Hindawi
International Journal of Clinical Practice
Volume 2024, Article ID 8830099, 9 pages
https://doi.org/10.1155/2024/8830099

Research Article

Guidelines for Treatment of Hyperemesis Gravidarum and Implementation in Clinical Practice in Norway: A Descriptive Study

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Received 22 August 2023; Revised 5 February 2024; Accepted 16 March 2024; Published 27 March 2024

Academic Editor: Harry H. X. Wang

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Background. The severe pregnancy complication hyperemesis gravidarum (HG) requires intravenous fluids, antiemetics, and nutrition to prevent maternal and fetal complications. Several guidelines exist for the treatment of HG within and across countries. The aim of this study was to investigate whether the guideline issued by the Norwegian Society for Obstetrics and Gynecology (NGF) was implemented in clinical practice by comparing department treatment protocols and assessing provided treatment. *Methods*. Department protocols for the treatment of HG were requested from all Norwegian gynecology departments and compared to the NGF guideline regarding the use of Pregnancy Unique Quantification of Emesis (PUQE-24) score, antiemetics, thiamine, and fluid and nutritional therapy. Additionally, we performed a retrospective chart review of provided treatment during 2017–2019 at four hospitals. *Results*. In all, 28 of 39 (72%) departments replied, of which 11 reported using the NGF guidelines unaltered. Of the 17 local department protocols in use, 16 closely resembled the NGF guidelines regarding the use of PUQE score, fluid therapy, nutritional treatment, and thiamine. Eight department protocols differed slightly from the NGF guidelines regarding the antiemetic medication treatment pathway, and two recommended antiemetic medication not supported by national or international guidelines. The retrospective chart review of 343 patients at four hospitals showed that the provided care aligned with the guidelines regarding intravenous fluids and the use of PUQE score, and the use of antiemetics mostly aligned with the treatment pathway provided in the NGF guideline. However, the proportion of patients receiving ondansetron varied between 32% and 79% and thiamine from 38 to 86% between hospitals. Overall, few patients were provided with nutritional treatment by partial peripheral nutrition (14%), enteral tube feeding (8%), or total parenteral nutrition (1.5%). *Conclusion*. The NGF guideline was used unaltered or largely integrated in department protocols. Treatment data suggest that the guideline was implemented in clinical practice, but differences in the provision of ondansetron and thiamine suggest geographical inequality of care. Infrequent use of nutritional treatment by parenteral nutrition or enteral feeding tube could suggest improvements in pharmacological symptom management or undertreatment of malnutrition.

1. Introduction

Hyperemesis gravidarum (HG), characterized by excessive nausea and vomiting in pregnancy, is a severe complication that often requires hospitalization [1]. Estimates of the prevalence of HG have ranged from 0.3% to 3.6% [2]. A study from the UK reported hospitalization for the treatment of HG in 2.1% of pregnancies [3], while our study group has previously found a hospitalization rate for the treatment of HG with metabolic disturbances of 1.2% of births [4]. HG has been associated with an increased risk of fetal growth restriction, preterm delivery, and neurodevelopment disorders [5–7], in addition to maternal malnutrition, thrombosis, postpartum depression, and posttraumatic stress disorder [5, 8]. Electrolyte disturbances and Wernicke's encephalopathy due to thiamine deficiency are acute and potentially life-threatening complications [1].

Several guidelines exist for the treatment of HG. Internationally, acknowledged guidelines are provided by the Royal College of Obstetricians and Gynaecologists and the American College of Obstetricians and Gynaecologists [9, 10]. In Norway, the Norwegian Society for Gynecology and Obstetrics (NGF) has issued national guidelines regarding gynecologic and obstetric care [11]. A chapter on the treatment of nausea and vomiting during pregnancy (NVP) and HG has been included since 1998 and in the following updates, last in 2020 [12]. In all these guidelines, a similar treatment approach for HG is outlined: correction of dehydration and potential electrolyte imbalances, antiemetic medication, and nutritional treatment [1, 9–11].

Clinical practice guidelines are developed and implemented to provide equal access to evidence-based treatment across healthcare levels and geographic regions and include a systematic literature review [13]. In HG, treatment guideline development is restricted by the currently available evidence as high-quality research on the optimal treatment of HG is scarce [14, 15]. The NGF HG treatment guideline is developed by a dedicated interprofessional team of experts in the field and provides support and guidance for healthcare professionals.

Generally, healthcare institutions in Norway are obliged to establish and conduct systematic management of their activities to ensure professionally sound care [16]. Current protocols and guidelines are managed in electronic quality control systems. Protocols in the electronic quality control systems might differ between hospitals and from national guidelines, for instance, by being fully developed locally, not being based on the current guideline, or by local adaptations caused by, for instance, differences in department size, geographical region, distance to hospital, availability of outpatient treatment options, and local treatment traditions.

The ability of guidelines to achieve the intended equality and evidence-based care depends on their implementation in clinical practice. Development and implementation of national guidelines have been identified among prioritized research topics in HG [17]. Although national guidelines for the treatment of HG have been available since 1998, its uptake in clinical practice has not been investigated. Thus, the aim of this study was to explore the implementation of the 2014 version of the NGF HG treatment guideline in secondary care in Norway by comparing department protocols for the treatment of HG in 2019 to the guideline [11] and assessing provided treatment at selected hospitals.

2. Material and Methods

A request was sent to all the gynecology departments in Norway asking for their HG treatment guideline or protocol in use in 2019. Department protocols were compared to the 2014 version of the NGF guideline valid in 2019 [11], with regards to the following:

(i) Use of the Norwegian version of the Pregnancy Unique Quantification of Emesis (PUQE-24) score in the assessment and monitoring of HG [18]

(ii) Fluid and electrolyte replacement if needed

(iii) Thiamine if persistent vomiting for two weeks or more

(iv) Antiemetic medication given in a stepwise treatment pathway: antihistamines, dopamine antagonists, metoclopramide, ondansetron, and steroids

(v) Nutritional treatment:

  (1) Partial parenteral nutrition over a brief period while correcting fluid and electrolyte imbalance or initiation of enteral tube feeding
  (2) Enteral tube feeding if lack of improvement or persistent weight loss
  (3) Total parenteral nutrition (TPN) only if enteral tube feeding has failed

A retrospective review of patient charts was conducted for all patients treated for HG at four of the six university hospitals in Norway from 2017 to 2019. The included departments cover approximately 25% of the birthing population in Norway and represent three out of four health regions [19]. The inclusion criteria were a diagnosis of hyperemesis gravidarum with metabolic disturbances in line with the International Classification of Disease-10 code O21.1 [20]. Women hospitalized for HG during the following time periods were included: hospital A and D between 1.1.2018 and 31.12.2019, hospital B between 1.1.2017 and 31.12.2018, and hospital C between 1.1.2017 and 31.12.2019.

Patient characteristics, provided treatment with antiemetic medication, fluids, thiamine, and nutrition, and assessments of PUQE-24 score at hospital admission, discharge, or at out-patient visits were registered. Nutritional treatment as parenteral supplementation was defined as short-time peripheral intravenous glucose ≥100 mg/mL or specific parenteral nutritional solutions. Enteral nutrition was defined as gastric or jejunal tube feeding. TPN was defined as nutrition provided by a peripheral inserted cubital central line or central venous catheter. All pregnancies during the study period were included, and if a woman had multiple pregnancies, these were considered independent in the analyses. Hospitalization rates were calculated as percentages of HG admissions of births recorded at the respective hospitals in the Medical Birth Registry of Norway [19].

2.1. Statistical Analyses. Frequencies were presented as numbers and percentages. Patient characteristics were presented as means with corresponding standard deviation (SD) or, if not normally distributed, as medians with interquartile range (IQR). Differences in the odds of being provided ondansetron prior to hospitalization between the hospitals were explored by logistic regression adjusted for a history of HG in prior pregnancies. The hospital with the highest number of patients was used as a reference. Results were presented as odds ratio (OR) with corresponding confidence intervals (CI) and *P* value. The analyses were conducted using Stata (StataCorp. 2023. *Stata Statistical Software: Release 18*. College Station, TX: StataCorp LLC).

2.2. Ethics Statement. Approvals for the retrospective chart review were granted by the Data Protection Officer and the Institutional Board at the respective hospitals. Due to the study design as a quality-affirming study, individual patient consent was waived by the Regional Ethics Committee. The Norwegian Directorate of Health (20/38416-2, November 13th, 2020) approved the comparison of provided treatment across hospitals. Results from the chart review were reported in accordance with the STROBE guidelines.

3. Results

In all, 28 of 39 (72%) departments in Norway replied. Of these, 11 (28%) reported using the NGF guidelines unaltered, while 17 (44%) used local department protocols. Distribution among the health regions in Norway is presented in Supplementary Table 1.

A comparison of the local department protocols and the NGF guidelines with regard to the use of PUQE score, fluid replacement therapy, antiemetic medication, thiamine, and nutritional treatment is summarized in Table 1. In half of the protocols, the stepwise treatment pathway recommendation for the antiemetic medication of the NGF guideline was worded slightly differently and was divided into fewer steps, or not divided into steps at all, although the suggested antiemetic medications were similar. In contrast, two protocols deviated in the use of antiemetic medication, one of which also lacked mention of PUQE score and nutritional management (Table 1).

A total of 343 women received in-patient treatment for HG with metabolic disturbances at the four university hospitals during the study period. The overall hospitalization rate for HG was 1.1% of births, ranging between 0.4% and 1.6% at the included hospitals. Table 2 lists the maternal and gestational characteristics of the included women.

The local treatment protocols at the four participating hospitals included in the retrospective chart review closely resembled the NGF guidelines with regard to fluid replacement, nutritional treatment, and thiamine. Enteral tube feeding was recommended by all if lack of improvement and persisting weight loss, and all but one recommended total parenteral nutrition if the tube feeding failed. Additionally, providing partial peripheral nutritional supplements for a limited period was mentioned in three of the department protocols. Differences in the stepwise treatment pathway for antiemetic medication compared to the NGF guidelines are illustrated in Figure 1. The use of antiemetics along the treatment pathway outlined in the NGF guideline at the four hospitals is shown in Figure 2.

Differences in provided treatment between the hospitals are presented in Table 3. PUQE-24 score to assess and monitor symptoms was utilized at all four university hospitals and was assessed at first hospitalization for 84% of the patients. Only 17 patients (5%) had no record of any PUQE score, while the remaining had between one and 17 assessments of PUQE score registered at admission, discharge, or out-patient treatment in their hospital charts. In 75% of the patients, the PUQE score was registered at least twice. Practically all the women received intravenous fluids. In total, three out of four women received thiamine, ranging from 38% to 86% (Table 3). Antiemetic medication was provided for nearly all the women, but the choice of antihistamine and dopamine antagonist differed slightly between the hospitals.

Figure 3 illustrates prehospital and in-patient use of antiemetic medication. The use of ondansetron varied between 32% at hospital B and 79% at hospital C. The odds of being treated with ondansetron prior to hospitalization were lower at hospital A (OR 0.10, CI 0.02–0.43, $P = 0.002$) and hospital B (OR 0.21, CI 0.05–0.93, $P = 0.004$), compared to hospital C (reference) and hospital D (OR 1.01, CI 0.37–2.74, $P = 0.979$). Additionally, the odds ratio of prehospital ondansetron treatment was doubled in women with a history of HG (OR 1.97, CI 1.01–3.87, $P = 0.047$) compared to women who were pregnant for the first time or had prior pregnancies without HG.

4. Discussion

Clinical practice guidelines are intended to equip clinicians with current evidence to provide quality care. Management strategies for HG have recently been assessed as similar across international HG treatment guidelines [21], to which the NGF guideline closely aligns [11]. In total, 26 of 28 participating departments used either the NGF guideline or local HG protocols which were comparable to the NGF guidelines. Yet, we discovered some variations in the stepwise treatment pathway for antiemetic medication as some protocols had fewer or no defined steps or omitted one or more medications mentioned in the guideline. Of particular concern were two protocols describing antiemetic treatment of HG not supported by international or national guidelines [9–11]. One of these additionally lacked mention of PUQE score and nutritional management.

On a group level, the provided care at the included university hospitals adhered well to their respective local protocol and national guidelines. Three in four patients having their PUQE score assessed more than once indicates that it is applied as a clinical tool to monitor symptoms and evaluate treatment effects in addition to initial assessment of severity, in line with treatment guidelines [10, 11]. Observed differences in the use of the antihistamines meclizine and promethazine and the dopamine antagonists metoclopramide, prochlorperazine,

Table 1: Proportion of the 17 participating hospitals that adhere to specific recommendations for treatment of hyperemesis gravidarum (HG) issued by the Norwegian Society for Obstetrics and Gynecology (NGF) in 2014.

Assessment and fluids	Number (%)
PUQE-24[a] recommended to assess and monitor symptoms	16 (94)
Intravenous fluid replacement	17 (100)
Antiemetic medication treatment pathway	
Equivalent to the NGF guideline	7 (41)
Slightly different treatment pathway from the NGF guideline[b]	8 (47)
Differs from the NGF guideline[c]	2 (11)
Thiamine and nutrition	
Thiamine if persistent vomiting for two weeks or more	17 (100)
Partial peripheral nutrition for a limited period of time	13 (76)
Enteral tube feeding if lack of improvement and weight loss	16 (94)
Total parenteral nutrition if tube feeding fails	16 (94)

[a]PUQE-24: Pregnancy Unique Quantification of Emesis, evaluated for the last 24 hours. [b]Same antiemetics, but different, fewer, or not steps defined in the treatment pathway. [c]Promethazine ($n = 1$). Metoclopramide and levomepromazine, PUQE score, and nutritional treatment not mentioned ($n = 1$).

Table 2: Maternal and gestational characteristics of 343 women hospitalized for treatment of hyperemesis gravidarum at four Norwegian hospitals.

Characteristics	Mean	Standard deviation
Age (years)	28.7	4.7
Prepregnancy body mass index (kg/m^2)[a]	25.5	5.2
Weight loss at first hospitalization (%)[b]	4.8	4.6
	Median	*Interquartile range*
Gravidity[c]	2	1–3
Parity[d]	1	0-1
Gestational age at first hospitalization[e] (weeks)	8	7–11
Total days in hospital	2	1–4
Number of hospital stays	1	1-2
PUQE[f] score at first hospitalization[g]	14	12–15
Number of PUQE assessments per patient	2	1–3
	Number	*%*
Previous pregnancy with HG[h]	122	51
Termination of pregnancy	17	5

[a]Missing: 34. [b]In % of prepregnancy weight, missing: 43. [c]Missing: 11. [d]Missing: 4. [e]Missing: 28. [f]Pregnancy Unique Quantification of Emesis. [g]Not assessed: 51. [h]Percent of multigravida ($n = 240$).

and chlorpromazine between the hospitals are interpreted to reflect local traditions or preferences with limited differences regarding clinical care. Of note, the risk of maternal adverse neurological effects led to the European Medicines Agency limiting the use of metoclopramide to a maximum of 5 days. We have previously shown that this resulted in a switch to prochlorperazine for in-patients at hospital C [4]. This change in dopamine antagonist was not observed for the remaining hospitals included in this study where metoclopramide remained a treatment option in the local protocols.

The serotonin antagonist ondansetron offers an alternative mechanism of action to dopamine antagonists and antihistamines which might provide additive antiemetic effects and is third-line treatment according to guidelines, advised to be reserved for severe cases [9–11]. In 2014, ondansetron was used by 22% of all pregnant women in a study from the USA [22], while only by 0.04% of pregnant women (2004–2017) in a French region [23]. Comparably, prescription fills for ondansetron were found in 1.0% of pregnancies in the Norwegian prescription database in 2017 [24]. In this study, we found that ondansetron was provided for 60% of the patients hospitalized for treatment of HG. Given a hospitalization rate for HG between 1 and 2% of births [3, 4], our findings suggest that the patients hospitalized for treatment of HG during their pregnancy account for most of the use of ondansetron in pregnancy in Norway.

Overall, we found that the odds of receiving ondansetron prior to hospitalization were twice as high in women with a history of HG. Prehospital use of ondansetron was also higher at the hospitals where in-patient use of ondansetron was more frequent, which suggests that physicians in primary care may be influenced by in-patient treatment provided for their patients in their region. As only patients with severe HG with metabolic complications were included in this study, the difference in utilization of ondansetron between 32% and 72% might indicate that it has not been provided for all the women for whom it could be appropriate and beneficial. As ondansetron was provided after hospitalization in most of the patients in this study, it would be compelling to investigate whether earlier initiation of ondansetron in primary care could reduce the need for in-patient treatment.

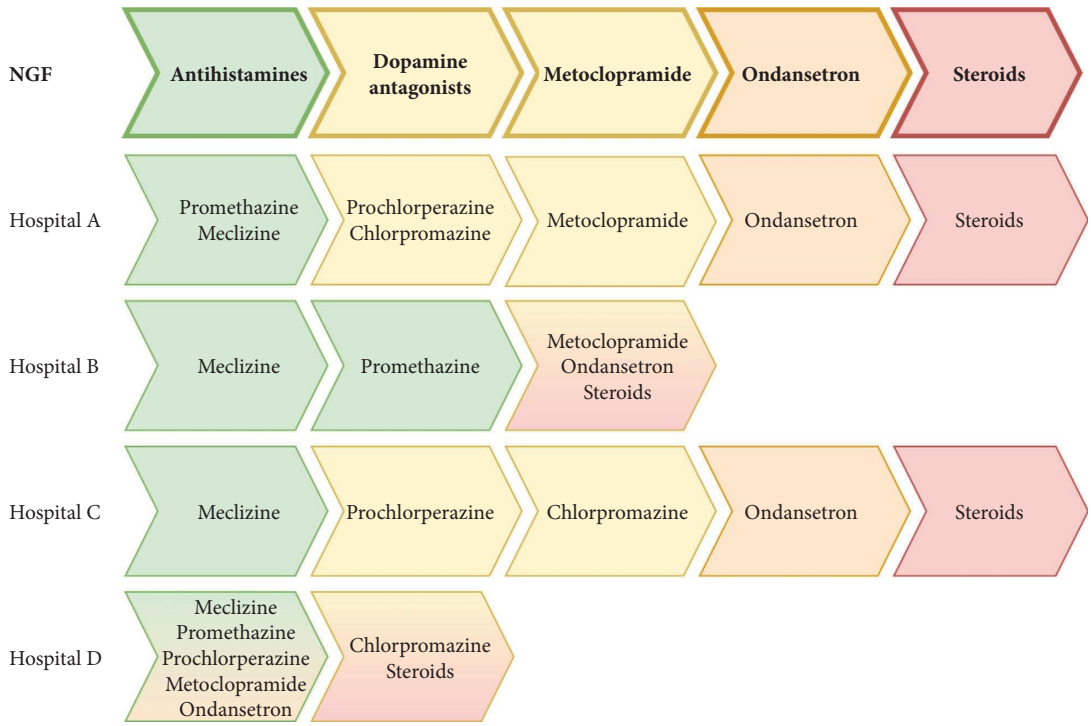

Figure 1: Comparison of the antiemetic medication treatment pathway in the department protocols for hyperemesis gravidarum illustrated by colors according to the stepwise treatment in the guidelines issued by the Norwegian Society for Gynecology and Obstetrics (NGF) in 2014: green = 1st line, yellow = 2nd line, orange = 3rd line, and red = 4th line.

Combining antiemetics with different mechanisms of action is recommended in guidelines if monotherapy fails to control symptoms of HG [9–11]. The foundation for detailed support on optimal treatment for individual women was very limited at the time of the publication of the 2014 guidelines. Decisions on when to step up in the treatment pathway or apply combinations of antiemetics were largely left to the prescriber's clinical judgement. This can be particularly challenging for clinicians with limited experience or knowledge of HG treatment, which might lead to the undertreatment of HG and inequality of care across geographical regions and healthcare levels. The latest update of the NGF guideline includes more detailed advice on the use of combinations of antiemetics with different mechanisms, when it is appropriate to attempt discontinuation and treatment for women with lower PUQE score but complications such as dehydration, weight loss, or greatly impacted well-being are also highlighted [12]. However, individualized treatment of severe cases of HG still relies on trial and error. The recent discovery of GDF15 as a causative agent in women with genetic predisposition for HG provides a foundation for future drug development and targeted treatment in a subset of women with HG [25].

Insufficient weight gain during pregnancy, or particularly lack of recovery of 1st trimester weight loss in HG, may cause an increased risk of infants small for gestational age [7]. Nutritional treatment was provided as partial peripheral nutrition for 14% and enteral tube feeding for 8% of the patients in this cohort, which is a decline compared to a former single center 10-year Norwegian cohort of women with HG where partial peripheral nutritional supplementation was provided for nearly half of the women and 19% received tube feeding [26]. In a randomized controlled trial from the Netherlands, early initiation of enteral tube feeding as standard HG treatment did not improve birth weight, and several participants discontinued due to discomfort [27]. Although improvements in the provision of antiemetic medication theoretically might reduce the need for nutritional treatment, the infrequent use of nutritional treatment in this study is concerning as it might reflect undertreatment of malnutrition in HG which should be investigated further.

The increasing number of hospitals using the NGF guideline unaltered could further promote equal access, increase the quality of HG care, and prevent unsubstantiated protocols which we found at two departments in this study. A further benefit of the NGF guideline is the rigorous development process to ensure high quality, as well as updates at reasonable intervals, most recently in 2020 [12]. In contrast, developing and maintaining local protocols are resource-intensive and vulnerable to time restraints and the availability of clinical expertise, particularly at smaller hospitals.

A strength of our study is the sample of participating gynecology departments including all health regions and hospitals of varied sizes, providing a representative description of HG treatment protocols in Norway (Supplementary Table 1). Despite covering 25% of the pregnant population in Norway, performing chart reviews only at university hospitals constitutes a weakness of the study which limits the generalizability of the results particularly towards smaller hospitals. This study applied strict inclusion

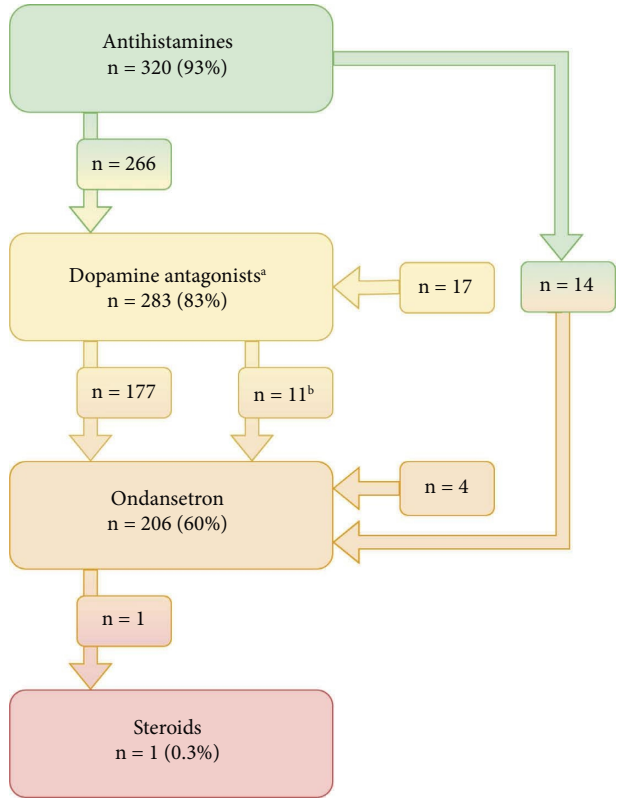

Figure 2: Overall use of antiemetic medications in 343 women hospitalized for hyperemesis gravidarum illustrated by colors representing the stepwise treatment pathway defined in the national guidelines issued by the Norwegian Society for Gynecology and Obstetrics (NGF) in 2014: green = 1st line, yellow = 2nd line, orange = 3rd line, red = 4th line. [a]Dopamine antagonists including metoclopramide. [b]$n = 11$ women of the $n = 17$ starting on dopamine antagonist also received ondansetron.

Table 3: Use of pregnancy unique quantification of emesis (PUQE) score, fluid replacement, thiamine, antiemetic medication, and nutritional treatment of hyperemesis gravidarum for 343 patients at four Norwegian university hospitals.

Hospital Assessment and fluids	A ($n^a = 87$) *n* (%)	B ($n = 44$) *n* (%)	C ($n = 183$) *n* (%)	D ($n = 29$) *n* (%)
PUQE-24 score	80 (92)	35 (80)	179 (98)	29 (100)
Intravenous fluids	86 (99)	44 (100)	183 (100)	29 (100)
Medication				
Any antiemetic prehospital	40 (46)	24 (55)	116 (63)	23 (79)
Any antiemetic in the hospital	87 (100)	44 (100)	178 (97)	27 (93)
Thiamine and nutrition				
Thiamine	75 (86)	24 (55)	141 (77)	11 (38)
Partial peripheral nutrition	0 (0)	0 (0)	46 (25)	1 (3)
Enteral feeding tube	5 (6)	1 (2)	19 (10)	3 (10)
Total parenteral nutrition	4 (5)	0 (0)	1 (1)	0 (0)

[a] n = number, [b]PUQE score assessed at any time while in hospital.

criteria for hospitalized women with metabolic disturbances. Our findings of the high degree of guideline adherence might not represent all women with HG, particularly those less severely affected who still are within the target group of the guideline. Out-patient care and treatment at municipal in-patient facilities have become more common, for instance, in the area of hospital D which left only one patient admitted for HG in 2019. Taking these aspects into consideration, the hospitalization rate for HG in this study should be interpreted as a minimum estimate.

Reviewing patient charts provides reliable information about the treatment beyond information available in registries. A challenge in this study is the unspecific prescription support for individual patients in the guidelines. This makes retrospective assessment of the quality of provided treatment for each patient challenging, leaving comparisons on the group level. We consider the risk of misclassification bias in this study to be limited and nondifferential, but missing information during data collection from electronic charts will introduce bias leaning towards underestimation.

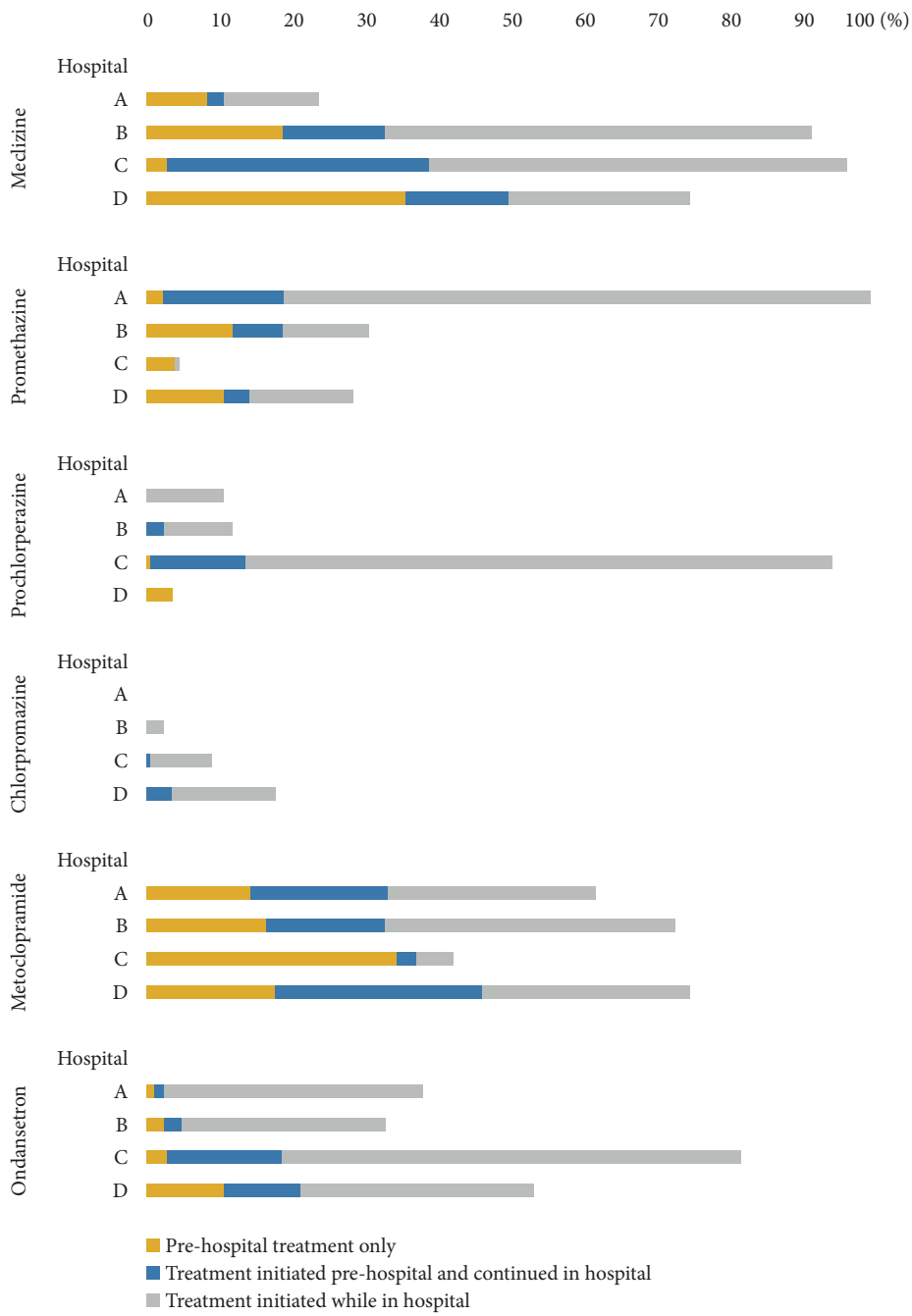

Figure 3: Percentage of 343 women with hyperemesis gravidarum treated with antiemetic medication prior to hospitalization, while at hospital, or both, at hospital A ($n = 87$), B ($n = 44$), C ($n = 183$), and D ($n = 29$).

5. Conclusions

The NGF HG treatment guideline of 2014 was integrated either as is or with minor adaptations in treatment protocols at most Norwegian gynecology departments by 2019. Overall, the provided antiemetic treatment at four university hospitals aligned with the treatment pathway outlined in the NGF guideline. The difference in the proportion of women being provided ondansetron between hospitals suggests geographical inequality of care and need for improved guideline compliance. Prehospital use of ondansetron was higher at hospitals where in-patient use of ondansetron was more frequent and among women with previous HG pregnancies. Geographic differences in an overall lower-than-expected use of nutritional treatment indicate undertreatment of malnutrition. These aspects should be highlighted in future guideline revisions. Future studies should investigate the sequence and combinations of antiemetic medication and associations between the provided treatment and outcomes such as readmissions and length of hospital stay.

Data Availability

Anonymous aggregated data are available from the corresponding author upon reasonable request.

Ethical Approval

The ethical approval of the project does not allow for sharing patient data.

Conflicts of Interest

JT has been a part of the group developing the NGF guidelines. The remaining authors declare that they have no conflicts of interest.

Authors' Contributions

JT initiated and designed the study. JT, IV, SA, and EAT facilitated the data collection performed by HE, JBB, and KBK. The data analyses, figures, and first draft were produced by HE. All authors have actively contributed to and approved the final version of the manuscript.

Acknowledgments

The authors thank the Bergen Hospital Trust, Stavanger University Hospital, the University Hospital of North Norway, and St. Olavs Hospital, Trondheim University Hospital, for facilitating the data collection and the medical students performing parts of the data collection. The University of Bergen has funded the work. Open access funding was enabled and organized by SIKT GOLD.

Supplementary Materials

Supplementary Table 1: use of department protocols or NGF guidelines for treatment of hyperemesis gravidarum among included departments by health region. (*Supplementary Materials*)

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