Famotidine

Section last reviewed and updated 5/23/2022

Last literature search conducted 4/30/2022

Recommendation 1 (NEW 5/23/2022): Among ambulatory patients with mild-to-moderate COVID-19, the IDSA panel suggests against famotidine for the treatment of COVID-19 (Conditional recommendation, low certainty of evidence)

Recommendation 2 (UPDATED 5/23/2022): Among hospitalized patients with severe COVID-19, the IDSA panel suggests against famotidine for the treatment of COVID-19. (Conditional recommendation, low certainty of evidence)

Why is famotidine considered for treatment?

Anecdotal reports from China and a cohort study from the United States had suggested that patients infected with SARS-CoV-2 who were receiving famotidine, an H2-receptor antagonist used for conditions such as gastroesophageal reflux and peptic ulcer disease, had improved survival *versus* those receiving proton pump inhibitors (PPIs) [1, 2]. This study led to interest in the drug, though no predominant theory describing a mechanism for its efficacy yet exists.

Our search identified two randomized controlled trials (RCTs) comparing treatment with famotidine against no famotidine among ambulatory persons with COVID-19 and persons hospitalized with severe COVID-19 [3, 4] (**Tables 1-2**).

Summary of the evidence

Ambulatory patients with mild-to-moderate disease

One patient and assessor blinded RCT examined high-dose famotidine at 80 mg three times daily for 14 days (n=27) vs placebo (n=28) in a predominantly younger population (35 years of age) at average risk for progression to severe disease [3]. Symptom resolution was the primary endpoint.

Hospitalized patients with severe disease

Oral famotidine at standard doses of 40 mg daily (n=89) vs placebo (n=89) was given to hospitalized patients with severe COVID-19 in an open-label RCT. The authors recorded

symptom resolution, length of hospital stay, need for ICU care, need for mechanical ventilation, or death [4].

Benefits

Ambulatory patients with mild-to-moderate disease

Symptom resolution in ambulatory patients at day 28 failed to show or to exclude a beneficial effect of high-dose famotidine (risk ratio [RR]: 1.1, 95% confidence interval [CI]: 0.76, 1.58 – not directly reported but estimated from the survival curve; low certainty of evidence [CoE]).

Hospitalized patients with severe disease

In hospitalized patients with severe COVID-19, famotidine at standard dose failed to show or exclude a beneficial effect on mortality, need for mechanical ventilation, or need for ICU care (RR: 0.89, 95% CI: 0.36, 2.2; RR: 0.88, 95% CI: 0.53, 1.45; RR: 0.9, 95% CI: 0.51, 1.58, respectively; all low CoE). Time to symptom resolution was shorter in the famotidine group (mean difference [MD] -0.9 days, 95% CI: -1.44, -0.36), as was length of hospital stay (MD -1.7 days, 95% CI: -2.77, -1.13), although due to lack of blinding these estimates remain less certain (low CoE) (**Table 2**).

Harms

At standard doses, famotidine is well tolerated. Common adverse events include diarrhea or constipation but occur in less than 5% of people. Severe adverse events occur in less than 1% of persons taking famotidine. Adverse events were rare in the ambulatory study examining high dose famotidine (RR: 0.69, 95% CI: 0.13, 3.8) and no severe adverse events were reported.

Other considerations

The panel determined the certainty of evidence for ambulatory patients with mild-to-moderate disease to be low due to concerns with imprecision due to small sample sizes and few events.

The panel determined the certainty of evidence for hospitalized patients with severe disease to be low due to concerns with risk of bias and imprecision from small sample sizes and few events.

Conclusions and research needs for this recommendation

The guideline panel suggests against famotidine for the sole purpose of treating COVID-19. Clinical trials with larger sample sized would be needed to determine the true effect of famotidine in patients with COVID-19.

Table 1. GRADE evidence profile, Recommendation 1

Question: Famotidine compared to no famotidine for ambulatory patients with mild-to-moderate COVID-19

New evidence profile developed 5/17/2022

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	high-dose famotidine (80 mg tid)	no famotidine	Relative (95% CI)	Absolute (95% CI)		
Symptom resolution (follow-up: 28 days) [a]												
1[1]	randomized trials	not serious	not serious	not serious	very serious [b]	none	19/27 (70.4%) [c]	18/28 (64.3%)	**RR 1.10** (0.76 to 1.58)	**64 more per 1,000** (from 154 fewer to 373 more)	⨁⨁◯◯ LOW	CRITICAL
Adverse events [d]												
1[1]	randomized trials	not serious	not serious	not serious	very serious [b]	none	2/27 (7.4%)	3/28 (10.7%)	**RR 0.69** (0.13 to 3.80)	**33 fewer per 1,000** (from 93 fewer to 300 more)	⨁⨁◯◯ LOW	IMPORTANT

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Risk of bias: Study limitations
Inconsistency: Unexplained heterogeneity across study findings
Indirectness: Applicability or generalizability to the research question
Imprecision: The confidence in the estimate of an effect to support a particular decision
Publication bias: Selective publication of studies

NB: Certainty ratings may be derived from evidence that includes pre-print articles, which have not been peer reviewed or published.

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Time to symptom resolution was the primary end point. However, the authors reported a faster (earlier) rate of symptom resolution with famotidine. No deaths were encountered.
b. Sparse data, few events and small sample size
c. Only p-value reported; number of events estimated from survival curve graph.
d. No SAEs were encountered. Transaminase elevation in 1 patient in both arms; nausea / vomiting in 1 patient with famotidine; thrombocytopenia and hives in 1 patient each in the placebo group.

Reference

1. Brennan CM, Nadella S, Zhao X, et al. Oral famotidine versus placebo in non-hospitalised patients with COVID-19: a randomised, double-blind, data-intense, phase 2 clinical trial. Gut **2022**; 71(5): 879-88.

Table 2. GRADE evidence profile, Recommendation 2
Question: Famotidine compared to no famotidine for hospitalized patients with severe COVID-19
Last reviewed and updated 5/17/2022

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	famotidine	no famotidine	Relative (95% CI)	Absolute (95% CI)		
Mortality												
1[1]	randomized trials	serious [a]	not serious	not serious	serious [b]	none	8/89 (9.0%)	9/89 (10.1%)	**RR 0.89** (0.36 to 2.20)	**11 fewer per 1,000** (from 65 fewer to 121 more)	⨁⨁◯◯ LOW	CRITICAL
Mechanical ventilation												
1[1]	randomized trials	serious [a]	not serious	not serious	serious [b]	none	21/89 (23.6%)	24/89 (27.0%)	**RR 0.88** (0.53 to 1.45)	**32 fewer per 1,000** (from 127 fewer to 121 more)	⨁⨁◯◯ LOW	CRITICAL
ICU care												
1[1]	randomized trials	serious [a]	not serious	not serious	serious [b]	none	18/89 (20.2%)	20/89 (22.5%)	**RR 0.90** (0.51 to 1.58)	**22 fewer per 1,000** (from 110 fewer to 130 more)	⨁⨁◯◯ LOW	CRITICAL
Time to symptom free												
1[1]	randomized trials	serious [a]	not serious	not serious	serious [b]	none	89	89	-	MD **0.9 days fewer** (1.44 fewer to 0.36 fewer)	⨁⨁◯◯ LOW	IMPORTANT
Length of hospital stay												
1[1]	randomized trials	serious [a]	not serious	not serious	serious [b]	none	89	89	-	MD **1.7 days fewer** (2.77 fewer to 1.13 fewer)	⨁⨁◯◯ LOW	IMPORTANT
Serious adverse events												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	famotidine	no famotidine	Relative (95% CI)	Absolute (95% CI)		
0	observational studies						Post-marketing and registrational reported common adverse events include constipation (1.2%-1.4%), diarrhea (1.7%), dizziness (1.3%) and headache (1%-4.7%), but overall famotidine is well tolerated. Rare but serious adverse events (<1%) include: Stevens-Johnson syndrome, toxic epidermal necrolysis, necrotizing enterocolitis, anaphylaxis, angioedema, rhabdomyolysis, seizure, hospital-acquired pneumonia, interstitial pneumonia. (Micromedex)				-	CRITICAL

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
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Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
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Risk of bias: Study limitations
Inconsistency: Unexplained heterogeneity across study findings
Indirectness: Applicability or generalizability to the research question
Imprecision: The confidence in the estimate of an effect to support a particular decision
Publication bias: Selective publication of studies

NB: Certainty ratings may be derived from evidence that includes pre-print articles, which have not been peer reviewed or published.

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

Explanations

a. Unclear allocation concealment in an unblinded study
b. Sparse data, small number of events or patients

Reference

1. Pahwani S, Kumar M, Aperna F, et al. Efficacy of Oral Famotidine in Patients Hospitalized With Severe Acute Respiratory Syndrome Coronavirus 2. Cureus **2022**; 14(2): e22404.

References

1. Borrell B. New York clinical trial quietly tests heartburn remedy against coronavirus. Available at: https://www.sciencemag.org/news/2020/04/new-york-clinical-trial-quietly-tests-heartburn-remedy-against-coronavirus.
2. Freedberg DE, Conigliaro J, Wang TC, et al. Famotidine use is associated with improved clinical outcomes in hospitalized COVID-19 patients: A propensity score matched retrospective cohort study. Gastroenterology **2020**; 159(3): 1129-31.
3. Brennan CM, Nadella S, Zhao X, et al. Oral famotidine versus placebo in non-hospitalised patients with COVID-19: a randomised, double-blind, data-intense, phase 2 clinical trial. Gut **2022**; 71(5): 879-88.
4. Pahwani S, Kumar M, Aperna F, et al. Efficacy of Oral Famotidine in Patients Hospitalized With Severe Acute Respiratory Syndrome Coronavirus 2. Cureus **2022**; 14(2): e22404.

Supplementary Materials

Study characteristics

- **Table s1.** Should patients with COVID-19 (ambulatory with mild-to-moderate disease, hospitalized with severe disease) receive treatment with famotidine vs. no famotidine?

Risk of bias

- **Table s2.** Randomized controlled studies (famotidine vs. no famotidine)

Table s1. Should patients with COVID-19 (ambulatory with mild-to-moderate disease, hospitalized with severe disease) receive treatment with famotidine vs. no famotidine?

Study/ year	Country/ hospital	Study design	N subjects (intervention /comparator)	% female	Age mean (SD)/ median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
Brennan/ 2022 [1]	U.S./ Northwell Health; New York City Health and Hospitals Corporation	RCT	55 (27/28)	63.6	Median age: 35.0 (15-50)	Unvaccinated adults with a positive SARS-CoV-2 PCR test within 72 hours and a minimum of three symptoms of moderate severity for 1-7 days	Famotidine 80 mg by mouth three times a day for 14 days	Placebo	None	Time to symptom resolution (symptom score ≤ 3 and no individual symptoms >1 for 2 consecutive days) Decreasing rate of symptom resolution from day 0 to 28 Cumulative incidence of symptom resolution (symptom score decreased to ≤ 1 for 2 consecutive days) of	Pershing Square Foundation Emergent Ventures Fast Grant Dr. Lee MacCormick Edwards Charitable Foundation Cancer Centre Support Grant

										each individual symptom that is >1 at baseline Relative change in CRP, ferritin Adverse events	
Pahwani/ 2022 [2]	Pakistan / Jinnah Sindh Medical University	RCT	178 (89/89)	39.3	Mean: Intervention: 52 (11) Control: 51 (12)	Patients 18-65 hospitalized with PCR-confirmed COVID-19 infection	Famotidine 40mg daily plus standard of care	Standard of care	None	Mortality Need for ICU care Need for mechanical ventilation Length of hospitalization Time to resolution of symptoms	None

Table s2. Risk of bias for randomized control studies (famotidine vs. no famotidine)

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Brennan 2022 [1]							
Pahwani 2022 [2]							

Low	High	Unclear

References for Supplementary Materials

1. Brennan CM, Nadella S, Zhao X, et al. Oral famotidine versus placebo in non-hospitalised patients with COVID-19: a randomised, double-blind, data-intense, phase 2 clinical trial. Gut **2022**; 71(5): 879-88.
2. Pahwani S, Kumar M, Aperna F, et al. Efficacy of Oral Famotidine in Patients Hospitalized With Severe Acute Respiratory Syndrome Coronavirus 2. Cureus **2022**; 14(2): e22404.