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Original Article

Paediatrics Section

Evaluating the Efficacy of Racecadotril in Combination with Oral Rehydration in Children with Acute Diarrhoea: A Randomised Controlled Trial

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ABSTRACT

Introduction: Acute watery diarrhoea in early childhood frequently necessitates hospital admission. Although Oral Rehydration Salts (ORS) with zinc effectively prevent and treat dehydration, they do not consistently shorten illness duration or reduce early stool losses. Racecadotril, a motility-sparing antisecretory agent, may help address this therapeutic gap.

Aim: To evaluate whether adding racecadotril to ORS plus zinc improves short-term clinical outcomes in hospitalised infants and toddlers with acute watery diarrhoea.

Materials and Methods: A randomised, double-blind, parallel-group, placebo-controlled trial was conducted in the paediatric wards of the Indira Gandhi Institute of Child Health (IGICH), Bengaluru, Karnataka, India. A total of 140 children aged 3-24 months with non dysenteric acute watery diarrhoea and mild-to-moderate dehydration were allocated (1:1) to receive either racecadotril (1.5 mg/kg every 8 hours, up to 5 days) plus ORS and zinc, or a matching placebo plus ORS and zinc. The primary endpoint was duration of hospital stay (hours). Secondary endpoints included stool frequency (Days 1-3), stool consistency (Days 1-3), and total ORS requirement. Analyses followed intention-to-treat principles; Mann–Whitney U and covariate-adjusted ANCOVA were used for continuous outcomes, and χ^2 tests for proportions. A p-value of <0.05 was considered as statistically significant.

Results: Racecadotril significantly improved outcomes in children with acute diarrhoea (p-value <0.001). Compared with the control group, it shortened hospital stay by nearly 17 hours (p-value <0.001) and consistently reduced stool frequency over the first three days of treatment (day 1, p-value=0.001; day 2, p-value=0.003; day 3, p-value=0.018). By day 2, a greater proportion of children receiving racecadotril passed formed stools (41.4% vs 21.4%; p-value=0.010), though this difference was no longer evident by day 3 (p-value=0.149). ORS requirement was also markedly lower in the racecadotril group (p-value <0.001). Adverse Events (AEs) were rare, mild, and comparable between groups (5.7% each; p-value>0.05), with no serious events reported, underscoring the favourable safety profile of racecadotril.

Conclusion: Racecadotril, when used as an adjunct to ORS and zinc in infants and toddlers with acute watery diarrhoea, may offer meaningful clinical benefits by accelerating recovery, reducing treatment burden, and enabling earlier discharge, all without added safety concerns.

Keywords: Antidiarrhoeals, Dehydration therapy, Enkephalinase inhibitors, Fluid therapy, Gastroenteritis therapy, Hospitalisation, Length of stay, Zinc/therapeutic use

INTRODUCTION

Acute watery diarrhoea remains a common cause of paediatric morbidity and hospital utilisation in low- and middle-income countries, with the highest vulnerability in infancy and early toddlerhood. Recurrent episodes during the first two years of life amplify nutritional risk, disrupt caregiving, and increase demand for ward beds, nursing time, and consumables [1]. Contemporary case management focuses on prompt assessment of dehydration, early feeding, and oral rehydration therapy using reduced-osmolarity ORS, with zinc supplementation recommended to reduce severity and subsequent episodes. This package is highly effective for preventing and correcting dehydration, yet it does not reliably shorten the symptomatic course once diarrhoea has developed, nor consistently reduce early stool losses in moderate-to-severe illness. In routine inpatient practice, persistent high stool output translates into larger ORS volumes, ongoing fluid balance monitoring, and longer observation periods even when guideline-based care is implemented [1,2]. The clinical challenge, therefore, is not a lack of effective rehydration, but the service-level burden created by ongoing secretion and stool losses while hydration is being maintained.

Racecadotril is a peripheral enkephalinase inhibitor that increases the availability of endogenous enkephalins in the intestinal mucosa, attenuating cyclic AMP–mediated chloride secretion and the downstream movement of water into the lumen during infectious gastroenteritis. Unlike antimotility drugs, its effect is "state-dependent," acting predominantly when secretory pathways are activated while preserving baseline transit and avoiding constipation-related complications [3]. Paediatric experience across a range of formulations and weight-based schedules, including dosing from early infancy, has generally been reassuring, although high-quality safety reporting remains essential, particularly in severe disease or in children with co-morbidities [4]. A second rationale is behavioural: when an adjunct reduces stool losses, caregivers and staff may find ORS regimens easier to sustain, indirectly improving adherence to core therapy.

However, the clinical effectiveness of racecadotril is not uniform across studies, and the direction of effect varies by setting, baseline severity, and outcome selection. Several hospital-based trials in infants and young children have demonstrated meaningful reductions in early stool output, total stool losses, and ORS requirements, with parallel reductions in time to recovery and length of stay [5-7]. In contrast, evidence from some studies is neutral. A randomised, placebo-controlled trial in Kenya, enrolling children with high-severity acute gastroenteritis, found no reduction

in stool frequency at 48 hours, duration of diarrhoea, or inpatient stay when racecadotril was added to ORS plus zinc, emphasising the importance of careful adverse-event surveillance in high-risk contexts [8]. Another hospital-based randomised trial in moderately to severely dehydrated children reported neutral effects for duration and stool frequency, but significantly better stool consistency at 24 and 48 hours, suggesting that the benefit may be endpoint-specific or modest in magnitude [9].

This inconsistency is echoed in systematic reviews, where heterogeneity in trial quality, background care (with or without zinc), inpatient versus outpatient recruitment, and outcome definitions (stool weight, stool counts, time to recovery, rehydration failure, or length of stay) limits certainty and dilutes pooled estimates [10-12]. Importantly, pragmatic endpoints relevant to hospital services, such as total ORS use, need for intravenous fluids, and length of stay, are not consistently powered as primary outcomes, leaving uncertainty about real-world ward-level value. Even probiotics have shown neutral effects in large, well-conducted paediatric trials when implemented alongside effective ORS and zinc regimens [13], indicating that existing care can diminish the potential for additional benefits, highlighting the importance of context-sensitive trial design.

Therefore, the present study was designed to evaluate racecadotril as an adjunct to standard ORS and zinc in hospitalised children with acute watery diarrhoea.

MATERIALS AND METHODS

This randomised, double-blind, parallel-group, placebo-controlled trial was conducted in the paediatric wards of the Indira Gandhi Institute of Child Health (IGICH), Bengaluru, Karnataka, India, from January 2017 to June 2018. The trial adhered to CONSORT recommendations and local Good Clinical Practice guidelines. Written informed consent was obtained from a parent or legally authorised guardian before any study procedures. The protocol was approved by the IGICH Institutional Ethics Committee (IEC No. IGICH/06/2016, dated 27 Oct 2016) and complied with the Declaration of Helsinki.

Sample size calculation: The sample size was determined a priori for the primary endpoint (hospital stay duration in hours), assuming equal allocation (1:1), a two-sided type I error of α=0.05, and 80% power.

$$n=\frac{2\sigma^2(Z_{1-\alpha/2}+Z_{1-\beta})}{\Delta^2}$$

Where ($Z_{1-\alpha/2}$=1.96) (two-sided α=0.05), ($Z_{1-\beta}$=0.84) (80% power) =((1.96+0.84)^2=7.84)

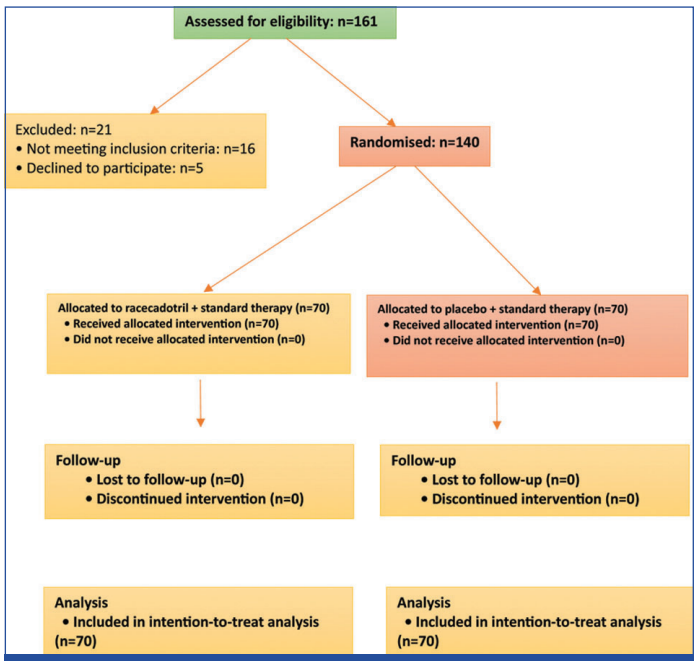
Anticipated common SD (σ)≈10.5 hours (pooled from 62.4±11.4 hours in the racecadotril arm and 95.6±9.5 hours in the placebo arm) [7].

Target difference (Δ)=0.53σ≈5.6 hours The calculated sample size was ~56 children per group. Allowing ~15% for attrition/withdrawal and to maintain block balance, the recruitment target was set at 70 per group (total N=140).

Inclusion criteria: Children aged 3–24 months admitted with acute watery diarrhoea, defined as ≥3 loose/watery stools in 24 hours, and mild-to-moderate dehydration graded according to Podewils LJ et al., [14] were included in the study.

Exclusion criteria: Dysentery (visible blood), persistent diarrhoea (≥14 days), severe dehydration requiring immediate intravenous therapy, severe acute malnutrition, chronic gastrointestinal disease, known Human Immunodeficiency Virus (HIV) infection, prior or current use of anti-diarrhoeal or anti-motility agents, drugs with secretory effects, antibiotics initiated for diarrhoea before admission, inability to tolerate oral fluids, or any condition judged by investigators to interfere with participation were excluded form the study.

Randomisation: Participants were randomly assigned in a 1:1 ratio to receive racecadotril plus standard therapy or standard therapy alone, using a computer-generated sequence with variable block sizes and Sequentially Numbered, Opaque, Sealed, Tamper-Evident (SNOSE) envelopes prepared by the pharmacy. At enrolment, the caregiver drew the next envelope, and the ward nurse dispensed sachets according to the concealed allocation. Packaging and labeling were uniform and code-based, ensuring that caregivers, bedside assessors, investigators, and data analysts remained blinded until database lock. The pharmacy safeguarded the master code list, and emergency unmasking was permissible only for safety reasons [Table/Fig-1].



[Table/Fig-1]: CONSORT diagram.

Study Procedure

All participants received low-osmolarity ORS and oral zinc according to guideline dosing [15]. Zinc was given at 10 mg/day for infants under six months and 20 mg/day for children six months or older, continued for 14 days. ORS administration followed dehydration grade and ongoing losses under standard ward protocols. The experimental arm received racecadotril at 1.5 mg/kg every eight hours, initiated at randomisation and continued for 3-5 days or until clinical recovery, whichever occurred first. Practical sachet dosing was standardised: <8 kg, 10 mg per dose; 8-10 kg, 15 mg per dose; 10-14 kg, 20 mg per dose (two 10-mg sachets). The control arm received coded placebo sachets on the same schedule alongside ORS and zinc [16]. Paracetamol for fever was allowed. Other antidiarrhoeals, antimotility agents, probiotics, and antibiotics were discouraged unless clinically indicated, with any such use recorded in real time. Demographic details including age, sex, anthropometry, feeding practice, illness duration, and baseline stool frequency were recorded.

Outcomes: The primary outcome was duration of hospital stay, measured in hours from randomisation until discharge once patients were medically fit according to ward criteria. Secondary outcomes included stool frequency over each 24 hours during days 1-3, stool consistency assessed on days 1-3 using the modified Bristol Stool Form (BSF) scale for watery or loose stools [17], and total ORS volume required to achieve and maintain hydration, recorded both as absolute milliliters and normalised to mL/kg/hour. For operational clarity, day 1 was defined as 0-24 hours after the first study dose, day 2 as 24-48 hours, and day 3 as 48-72 hours. Nursing staff prospectively documented stool episodes in 24-hour logs, cross-checked against caregiver notes, while stool consistency was recorded during daily assessments and again at discharge. ORS intake was calculated

using the difference method from prepared sachets and bedside fluid charts, with redosing required if vomiting occurred within 10 minutes, according to ward protocol. Dehydration status was graded per Podewils LJ et al., including general condition, sunken eyes, thirst, and skin pinch. Safety monitoring encompassed Adverse Events (AEs), their severity and relatedness, as well as Serious Adverse Events (SAEs) throughout the hospital admission [14].

STATISTICAL ANALYSIS

Data were analysed using IBM SPSS Statistics version 25.0 (IBM Corp). Continuous outcomes with skewed distributions were compared unadjusted using the Mann-Whitney U test. Adjusted effects were estimated with ANCOVA (robust SEs), including prespecified covariates: baseline stool frequency, illness duration, dehydration grade, feeding status, age, sex, weight, and length. As a sensitivity model for counts, negative binomial regression was fitted to estimate rate ratios. Categorical outcomes were compared using χ^2 tests or Fisher's exact test as appropriate. A p-value <0.05 was considered as statistically significant.

RESULTS

A total of 140 children were randomised equally to racecadotril plus standard therapy (n=70) or standard therapy alone (n=70). Baseline demographics and anthropometry were closely matched across arms, with only minor differences in feeding practices. Pre-admission duration and entry stool counts were slightly lower in the racecadotril arm. Most children had mild-to-moderate dehydration, with a similar distribution across arms (p-value=0.497), supporting comparability in initial illness severity [Table/Fig-2].

Variables	Overall (n=140)	Racecadotril (n=70)	Standard therapy (n=70)
Age, years (mean±SD)	0.94±0.50	0.95±0.55	0.92±0.45
Weight, kg (mean±SD)	7.80±2.29	7.64±2.20	7.90±2.30
Height, cm (mean±SD)	69.89±8.73	69.70±6.40	70.00±10.50
Male, n (%)	85 (60.7)	42 (60.0)	43 (61.4)
Female, n (%)	55 (39.3)	28 (40.0)	27 (38.6)
Bottle-feeding, n (%)	79 (56.4)	37 (53.0)	42 (60.0)
Preillness duration before admission, days (mean±SD)	2.16±1.10	1.91±1.02	2.41±1.12
Duration before admission, days (median, IQR)	2 (1-3)	2 (1-3)	2 (2-3)
Stool frequency at admission, episodes/day (mean±SD)	7.54±2.52	6.79±2.30	8.30±2.52
Stool frequency at admission (median, IQR)	7 (5-9.75)	6 (5-8.25)	8 (6-10)
Dehydration grade - Mild, n (%)	64 (45.7)	34 (48.6)	30 (42.9)
Dehydration grade - Moderate, n (%)	76 (54.3)	36 (51.4)	40 (57.1)

[Table/Fig-2]: Baseline characteristics of participants (experimental vs. control). Covariates (illness duration, stool frequency, and dehydration grade) were used to adjust outcome models to mitigate baseline imbalance. Statistical test: χ^2 test (2×2) for dehydration grade: $\chi^2(1)=0.46$; p-value=0.497 (not significant)

Racecadotril shortened hospitalisation in the adjusted analysis by approximately 17 hours (adjusted mean difference -16.9 h; p-value <0.001), and unadjusted comparisons also favoured racecadotril (p-value <0.001) [Table/Fig-3]. Clinically, this reflects earlier discharge readiness under standard ward criteria.

Group	Mean±SD	Median	Min-Max	ANCOVA EMM*
Racecadotril	43.4±15.1	47.5	13-89	44.74
Standard therapy	63.6±13.9	66.0	30-96	61.62

[Table/Fig-3]: Duration of hospital stay (hours) of both groups postintervention. Mann-Whitney U, p-value <0.001. Adjusted comparison: ANCOVA with robust SEs; EMM: Estimated marginal mean

Between-group separation in stool frequency emerged by day 1 and persisted through day 3 (p-value≤0.018 each day), while within-group decline over time was significant in both arms (Friedman p-value <0.001) [Table/Fig-4]. Stool consistency improved earlier with racecadotril by day 2 (p-value=0.010), with convergence by day 3 as recovery was completed (p-value=0.149) [Table/Fig-5]. ORS requirements (total volume and weight-indexed rate) were substantially lower with racecadotril; effects remained significant after covariate adjustment (all p-value <0.001), including an adjusted reduction of 752.7 mL in total ORS and 0.64 mL/kg/h in ORS rate [Table/Fig-6].

Day	Racecadotril Mean±SD (Median)	Standard therapy Mean±SD (Median)	Between-group p (Mann-Whitney)
Day 1 (0-24 h)	4.91±2.10 (5)	6.34±2.39 (6)	0.001
Day 2 (24-48 h)	2.61±1.94 (2)	3.74±2.24 (3.5)	0.003
Day 3 (48-72 h)	0.91±1.19 (0)	1.51±1.62 (1)	0.018

[Table/Fig-4]: Stool frequency over days 1-3.
Note. Daily stool counts in fixed 24-h windows after the first dose, Mann-Whitney U at each day (p-values shown). Intragroup trend (bias control): Friedman test across Days 1-3, racecadotril p-value <0.001; standard therapy p-value <0.001.
Post-hoc Wilcoxon signed-rank with Bonferroni correction showed significant Day 1 →Day 2 and Day 2→Day 3 reductions within each arm (corrected p-value <0.05). Sensitivity: Negative binomial regression with treatment term confirmed between-group differences across days (treatment effect p-value <0.01)

Day	Group	Watery n (%)	Formed n (%)	Discharged n	χ^2 (df)†	p-value†
Day 1	Racecadotril	70 (100.0)	0 (0.0)	0	-	-
	Standard therapy	70 (100.0)	0 (0.0)	0	-	-
Day 2	Racecadotril	39 (55.7)	29 (41.4)	2	6.63 (1)	0.010
	Standard therapy	55 (78.6)	15 (21.4)	0	-	-
Day 3	Racecadotril	0	66 (94.3)	4	2.08 (1)	0.149
	Standard therapy	2 (2.9)	67 (95.7)	1	-	-

[Table/Fig-5]: Stool consistency trajectory.
Note. Fixed daily assessment; discharged children excluded from that day's formed/watery analysis. Statistical tests. Between-group comparisons by χ^2 on formed vs watery for each day (df=1). Day 1 not estimable (all watery). χ^2 values for Days 2-3 are shown with corresponding p-values

Measure	Racecadotril	Standard therapy	Between-group
Total ORS, mL (mean±SD)	1102.14±506.80	2088.57±850.50	p<0.001
Total ORS, mL (median; min-max)	1000; 250-2500	2000; 700-4500	-
ANCOVA EMM, mL	1206.59	1959.27	p<0.001
Adjusted mean difference (EMM), mL	-752.7	-	-
ORS, mL/kg/h (mean±SD)	3.41±0.96	4.19±0.81	p<0.001
ORS, mL/kg/h (median; min-max)	3.2; 2.0-7.3	4.2; 2.7-6.3	-
ANCOVA EMM, mL/kg/h	3.40	4.04	p<0.001
Mean difference (EMM), mL/kg/h	-0.64	-	-

[Table/Fig-6]: ORS requirements during hospitalisation.
Note. ORS recorded via difference method from prepared sachets and bedside charts. Statistical tests. Unadjusted: Mann-Whitney U (both p-value <0.001). Adjusted: ANCOVA with robust SEs using the same prespecified (all p-value <0.001). EMM: Estimated marginal mean

Treatment was well tolerated in both groups. AEs were infrequent, mild, and balanced between arms [Table/Fig-7]. Four children (5.7%) in each group experienced at least one mild AE during the inpatient stay. The most common events were transient fever in both groups; one rash occurred in the racecadotril group (considered mild and self-limited). No SAEs, such as intensive care transfer, shock, or death, were observed in either arm. There were also no cases of abdominal distension or ileus, consistent with the mechanism of racecadotril, which does not affect motility.

Event	Racecadotril (n=70)	Standard therapy (n=70)
Rash (transient)	1	0
Fever	3	4
Serious Adverse Events (AE)	0	0

[Table/Fig-7]: Safety Adverse Events (AE).
No significant between-group differences in event incidence were noted (all p>0.5 by Fisher's-exact test)

DISCUSSION

In this inpatient cohort receiving reduced-osmolarity ORS and zinc, the addition of racecadotril resulted in faster clinical recovery. Children in the racecadotril group passed fewer stools during the early treatment period, showed quicker improvement in stool consistency, and required substantially less ORS for rehydration. Clinically, this adjunctive benefit is meaningful: by curtailing ongoing intestinal secretion without affecting normal gut motility, racecadotril reduced the volume of replacement fluids needed and minimised high-frequency stool losses that demand intensive nursing care. Importantly, no increase in AEs was observed, indicating that these efficiency gains were achieved without compromising safety.

Given that modern oral rehydration and zinc therapy are highly effective in preventing dehydration but do not appreciably shorten diarrhoea duration or early stool output [18,19], an antisecretory agent that targets the secretory component while preserving intestinal transit represents an attractive complementary strategy in high-burden settings.

Present study findings align with results from other hospital-based trials of racecadotril. For instance, a recent randomised study in an Indian tertiary hospital reported significant reductions in 48-hour stool output and shorter length of stay with racecadotril therapy, particularly among children with rotavirus-positive diarrhoea [7]. Similarly, a controlled trial in Egypt found that adding racecadotril to ORS and zinc markedly decreased total stool volume and shortened the duration of diarrhoea in hospitalised children [20].

At a broader level, multiple meta-analyses reflect these improvements but also highlight variability between studies. Some analyses indicate that racecadotril accelerates recovery and lowers cumulative stool losses, whereas others, including a Cochrane review, have judged the evidence as low-certainty, with inconsistent effects on outcomes such as length of hospital stay [10-12]. This heterogeneity likely stems from differences in patient severity, timing of treatment initiation, and endpoints measured across trials.

Not all studies have demonstrated benefits from racecadotril, especially in more severe or advanced illness. A trial in Kenya involving children with profuse diarrhoea and dehydration found no significant reduction in stool frequency, diarrhoea duration, or hospitalisation time with racecadotril [8]. Another trial in children presenting with moderate to severe dehydration reported no difference in overall diarrhoea duration or stool count, although stool consistency improved faster in the racecadotril arm [9]. These divergent results suggest that the efficacy of racecadotril may depend on illness context. In cases of very severe or protracted diarrhoea, where inflammatory or malabsorptive mechanisms contribute alongside secretion, a purely antisecretory drug may have limited impact on gross clinical endpoints. Additionally, timing and measurement can influence observed effects. Trials that initiated racecadotril early in the course of illness and measured stool output quantitatively (by weight) tend to show clearer benefits [5-7], whereas those focusing on stool frequency or starting treatment later may underestimate its effect. Mechanistically, racecadotril only acts when secretory pathways are activated [3], so its benefit is most pronounced in the early, high-secretion phase of acute diarrhoea.

Beyond patient recovery metrics, incorporating health-system outcomes is important for appreciating the full value of adjunct therapies. In present study, racecadotril's ability to reduce ORS consumption and shorten stay hints at potential resource savings. Economic modeling studies in low- and middle-income countries support this, showing that adding racecadotril can be cost-saving by averting prolonged diarrhoea and the need for escalation to intravenous therapy [21,22]. By decreasing fluid losses and facilitating earlier discharge, such an intervention may alleviate strain on hospital resources and families—an aspect that warrants further prospective evaluation.

Limitation(s)

This study had several limitations. The sample size was powered for hospital stay reduction, and future trials should align power calculations with key outcomes such as time to discharge. Stool output by weight was not measured, limiting comparability with benchmark trials where stool weight demonstrated clear benefits of racecadotril. Pathogen identification was not performed, restricting assessment of efficacy by diarrhoea aetiology, and the single-centre design may limit generalisability to settings with different pathogen profiles or higher malnutrition rates. Small baseline differences in illness duration or stool frequency could bias unadjusted comparisons, although adjusted analyses were used to mitigate this. Finally, while no safety issues emerged in our moderate-severity sample, continued vigilance is warranted, particularly in higher-risk populations.

At the time of study initiation, CTRI registration was not performed. Prospective registration in CTRI became mandatory from April 2018, after enrollment for this study had already commenced. Authors acknowledge this limitation and affirm that all future trials will be prospectively registered in CTRI in accordance with ICMR and international guidelines.

CONCLUSION(S)

In this double-blind randomised trial of hospitalised infants and toddlers with non dysenteric acute watery diarrhoea, adjunctive racecadotril added to standard ORS plus zinc yielded clinically and operationally meaningful benefits. These findings support racecadotril as a useful inpatient adjunct to accelerate recovery and reduce fluid burden in similar settings. Larger multicentre trials, powered for time-to-discharge and incorporating stool-weight measurement and pathogen analysis, are warranted to refine patient selection criteria and confirm the health-economic impact of routine racecadotril use.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Oct 23, 2025
- Manual Googling: Jan 08, 2026
- iThenticate Software: Jan 10, 2026 (1%)

ETYMOLOGY: Author Origin

EMENDATIONS: 8

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

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