

Precipitating factors in hepatic encephalopathy

Factors	Mode of action	Management
Azotemia (29%)	Urea in colon, urease increases ammonia production, excessive diuresis, prerenal azotemia	Lactulose, discontinue diuretics, volume expansion with albumin
Sedatives, tranquilizers, analgesics (24%)	Direct depressant action on brain	Avoid sedatives, lactulose
Gastrointestinal bleeding (18%)	15 to 20 g protein per 100 mL blood, ↑ammonia production, hypovolemia, prerenal azotemia	Lactulose, blood or plasma transfusion, volume expansion
Excess dietary protein (9%)	Excess nitrogenous substances	Lactulose, ↓protein in diet
Metabolic alkalosis (11%)	↑Diffusion of ammonia across blood-brain barrier	Correct hypokalemia with infusion of potassium
Infection (3%)	↑Peripheral ammonia production, ↑tissue catabolism leading to ↑ammonia production	Treat infection, administer lactulose
Constipation (3%)	Retention of ammonium in colon, more efficient formation of ammonia by colonic bacteria	Laxatives (eg, lactulose)

↑, increased; ↓, decreased.

Rifaximin (Xifaxan®) for the Treatment of Hepatic Encephalopathy

Indications and Clinical Pharmacology:

Rifaximin is currently indicated for the treatment of patients greater than 12 years of age with travelers' diarrhea caused by noninvasive strains of Escherichia coli.

Rifaximin is structurally related to rifampin and similarly binds to the beta subunit of bacterial DNA-dependent RNA polymerase of susceptible organisms, leading to inhibition of bacterial RNA synthesis and subsequent cell death.

Rifaximin is an **effective agent in the treatment of hepatic encephalopathy** via a decrease in the load of intestinal bacteria which produce urease (and is in turn metabolized to ammonia).

Pharmacokinetics:

Systemic absorption of rifaximin is low (~0.4% of oral dose) and therefore it exerts antimicrobial effect only on organisms confined to the gastrointestinal tract.

A small amount of drug is distributed to liver and kidney (<0.2%) and other tissues (<0.01%).

Rifaximin is **primarily excreted in the feces** (~97% of oral dose) as unchanged drug with a small amount being excreted in the urine (0.32%).

Comparative Efficacy:

Compared to baseline, the PSE score or index improved for all patients receiving rifaximin, lactulose, or neomycin. **Only two** studies have showed a statistically significantly greater improvement with rifaximin compared to lactulose

Adverse Reactions:

Rifaximin has a benign side effect profile when compared to other antimicrobial agents due to its very low absorption. In placebo controlled trials there were no adverse effects which showed significant difference compared to placebo. Events which occurred can most likely be attributed to the diarrhea and included headache, constipation, vomiting, flatulence, abdominal pain, rectal tenesmus, defecation urgency, nausea and pyrexia.

Drug Interactions:

An analogue of rifampin, rifaximin was shown to induce the CYP450 liver enzyme system, isoenzyme 3A4 in an in vitro hepatocyte induction model. Drug-drug interaction trials were performed with concomitant rifaximin therapy and either midazolam or ethinyl estradiol/norgestimate, both substrates of CYP 3A4.

No significant difference was observed in the pharmacokinetics of midazolam or ethinyl estradiol and norgestimate. Therefore, no clinically significant drug interactions via the CYP450 enzyme system are expected with rifaximin.

Dosing:

Dosage used in treatment of hepatic encephalopathy ranges from 200mg TID to 800mg TID for 7 days for acute encephalopathy and indefinitely for chronic encephalopathy.

Contraindications and Precautions:

Prolonged therapy with rifaximin has the potential to alter the colonic normal flora leading to overgrowth of Clostridium difficile and subsequent pseudomembranous colitis. Patients should be monitored for diarrhea persisting for more than 24-48 hours since this may be evidence for development of pseudomembranous colitis.

Cost Analysis:

Drug	Strength	AWP Cost per unit	OHSU Acquisition Cost per Unit	Dose	OHSU Drug Cost per Patient	
					7 day	14 day
Rifaximin	200mg	\$3.78	\$3.20	400mg q8h	\$134.40	\$268.80
Neomycin	500mg	\$1.97	\$1.20	500 mg q6h	\$55.16	110.32
Lactulose	20g/30mL	\$2.98/16 Oz	\$0.51	20-30g q6-8h	\$10.71	\$21.42

Appropriate Use

There are some concerns about the cost and appropriate use of rifaximin. Rifaximin should be reserved as a second-line agent, after initiation of treatment with lactulose.