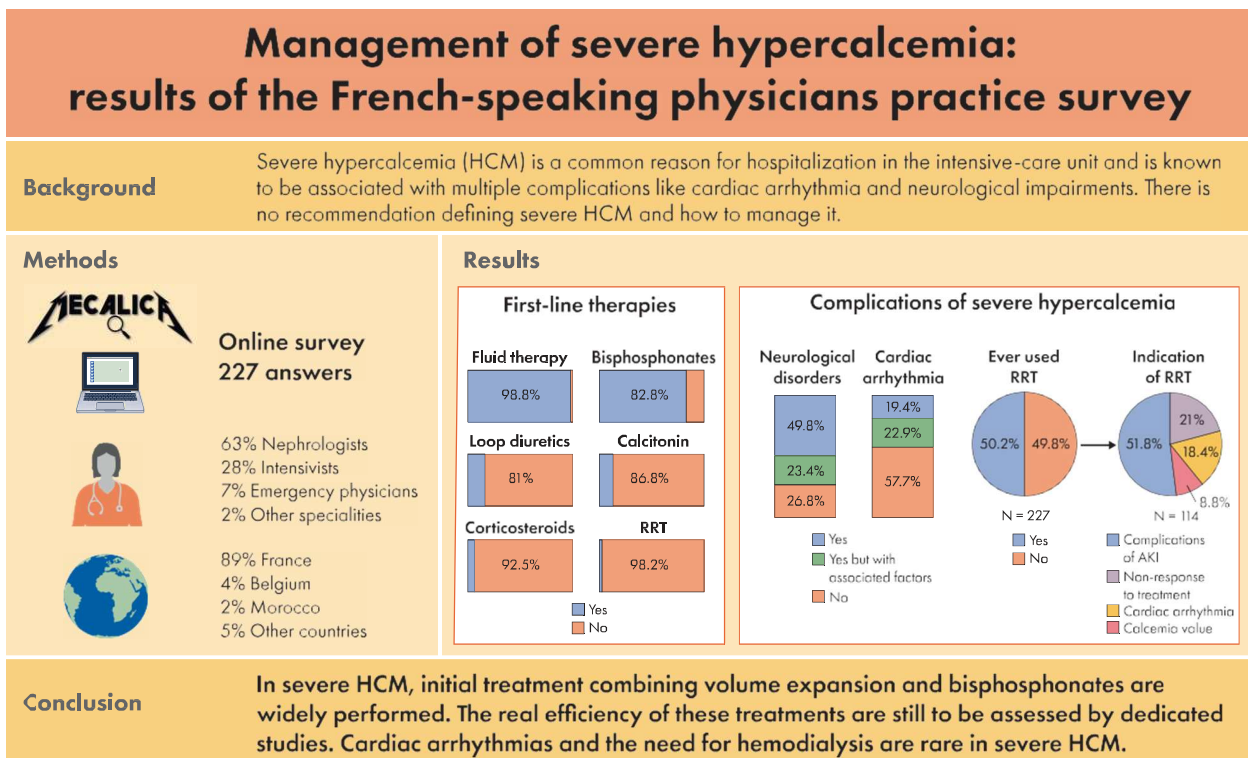
Management of severe hypercalcaemia: results of the French-speaking physicians' practice survey

Cyril Mousseaux^{1,2,3}, Romain Arrestier^{4,5}, Khalil Chaibi^{2,3,6}, Antoine Braconnier⁷, Aldjia Hocine^{8,9}, Antoine Lanot^{10,11}, Justine Serre^{2,3} and Mickaël Bobot^{12,13}; on behalf of the Club des Jeunes Néphrologues

¹Soins Intensifs de Néphrologie et Rein Aigu, Hôpital Tenon, AP-HP, Paris, France, ²INSERM UMR_S1155, CoRaKID, Hôpital Tenon, Paris, France, ³Faculté de Médecine, Sorbonne Université, Paris, France, ⁴Service de Médecine Intensive Réanimation, AP-HP, Hôpitaux Universitaires Henri Mondor, Créteil, France, ⁵Groupe de Recherche Clinique CARMAS, Faculté de Médecine de Créteil, Créteil, France, ⁶Service de Réanimation Médico-Chirurgicale, AP-HP, Hôpital Avicenne, Bobigny, France, ⁷Service de Néphrologie-Dialyse-Transplantation, Hôpital Maison Blanche, Reims, France, ⁸Service de Néphrologie, Clinique du Landy, Saint-Ouen, France, ⁹Service de Néphrologie, Hôpital Bichat Claude Bernard, AP-HP, Paris, France, ¹⁰Service de Néphrologie, CHU de Caen Normande, Normandie Université, Caen, France, ¹¹U1086 INSERM-UCN, "ANTICIPE", Centre François Baclesse, Caen, France, ¹²Centre de Néphrologie et Transplantation Rénale, Hôpital de la Conception, AP-HM, Marseille, France and ¹³INSERM 1263, INRAE 1260, C2VN, Aix-Marseille Université, CERIMED, Marseille, France

Correspondence to: Cyril Mousseaux; E-mail: cyril.mousseaux@aphp.fr

GRAPHICAL ABSTRACT



Severe hypercalcaemia is a frequent cause of hospitalization in the intensive care unit. The two most frequent causes of hypercalcaemia are primary hyperparathyroidism and malignancy [1, 2]. Hypercalcaemia is known to be associated with multiple complications, including cardiac arrhythmia, acute kidney injury (AKI), acute pancreatitis and neurological impairments (seizures, delirium, coma) [3, 4] and with increased mortality in intensive care [5]. Yet, few solid data exist in the literature about the efficacy of treatments used in severe hypercalcaemia. Since there is no recommendation defining what severe hypercalcaemia is and how to manage it, we decided to survey French-speaking physicians managing patients with severe hypercalcaemia.

Through our survey, Management of hyperCALcemia in Intensive Care (MECALICA), promoted by the Club des Jeunes Néphrologues (French Young Nephrologists Association), we sought to determine how physicians are defining severe hypercalcaemia and how they manage these patients.

A total of 227 physicians practicing in 11 countries [France, $n = 201$ (89%) and Belgium, $n = 9$ (4%)] responded to the survey sent in April 2022. Respondents were nephrologists [$n = 143$ (63%)], intensivists [$n = 64$ (28%)] and emergency medicine practitioners [$n = 16$ (7%)]. The three main specialties were nephrology [$n = 143$ (63%)], intensive care medicine [$n = 64$ (28%)] and emergency medicine [$n = 16$ (7%)]. Severe hypercalcaemia remains rare in current practice in our survey: 50% ($n = 114$) of the respondents managed <5 patients with severe hypercalcaemia per year, 38%

($n = 85$) managed 5–10 patients and 12% ($n = 28$) managed >10 patients.

Among the methods for estimating blood calcium levels, ionized calcium [$n = 105$ (46%)] and albumin-corrected calcium [$n = 76$ (33%)] were used the most (Fig. 1A). Most of the participants [$n = 147$ (65%)] considered that a biological threshold defining severe hypercalcaemia exists (Fig. 1B). Depending on the formula used, this mean threshold was 2.03 ± 0.5 mmol/l for ionized calcium and 3.55 ± 0.5 mmol/l for total calcium (see Supplementary Table S1 for details).

A total of 51% ($n = 116$) of the physicians believed that there is a biological threshold for cardiac monitoring in case of hypercalcaemia and 42% ($n = 96$) had patients who experienced cardiac arrhythmia due to hypercalcaemia (Fig. 1C). Among them, 46% estimated that these arrhythmias resulted from hypercalcaemia alone, while 54% considered these disorders multifactorial (mainly associated with hypokalaemia and hypovolaemia). Neurological disorders related to hypercalcaemia were more frequently reported [$n = 166$ (73%)]. These neurological abnormalities were thought to result from hypercalcaemia alone [$n = 113$ (68%)] and 23% with other associated factors.

The most frequent laboratory investigations were parathyroid hormone [PTH; $n = 216$ (95%)], phosphataemia [$n = 206$ (91%)], serum protein electrophoresis [$n = 186$ (82%)] and calcidiol [$n = 143$ (63%)]. Even when an obvious cause of hypercalcaemia is present (e.g. the context of multiple myeloma or metastatic cancer), most physicians still order a PTH test [$n = 170$ (75%)].

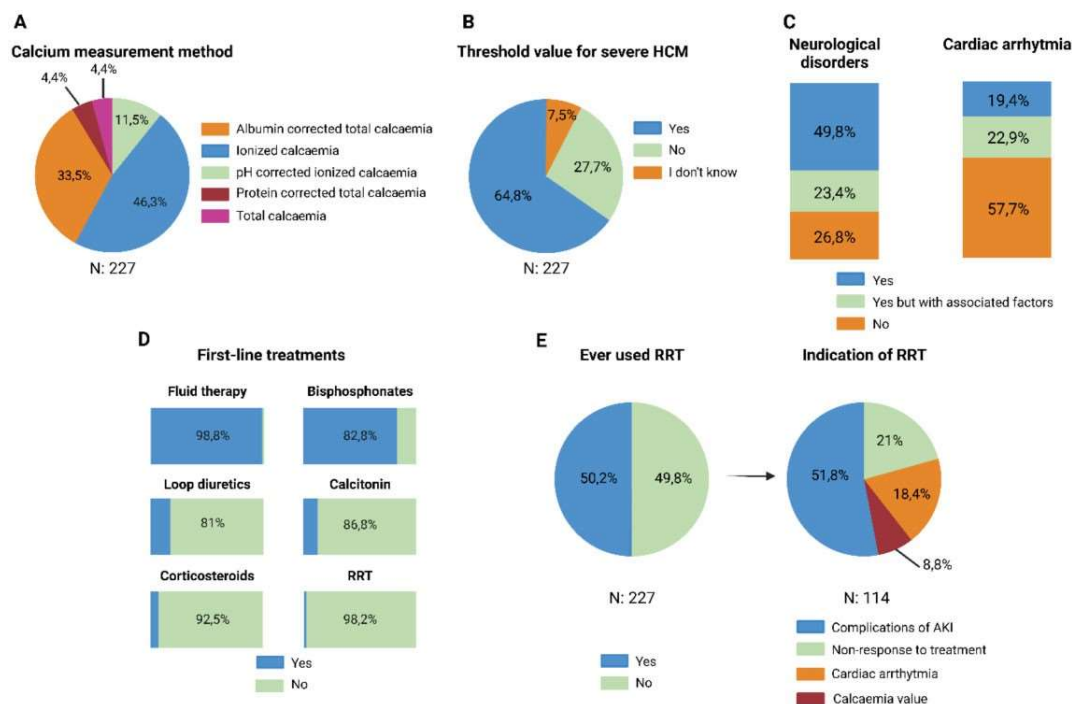


Figure 1: Survey results from French-speaking physicians about the management of severe hypercalcaemia. HCM: hypercalcaemia. Figure created with Biorender.com.

For most of the surveyed practitioners, the treatment of hypercalcaemia was based on a combination of volume expansion [$n = 224$ (99%)] and bisphosphonates [$n = 188$ (83%)] (Fig. 1D). Other first-line treatments included loop diuretics [$n = 43$ (19%)], calcitonin [$n = 30$ (13%)] and corticosteroids [$n = 17$ (7.5%)]. Only 2% ($n = 4$) of the respondents used renal replacement therapy (RRT) as first-line therapy in severe hypercalcaemia and none used denosumab.

The bisphosphonates administered were pamidronate [$n = 128$ (59%)] and zoledronate [$n = 74$ (34%)], followed by alendronate [$n = 10$ (4.5%)] and ibandronate [$n = 4$ (1.8%)]. AKI and lack of dental examination were not considered a contraindication to bisphosphonates by 79% and 83.2% of physicians, respectively. When a bisphosphonate reinjection was planned (63% of the practitioners reinjected the bisphosphonates), it was based on the blood calcium level 72 hours after the start of treatment (in 65%). Half of the participants have used RRT in the case of hypercalcaemia [$n = 114$ (50%)] (Fig. 1D). The main reasons for RRT (Fig. 1E) were AKI associated with hypercalcaemia and its complications (53%), the presence of electrocardiogram (EKG) signs of hypercalcaemia (20%), lack of response to hypocalcaemic treatment (22%) and, rarely, the calcium level (9%).

The criteria for discharge from the intensive care unit were as follows: normalization of the EKG [$n = 188$ (85%)], normalization of the state of consciousness [$n = 181$ (82%)], beginning of a decrease in serum creatinine [$n = 95$ (43%)] and a reduction [$n = 84$ (38%)] or even normalization of the calcium level [$n = 55$ (25%)].

The complete survey results are presented in Supplementary Table S1.

This survey is the first to provide insights into the diagnostic and therapeutic practices of a wide range of physicians managing patients with what is thought to be severe hypercalcaemia.

A little more than half of the respondents believe that there is a biological threshold defining severe hypercalcaemia, although several questions remain unanswered: Does this threshold really exist, or should the severity of hypercalcaemia be defined by clinical outcome? What is the specificity of organ damage in hypercalcaemia, and is it associated with poorer outcome? This last point is of paramount importance because one of the main reasons for admission to intensive care is the fear of cardiac rhythm disorders. However, consistent with the literature, our survey shows that they are rare [6]. Conversely, neurological manifestations seem more common [3]. Associated emergencies like ionic disorders and severe AKI seem to worsen the risk of arrhythmia and increase the need for RRT.

Another aspect is the therapeutic management of these patients. Despite the absence of a recommendation in this regard, first-line management is homogeneous among physicians. An initial treatment combining volume expansion and bisphosphonates and systematic PTH measurement (as 21% of the patients with active neoplasia may have hypercalcaemia of a non-tumoral cause [7]) are thus widely performed. Interestingly, the need for haemodialysis is rare. When performed, it is mostly explained by the associated AKI. However, a lot of essential data are still missing and the real efficiency of

these treatments in hypercalcaemia is still to be assessed by dedicated interventional studies, as most of the data are ancient and concern patients with malignancies and variable levels of hypercalcaemia [2].

Future work on severe hypercalcaemia should focus on its definition and provide more recent data about evaluation of treatment effectiveness in its acute phase and with the objective of establishing management guidelines.

SUPPLEMENTARY DATA

Supplementary data is available at *ndt* online.

ACKNOWLEDGEMENTS

We thank the societies who disseminated this survey: the Club des Jeunes Néphrologues (French Young Nephrologist Association), the Société Francophone de Néphrologie, Dialyse et Transplantation (SFNDT; French Society of Nephrology), the Association des Jeunes Anesthésistes-Réanimateurs de France (AJAR; French Young Anesthetists-Intensivists Association), the French Intensive Care Renal Network (FIRN), the Société de Réanimation de Langue Française (SRLF; French Intensive Care Society) and the Groupement des Néphrologues Francophones de Belgique (GNFB; French-speaking Belgian Society of Nephrology).

FUNDING

None declared.

AUTHORS' CONTRIBUTIONS

C.M. and M.B. were responsible for conceptualization and wrote the original draft. C.M., R.A., J.S., A.L. and M.B. were responsible for the design. All authors were responsible for dissemination of the survey, revised the manuscript critically and approved the final version.

CONFLICT OF INTEREST STATEMENT

None of the authors declare any competing interests.

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