

RESEARCH ARTICLE

Issuing of isotonic crystalloid solutions to Danish public hospitals in 2021—A retrospective nationwide observational study

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Abstract

Background: Intravenous (IV) fluid therapy is a ubiquitous intervention in daily clinical practice. However, nationwide detailed hospital- and departmental-level information on IV fluid use is limited. Hence, we aimed to describe the current issuing of isotonic crystalloid solutions across Danish public hospitals.

Methods: We conducted a nationwide, retrospective observational study describing the issuing of isotonic crystalloid solutions for IV administration, including 0.9% saline, acetate- and lactate-buffered crystalloid solutions. We assessed fluid issuing at national-, regional-, hospital- and departmental-level from 1 January 2021 to 31 December 2021. We obtained sales figures from the Danish Regional Hospital Pharmacies. Regional characteristics were acquired from the Danish Health Data Authorities online resources. Results are presented graphically and descriptively, including frequencies (%).

Results: The total amount of isotonic crystalloid solutions issued across Danish public hospitals in 2021 was 1,487,144 L (67.4% saline, 25.9% acetate- and 6.7% lactate-buffered solutions) equivalent to 2.1 L per hospitalised patient within the study period. Both the issuing of saline versus buffered crystalloid solutions and the issuing of acetate- versus lactate-buffered solutions varied across geographical regions. Medical departments used saline more frequently (85.3%) than emergency departments (71.5%), surgical departments (70.6%) and anaesthesiological departments including intensive care units (43.0%).

Conclusions: In this nationwide observational study, we found that the issuing of different isotonic crystalloid solutions varied based on geographical location. Furthermore, the issuing of different crystalloid solutions differed across departmental settings with medical departments using the highest proportion of saline and

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anaesthesiological departments using the highest proportion of buffered crystalloid solutions.

Editorial Comment: IV fluid administration practices can be assessed across specialties by examining hospital purchasing. This study analysed the use of IV isotonic crystalloid solutions across all major departments of Danish public hospitals for 1 year. Isotonic sodium chloride was the most commonly used fluid in emergency medicine (71%), internal medicine (85%) and surgical departments (71%). Only anaesthesia and intensive care medicine departments used more buffered crystalloid solutions (57%) than isotonic sodium chloride.

1 | BACKGROUND

Intravenous (IV) fluid therapy with isotonic crystalloid solutions is used in healthcare systems worldwide.^{1,2} Over the past decade, fluid therapy has received widespread attention questioning both the optimal type, timing and volume of IV fluid therapy.^{3,4}

Isotonic crystalloids comprise 0.9% saline and the so-called buffered crystalloid solutions in which the natural buffer hydrogen carbonate is replaced with alternative anions (i.e., acetate or lactate) to obtain a chemical composition closer to that of extracellular fluid.^{3,5}

A replacement needed due to the instability of bicarbonate-containing solutions in soft plastic containers.⁶

Saline has been associated with undesirable effects, including hyperchloremic acidosis and possibly increased risk of acute kidney injury and mortality.⁷⁻¹⁰ Despite inconclusive results, clinical guidelines increasingly recommend using buffered crystalloid solutions over isotonic saline as first-line IV fluid treatment.¹¹⁻¹³ However, the choice between different types of buffered solutions is still subject to debate, and the current use and factors associated with the use of either 0.9% saline, acetate- or lactate-buffered crystalloid solutions are poorly described.^{14,15}

Hence, the aim of this nationwide observational study was to describe the issuing of isotonic crystalloid solutions in all Danish public hospitals in 2021. We hypothesised that the issuing of isotonic crystalloid solutions differed between regions, hospitals, and departments due to factors beyond what can be explained by differences in patient populations.

2 | METHODS

We conducted a retrospective, nationwide observational study assessing the issuing of isotonic crystalloid solutions across all public hospitals in Denmark from 1 January 2021 to 31 December 2021. We adhered to a prespecified protocol (Supporting Information S1). Any amendments or deviations to the initial protocol are addressed in the Supporting Information S2. We planned and report this study according to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement.¹⁶

2.1 | Setting and population

We collected data from adult clinical somatic in-hospital departments in all Danish public hospitals, including all medical-, surgical- and emergency departments, anaesthesiological departments, and intensive care units (ICUs).

We excluded data from private hospitals, psychiatric hospitals/departments, paediatric departments, non-clinical departments (e.g., pharmacology-, radiology-, nuclear medicine-, administrative-, educational- or research departments), physiotherapy-, occupational therapy- and nutritional departments, hospice facilities and prehospital ambulance services. Finally, we excluded data from departments providing only out-patient services and temporary departments set up during the Covid-19 pandemic (Supporting Information S3).

2.2 | Intervention

We assessed the issuing of any isotonic crystalloid solution for IV administration stratified by type of solution (i.e., 0.9% saline, primarily acetate- or primarily lactate-buffered crystalloid solutions) using issuing data as a surrogate for the use of the corresponding product. We included all relevant solutions regardless of manufacturing origin.

We excluded solutions of different tonicity than isotonic (i.e., hypotonic- or hypertonic solutions) and solutions containing other electrolytes including glucose/dextrose-, potassium chloride-, calcium gluconate- and hydrogen-carbonate solutions. Finally, in order to describe the issuing of fluids used for IV fluid therapy rather than carrier fluids for medication and so forth, we excluded fluids sold in containers holding ≤ 250 ml (Supporting Information S4: Tables S1 and S2).

2.3 | Data collection

Data on issuing of crystalloid solutions were obtained from the Danish Regional Hospital Pharmacies which holds information on sales figures. According to Danish legislation, acquisition of any medical drug,

	Na ⁺	Cl ⁻	K ⁺	Ca ²⁺	Mg ²⁺	Acetate	Lactate	Gluconate (G)/ Malate (M)	pH
NaCl	154 mmol/l	154 mmol/l	-	-	-	-	-	-	4,5 - 7
Plasmalyte	140 mmol/l	98 mmol/l	5 mmol/l	-	1,5 mmol/l	27 mmol/l	-	(G) 23 mmol/l	6,5 - 8
Ringer's acetate	130 mmol/l	112 mmol/l	4 mmol/l	2 mmol/l	1 mmol/l	30 mmol/l	-	-	6
Ringer's fundin	145 mmol/l	127 mmol/l	4 mmol/l	2,5 mmol/l	1 mmol/l	24 mmol/l	-	(M) 5 mmol/l	5,1 - 5,9
Ringers lactate	130 mmol/l	109 mmol/l	4 mmol/l	1,5 mmol/l	-	-	28 mmol/l	-	6,5

FIGURE 1 Composition of isotonic crystalloid solutions issued to Danish public hospitals in 2021. Presented in alphabetical order. Compositions are subject to small variations depending on manufacturer.

including IV fluids, must be obtained through pharmacies. We collected data on sales figures from 1 January 2021 to 31 December 2021. We extracted data based on the Anatomical Therapeutic Chemical Classification (ATC) System (ATC code B05BB01 “Electrolytes”), defined by the WHO Collaborating Centre for Drug Statistics.¹⁷ Fluid amounts were provided as volume per package of individual product-identifying numbers, and as number of packages purchased at the regional-, hospital- and departmental-level. We calculated and report total volumes in litres.

We collected data on number of patients admitted per geographical region from the National Danish health data Authorities online resources.¹⁸ A hospital admission was defined as a physical attendance to a public non-psychiatric hospital of >12-h duration. We were not able to obtain data on the number of hospital admissions at hospital or departmental level (Supporting Information S2).

Departments were grouped based on medical specialty categorised as medical-, surgical-, emergency department or anaesthesiologic department/ICU. This classification was done manually by the primary author based on departmental names. In case of doubt the relevant regional pharmacy was contacted for further details on department type.

2.4 | Data Management

The primary author carried out data-cleansing in accordance with the predefined inclusion and exclusion criteria. Any doubt of eligibility was resolved with a senior author (M.H.M. or A.P.) (Supporting Information S5).

Due to purchasing arrangements, it was not possible to identify fluid use in all ICUs separately within our original data. Data on crystalloid use within individual ICUs were therefore collected

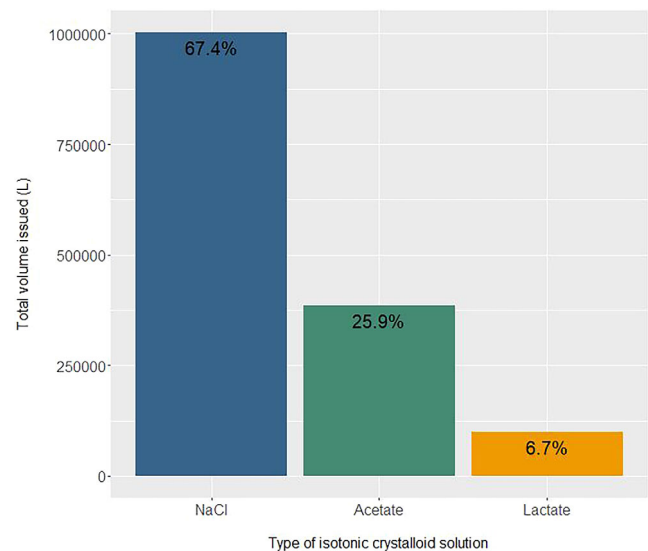


FIGURE 2 Total volumes in litres (L) of different isotonic crystalloid solutions in Danish public hospitals in 2021 including the percentwise distribution of individual type of solutions.

separately and merged with the original dataset by the primary author.

As no analyses on patient attributable data was undertaken, we did not take specific measures to ensure confidentiality of data.

2.5 | Statistical analysis

All analyses and graphical output was carried out using R version 4.0.2 (R Core Team, R Foundation for Statistical Computing) with the *tidyverse*, *dplyr*, *scales* and *ggplot2* packages. Data were analysed descriptively with proportions/percentages for categorical data and presented graphically.

3 | RESULTS

We included a total of five different types of isotonic crystalloid solutions equivalent to 19 individual product-identifying numbers (Figure 1). The total issuing of IV isotonic crystalloid solutions to Danish public hospitals amounted to 1,487,144 L equivalent to 2.1 L per hospitalised patient within the period. Saline (0.9%) constituted 67%, and buffered crystalloid solutions 33%, with a clear preference for acetate-buffered solutions over lactate-buffered solutions (Figure 2 and Supporting Information S6: Table S1).

3.1 | Regional level

We assessed the issuing of crystalloid solutions across the five geographical regions of Denmark, which ranged from 1.9 to 2.5 L per hospital admission (Figure 3) throughout the study period (Supporting Information S6: Table S1). In four out of five Danish hospital regions, saline constituted 65%–75% of the total volume of crystalloid solutions issued, with very limited issuing of lactate-buffered solutions (<2%) (Figure 4 and Supporting Information S6: Table S1). In the remaining region (the Capital Region), buffered solutions constituted

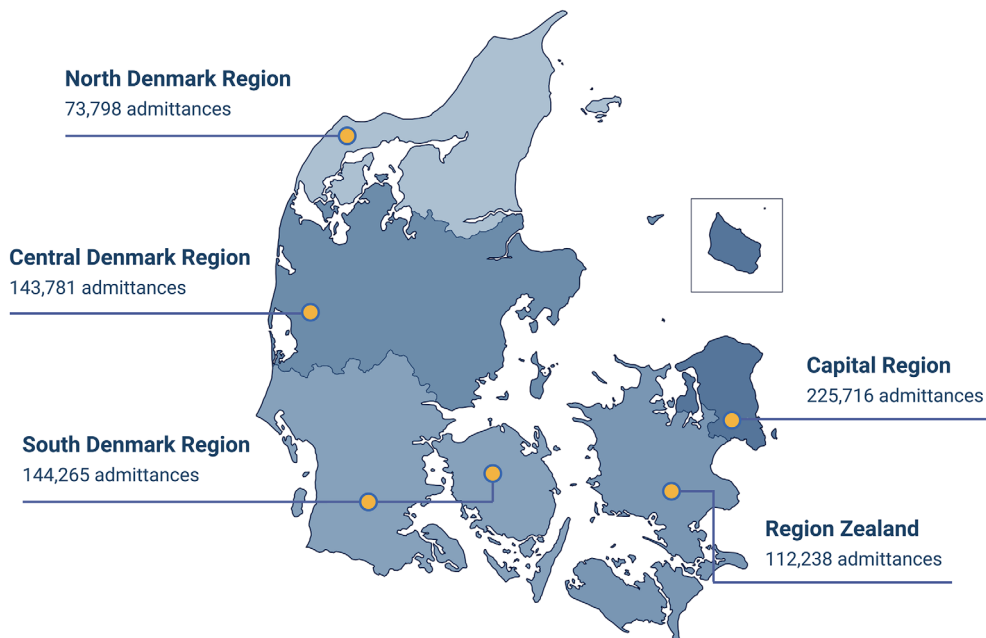


FIGURE 3 Hospital admittances per geographical region of Denmark in 2021. A hospital admission was defined as a physical attendance to a public non-psychiatric hospital of >12 h duration. Admissions include paediatric admissions.

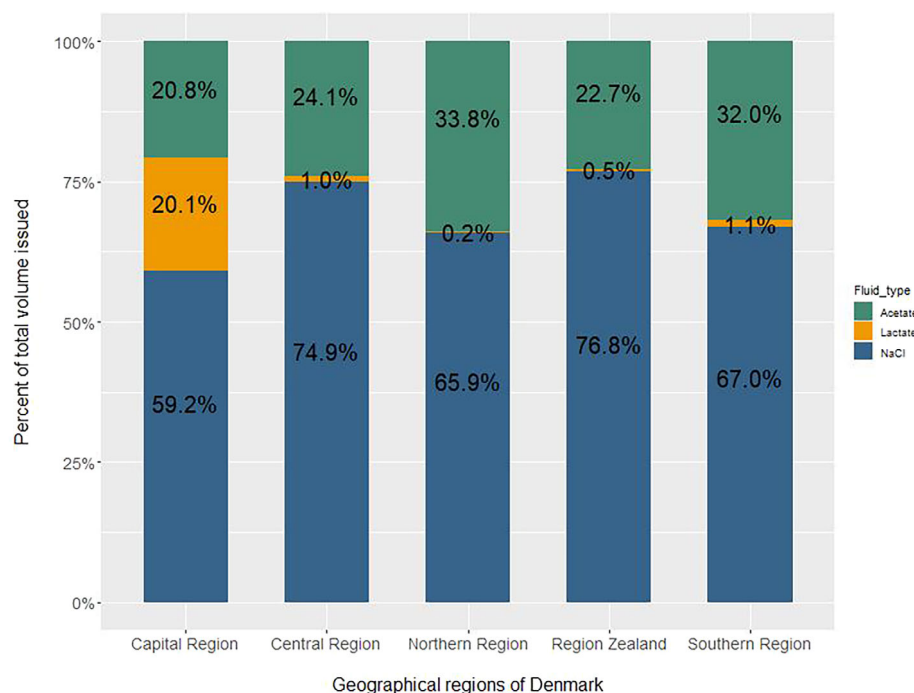


FIGURE 4 Percentwise distribution of different isotonic crystalloid solutions across geographical regions of Denmark in 2021.

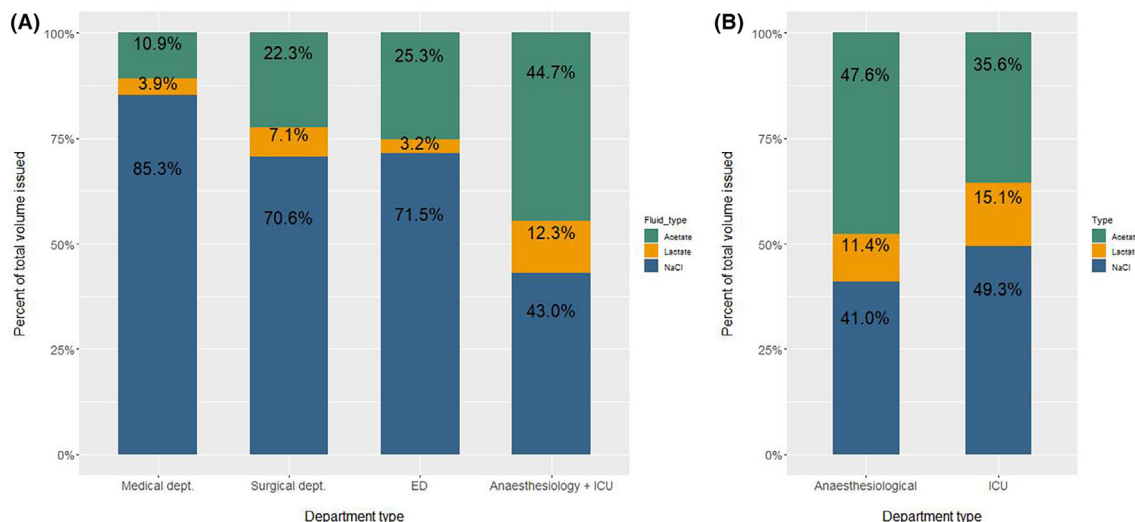


FIGURE 5 (A) Percentwise distribution of different isotonic crystalloid solutions across different department types*. (B) Percentwise distribution of different isotonic crystalloid solutions in anaesthesiological departments and ICUs separately. *We could not account for the further distribution of fluids from common regional stocks (to which 186,130 L of fluid were issued throughout the study period equivalent to 12.5% of the national volumes issued). Hence, fluids from these stocks are not accounted for at departmental level. Furthermore, some departments could not be categorised as a medical or surgical department, as they were combined (e.g., medical and surgical gastroenterology department).

41% of the total volume issued, equally distributed between acetate (21%) and lactate-buffered solutions (20%) (Figure 4 and Supporting Information S6: Table S1).

3.2 | Hospital level

We assessed the issuing of crystalloid solutions across 24 Danish public hospitals. The proportional volume of 0.9% saline ranged from 40% to more than 90% of the total volume of crystalloid solutions issued to hospitals (Supporting Information S6: Table S2). A total of 20 out of 24 (83%) hospitals primarily used acetate-buffered solutions as compared to lactate-buffered solutions (Supporting Information S6: Table S2).

When comparing issuing of fluids to university vs non-university hospitals, we found that university hospitals had a higher proportional use of 0.9% saline compared to non-university hospitals (Supporting Information S7: Table S1; Figure S1).

3.3 | Departmental level

Issuing of crystalloid solutions differed by type of department (Figure 5A and Supporting Information S8: Table S1). Medical departments primarily used saline (85%), as compared to surgical departments and emergency departments where saline constituted close to 70% of the total volume issued. In contrast, the issuing of saline to anaesthesiologic departments including ICUs constituted 43% of the total volume of crystalloids issued (Figure 5A and Supporting Information S8: Table S1).

The largest proportional use of saline was within ophthalmology (100%), rheumatology (98%) and haematology (96%) followed by cardiology (95%). In contrast, the largest proportional use of buffered solutions was within in anaesthesiologic departments including ICUs (67%), gastrointestinal surgery (42%), cardiothoracic surgery (40%) and plastic surgery (35%) (Supporting Information S8: Table S2; Figures S1 and S2).

All medical specialties favoured acetate as compared to lactate-buffered solutions, whereas the surgical specialties primarily preferred acetate-buffered solutions however with few exceptions (Supporting Information S8: Table S2). Both emergency departments, anaesthesiologic departments and ICUs had a higher proportional use of acetate-buffered solutions compared to lactate-buffered solutions (Figure 5A,B and Supporting Information S8: Tables S1–S3).

4 | DISCUSSION

In this retrospective, nationwide observational study of fluid issuing of IV isotonic crystalloid solutions in Danish public hospitals in 2021, we observed considerable practice variation at the regional-, hospital-, and departmental-level. We found that the issuing of 0.9% saline versus buffered crystalloid solutions as well as the issuing of acetate- versus lactate-buffered solutions varied based on geographical location. The issuing of 0.9% saline versus buffered solutions also differed across departmental settings with medical departments using the highest proportion of 0.9% saline and anaesthesiologic departments including ICUs using the highest proportion of buffered solutions.

4.1 | Relation to current evidence

The use of isotonic crystalloid solutions in healthcare settings has previously been assessed, however mostly limited to the ICU setting. In a cross-sectional study in 391 ICUs across 25 countries from 2007, the choice of fluid type varied markedly between countries.¹⁹ Similarly, when assessing the use of resuscitation fluids across 426 international ICUs from 2007 to 2014, Hammond et al. identified geographical location as a strong predictor of the type of fluid administered for resuscitation therapy.²⁰ We observed considerable practice variation in the issuing of different isotonic crystalloid solutions across the five geographical regions of Denmark. Among the most marked differences was the higher proportional use of lactate-buffered solutions in the Capital Region compared to the four other regions. This difference seemed largely due to a greater use of lactate- vs acetate-buffered solutions in the two largest hospitals in the Capital Region.

We also observed variation in the issuing of saline vs. buffered solutions according to the type of department. Medical-, surgical- and emergency departments primarily used saline over buffered solutions, while anaesthesiologic departments including ICUs primarily used buffered solutions. The latter is in line with a study by Jacobs et al. assessing purchasing of isotonic crystalloid solutions in EDs and ICUs in Johannesburg, South Africa from 2015 to 2018 which found that buffered crystalloid solutions were the most used solutions.²¹ Furthermore, the use of acetate (Plasmalyte) versus lactate (Ringers Lactate) buffered solutions was attributed to differences in departmental characteristics (emergency departments vs. ICUs).²¹ This contrasts with our data in which differences in the use of acetate- versus lactate-buffered solutions were primarily at the regional level. The reason for the dominating use of saline across non-anaesthesiologic/ICU settings is unknown, however, as most of the recent larger trials conducted originate from anaesthesiologic/ICU settings²²⁻²⁵ a more pronounced translation of research findings into clinical practice in this setting seems likely.

We found that the proportional use of buffered solutions was greater across surgical departments compared to medical departments across Denmark. This is supported by Jonsson et al. who investigated the issuing of IV fluids across the Capital Region of Denmark from 2012 to 2015 and found a significant increase in the issuing of buffered crystalloid solutions in surgical- compared to medical departments.²⁶ In our data, the difference seems partly explained by a high proportional use of buffered solutions specifically in surgical gastrointestinal departments (which account for >35% of the total use of isotonic crystalloid solutions across surgical specialties).

Throughout the last decade, the choice of IV crystalloid solutions in clinical practice has been subject to debate. Initially, the use of saline caused concern in clinical practice as it, due to its higher chloride content compared to that of plasma, was thought to be associated with undesirable effects such as hyperchloremic acidosis.²⁷⁻³⁰ Since then, several larger trials have compared the use of saline vs. buffered solutions with diverging results. In 2017 and 2018 two single-centre cluster randomised trials SALT-ED and SMART assessed the use of buffered crystalloids versus saline in the noncritically ill and

critically ill, respectively.^{22,31} Both found benefit from use of buffered crystalloids compared to saline.^{22,31} In contrast, the later published trials BASICS and PLUS both reported no benefit of the use of saline versus buffered solutions in ICUs.^{23,25} However, a post hoc Bayesian analysis of the BASICS trial found a high probability (92%) that the use of buffered solutions reduces mortality in the ICU for patients who exclusively received buffered solutions prior to enrolment in the trial.³² Furthermore, a recent systematic review with Bayesian meta-analysis pooling, among others, the results of the above trials, found a high probability that using buffered solutions reduces the risk of death.¹⁰ As a result, several clinical practice guidelines now recommend the use of buffered solutions over 0.9% saline.^{12,13} However, the choice of different buffered solutions (e.g., acetate- vs. lactate-buffered solutions) remains unclear with very limited evidence on the potential benefits and harms of either solution.^{14,15}

Historically, the selection and use of IV fluids has been based on physiological principles rather than high quality research evidence.³³ Importantly, a practitioner survey conducted across ICUs suggests little consistency with respect to choice of fluids for specific groups of patients or clinical scenarios.³⁴ Hence, many clinicians are seemingly guided predominantly by local practice which, as is evident from our results, varies across geographical settings. Considering the vast use of isotonic crystalloid solutions worldwide and the apparent difference in use even within a single country, randomised clinical trials are warranted to inform clinicians and policymakers on the safety and efficacy of these different fluids.

4.2 | Strengths and limitations

We conducted this study according to a prespecified protocol, and planned and reported it according to the STROBE statement.¹⁶ Furthermore, this study describes the overall nationwide use of isotonic crystalloid solutions stratified by type of solution, which allows for detailed evaluation of possible differences in use across geographical-, hospital- and department settings.

The study also has limitations. First, we used fluid issuing data as a surrogate for actual fluid use. This may not correlate perfectly, but previous research shows that purchase data may mirror international usage trends.² Since we based estimates of use on issuing data, we cannot exclude the possible influence on the results of purchasing arrangements, manufacturing shortages, sharing of inventory between departments or expiring fluids. Second, detailed reporting of volumes purchased at hospital and departmental levels in the Central Denmark Region were challenged by the presence of a regional stock accounting for approximately 69% of the regions total purchasing. Details on distribution of fluids from this regional stock at hospital and department level could not be obtained. Third, we planned to describe the use of single solutions per number of patients at the hospital and departmental level, however, this was abandoned post hoc, as numbers could not be obtained due to transition in registry systems (National Danish Patient Registry vol. 2 to vol. 3). Finally, we did not address fluid acquisition cost, which may affect purchasing patterns.

5 | CONCLUSIONS

In this retrospective, nationwide observational study of the issuing of isotonic IV crystalloid solutions in Danish public hospitals in 2021, the total issuing amounted to 1,487,144 L equivalent to 2.1 L per hospitalised patient within the period. We observed considerable practice variation at the regional-, hospital-, and departmental-level. We observed that the use of saline vs. buffered crystalloid solutions as well as the use of acetate- versus lactate-buffered solutions varied based on geographical location. Furthermore, the use of saline versus buffered solutions differed across departmental settings with medical departments using the highest proportion of saline and anaesthesiologic departments including ICUs using the highest proportion of buffered solutions.

AUTHOR CONTRIBUTIONS

Karen Louise Ellekjaer: Study design, data extraction, data analysis and drafting of manuscript. **Anders Perner:** Study design, data analysis and critical revision of manuscript for important intellectual content. **Kathrine Bruun Svan:** Data extraction and critical revision of manuscript for important intellectual content. **Morten Hylander Møller:** Study design, data analysis and critical revision of manuscript for important intellectual content.

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CONFLICT OF INTEREST

The Department of Intensive Care at Rigshospitalet from which this study originates, has received funding for other research projects from the Novo Nordisk Foundation, Pfizer, Ferring and Fresenius Kabi, and conducts contract research for AM-Pharma.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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