Long-term use and overuse of proton pump inhibitors in the Indian Health Service: Results from a National Pharmacy and Therapeutics Committee medication use evaluation

The Indian Health Service National Pharmacy and Therapeutics Committee, http://www.ihs.gov/nptc. Correspondence: IHSNPTC1@ihs.gov

Background
Omeprazole was the first proton pump inhibitor (PPI) approved by the Food and Drug Administration (FDA) in 1990 for the short-term treatment of gastroesophageal reflux disease (GERD), active duodenal ulcer, severe erosive esophagitis, and pathological hypersecretory conditions. Since that time, the PPI class has expanded to include six agents, with two available in generic, over-the-counter (OTC) preparations. The PPIs are among the highest selling classes of drugs in the United States and ranked ninth in all drug categories purchased in 2014 by the Indian Health Service (IHS)1,2. The current prevalence of PPI use is justified by comparative reviews and practice guidelines which support PPI’s superior efficacy over histamine2-receptor antagonists (H2RA), sucralfate, prokinetics and placebo in treating common gastrointestinal conditions including GERD and non-erotic reflux disease3-6.

Despite their role in effectively managing acid-related disorders, the low acquisition cost, OTC availability and documented effectiveness of PPIs could lead to potential overutilization, exposing patients to potential adverse drug events (ADEs) associated with long term use. Additionally, although PPIs are approved by the FDA for short-term use, many patients remain on these medications for long periods of time. Two recent studies from the Department of Veterans Affairs (VA) evaluating typical usage of PPIs within their agency support this concern. One study revealed that 90.5% of patients were given an initial prescription for ≥ 90-day supply with a mean number of annual refills of 2.9. Only 16.2% of patients received the initial prescription without refills and only 3.3% of patients had step-down efforts introduced within the two years of the study7. The second study showed 65.8% of patients were given an initial prescription for ≥ 90-day supply with a mean number of annual refills of 2.9. Only 16.2% of patients received the initial prescription without refills and only 3.3% of patients had step-down efforts introduced within the two years of the study8.

Although recognized as one of the safest classes of medications, the misperception that PPIs have no adverse outcomes associated with prolonged use further contributes to potential overutilization9. Reports continue to emerge describing PPI overuse and ADEs. Documentation exists associating extended PPI duration of therapy and higher dosing to enteric infections with Clostridium difficile, bone fractures of the hip, spine, and wrist, community-acquired pneumonia, rebound acid hypersecretion and hypergastrinemia, interstitial nephritis, and nutritional deficiencies including vitamin B12, iron, and magnesium9-11.

In this Issue...
24 Long-term use and overuse of proton pump inhibitors in the Indian Health Service 18 NPTC Formulary Brief: Alcohol Use Disorders
31 NPTC Formulary Brief: Cirrhosis and complications
35 Electronic Subscriptions Available
While evidence of long-term PPI use and ADEs is limited by the absence of epidemiologic, observational and randomized controlled studies, the current body of literature highlights the importance of continual review for PPI overutilization. The 2013 American College of Gastroenterology guidelines for the diagnosis and management of GERD recommend patients requiring long-term PPI therapy be administered the lowest effective dose, including on-demand or intermittent therapy. In some patients, PPI step-down management of their therapy may be warranted which has been shown to be feasible without adversely affecting quality of life. Various PPI step-down methods have been described in the literature. By tapering PPI doses, duration or eliminating the inappropriate use of PPIs altogether, it is hopeful that potential ADEs are attenuated.

In addition to inappropriate and overuse, a known drug-drug interaction exists between omeprazole and clopidogrel which significantly decreases the metabolism of clopidogrel to its active form. This interaction mitigates the effect of clopidogrel and potentially increases cardiovascular risk, which has led to warnings about avoiding concomitant use. This interaction, as well as clopidogrel with other PPIs, has not been shown in long-term clinical trials or systematic reviews to increase cardiovascular events however, providers remain cautioned about the combined use.

A presentation on long-term and overuse of PPIs was delivered to the IHS National Pharmacy and Therapeutics Committee (NPTC) on February 4, 2014. Based on the findings, the NPTC implemented an agency-wide medication utilization evaluation (MUE) to evaluate the use (and potential overutilization) of PPIs in March 2014. The objectives of this article are to: (1) describe the MUE findings and (2) identify common, successful options of PPI step-down therapy for IHS clinicians.

Methods
Design. On March 11, 2014, an electronic mail (e-mail) message was distributed to 219 pharmacists identified as a “pharmacy director” by the IHS’s prime pharmaceutical vendor, the resource used to obtain e-mail addresses. The 219 pharmacists represented 210 IHS facilities in 31 states within the agency. The e-mail message requested voluntary participation and provided recipients with MUE documents and directions for secure data transfer. All data were transferred through the IHS Secure Data Transfer Service (SDTS). A second e-mail was distributed on September 30, 2014 to encourage remaining, nonresponsive facilities to submit MUE data. Data were collected from March 11 to October 31, 2014. All data were collected without linkage to individual patient identity to ensure anonymity. Only identification of IHS Area (multi-state regions) was left purposefully identifiable for internal agency benchmarking. All data were received through the IHS SDTS and analyzed in aggregate.

Sample. Inclusion criteria required facilities to self-identify a minimum of 30 patients actively receiving a PPI (any) from the participating IHS facility for more than 16 consecutive weeks. Given the voluntary nature of the request to participate in the MUE, it was felt that the 30-patient sampling size would provide ample volume of patient charts for review without creating a significant workload burden. Eligible outpatient prescriptions for PPIs included omeprazole, esomeprazole, lansoprazole, dexlansoprazole, pantoprazole and rabeprazole. Due to inter-facility differences in health record systems across the agency, strategies for identifying MUE patients were intentionally unspecified. A comprehensive MUE toolkit was also developed, containing details of the MUE (e.g., inclusion and MUE core criteria), the data collection instrument and the NPTC Formulary Brief on PPI overuse. A customized Microsoft Excel worksheet containing optional pre-specified categorical choices, served as the data collection instrument. The MUE core criteria were identified and selected by key NPTC personnel using supporting literature and presentation results for guidance. Five core criteria were identified and included the documentation of: (1) a FDA-approved indication for the PPI; (2) a FDA-approved dose for the PPI; (3) an indication for extended PPI therapy (i.e., pathological hypersecretory conditions or healing of erosive esophagitis); (4) selected ADEs (within the prior 12 months) associated with long-term PPI use; (5) concomitant use of clopidogrel and omeprazole or esomeprazole. Adverse drug events were selected from published reports on PPI overuse and included Clostridium difficile-associated diarrhea, community-acquired pneumonia, bone fracture of the hip, spine or wrist, B<sub>12</sub> deficiency, iron-deficiency anemia, and hypomagnesemia.

Measurements. Overutilization was defined as utilizing a higher daily PPI dose and/or longer duration of therapy than recommended in the prescribing information and use in patients with no documented indication. The MUE core criteria response set was dichotomous (i.e., Y/N) for three of five core criteria including documentation of correct PPI dose, indication of extended PPI therapy and concomitant use of clopidogrel and omeprazole or esomeprazole. The remaining two core criteria responses required manual participant selection from pre-specified categorical choices embedded within the data collection instrument (i.e., FDA-approved PPI indication, adverse drug events). Missing data were omitted from aggregate review.

Additional information requested included patient eligibility for PPI step-down therapy, whether PPI step-down therapy was performed when eligible, which step-down options were selected and if step-down was successful following an eight-week trial period. Step-down options were provided to participating facilities and were selected from published literature. A comprehensive list of step-down therapy options are outlined in Table 3. Step-down therapy was reported as successful when the PPI dose remained reduced, discontinued, transitioned to an intermittent basis, switched to (solely or in combination with) a H<sub>2</sub>-RA following the trial period or if “other step-down plan used” was documented.

Analytical plan. Descriptive statistics including frequencies and percentages were reported to describe
demographic characteristics of both MUE facilities and patients. Descriptive statistics including frequencies and percentages were also reported to describe MUE core criteria, PPI step-down therapy options and success rates. As this was a descriptive study without predefined hypothesis testing, inferential statistics were not reported.

Results

Of 210 facilities receiving an e-mail request to participate, 35 facilities consented, yielding an initial response rate of 16.7%. At the conclusion of the data collection period however, data were received from only 26 of 35 facilities, representing participation from 12.4% of all facilities. Ten of 12 (83%) IHS Areas were represented by at least 1 facility from each area participating in the MUE. The Great Plains and Oklahoma City Areas each had five facilities participate, representing the highest individual Area response rate. Federal sites composed 73.1% (19/26) of participating MUE facilities. A total of 961 MUE patients were included although one facility provided only partially completed data. Completed categorical portions (i.e., PPI dosing frequency, duration of use, clopidogrel/omeprazole co-administration) of the incomplete facility data were included in the analysis.

Table 1. Participating facility and patient characteristics

<table>
<thead>
<tr>
<th>MUE Demographic</th>
<th>Result (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHS facility designation</td>
<td>Federal (73.1)(^a)</td>
</tr>
<tr>
<td>Most common IHS Area represented</td>
<td>Aberdeen (19.2)(^a)</td>
</tr>
<tr>
<td></td>
<td>Oklahoma (19.2)(^a)</td>
</tr>
<tr>
<td>Number of female patients</td>
<td>574 (61.7)</td>
</tr>
<tr>
<td>Mean age of patients</td>
<td>58.5 years</td>
</tr>
<tr>
<td>Most common PPI reported</td>
<td>Omeprazole (88.1)</td>
</tr>
<tr>
<td>Most common indication for PPI use</td>
<td>GERD (72.6)</td>
</tr>
<tr>
<td>Mean omeprazole daily dose (with GERD indication)</td>
<td>27.9 milligrams</td>
</tr>
<tr>
<td>Most commonly reported PPI dosing frequency</td>
<td>Once-daily (72.9)(^b)</td>
</tr>
<tr>
<td>Mean duration of PPI use</td>
<td>45.2 months(^b)</td>
</tr>
</tbody>
</table>

Denominator = 931 unless otherwise noted

\(^a\) Denominator = 26
\(^b\) Denominator = 961

Facility and patient demographic data are described in Table 1. Females represented 61.7% of all study patients and the mean age was 58.5 years (range; 12-92 years) for all patients. The most prevalent PPI used was omeprazole (88.1%), followed by pantoprazole (9.5%) and lansoprazole (1.6%). Gastroesophageal reflux disease was the most

Table 2. MUE criterion results

<table>
<thead>
<tr>
<th>MUE Criteria Results</th>
<th>No. (%)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Criterion 1</td>
<td>Documentation of FDA-approved PPI indication</td>
<td>851 (91.4)</td>
</tr>
<tr>
<td>Criterion 2</td>
<td>Documentation of correct PPI dose</td>
<td>539 (57.9)</td>
</tr>
<tr>
<td>Criterion 3</td>
<td>Documentation of indication for extended PPI therapy</td>
<td>38 (4.1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diagnoses of pathological hypersecretory conditions and healing of erosive esophagitis</td>
</tr>
<tr>
<td>Criterion 4</td>
<td>Documentation of ADEs associated with long-term PPI use</td>
<td>219 (23.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;1 ADEs</td>
</tr>
<tr>
<td>Criterion 5</td>
<td>Documentation of concomitant clopidogrel and omeprazole or esomeprazole use</td>
<td>50 (5.2)(^a)</td>
</tr>
</tbody>
</table>

Denominator for calculations = 931 unless other noted

\(^a\) Denominator for calculation = 961
common indication (72.6%) while once-daily PPI administration was the most commonly reported dosing frequency (72.9%). The mean reported duration of PPI use was 45.2 months.

Of 931 patients included in the analysis, 91.4% (n=851) had a FDA-approved indication for PPI use documented in the health record. Those reported to be taking a FDA-approved dose totaled 57.9% (n=539) of the study sample. Only 4.1% (n=38) of the sample had a documented indication for extended PPI therapy (i.e., pathological hypersecretory conditions or healing of erosive esophagitis). Two hundred and nineteen patients had at least one ADE identified in their health record over the previous 12 months, representing 23.5% of MUE sample. Lastly, 961 patients were included in the analysis of concomitant administration of clopidogrel and omeprazole or esomeprazole. Of those, 5.2% (n=50) were reported to have received the interacting therapies.

Table 3. PPI step-down therapy options and corresponding frequencies of use

<table>
<thead>
<tr>
<th>Step-down approaches</th>
<th>No. (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinue the PPI and start a histamine$_2$ receptor antagonist (H$_2$RA)</td>
<td>78 (36.1)</td>
</tr>
<tr>
<td>Discontinue the PPI; no further therapy given</td>
<td>51 (23.6)</td>
</tr>
<tr>
<td>Decrease the PPI dose to a minimal, continuous treatment dose</td>
<td>44 (20.4)</td>
</tr>
<tr>
<td>Decrease the PPI dose to an intermittent or “on-demand” (PRN) treatment schedule</td>
<td>22 (10.2)</td>
</tr>
<tr>
<td>Decrease the PPI dose and start H$_2$RA combination treatment</td>
<td>11 (5.1)</td>
</tr>
<tr>
<td>“Other stepdown plan used”</td>
<td>10 (4.6)</td>
</tr>
</tbody>
</table>

*Denominator for calculations = 216

Step-down therapy options and corresponding frequencies of use are described in Table 3. Thirty-two percent of all patients (n=288) were documented to be eligible for PPI step-down. The most common approach to PPI step-down therapy was to discontinue the PPI and substitute with a H$_2$RA and was used in 36.1% of the patients. PPI step-down therapy was successful in 67.1% of patients who were initiated on it. Individual rates of success for each step-down therapy strategy are listed in Table 4. In patients reported to have successful step-down therapy, discontinuing the PPI and alternating to a H$_2$RA had the highest rate of success (38.3%). Other successful approaches commonly reported included reducing the PPI dose (26.2%) or discontinuing the PPI with no further acid-suppressive therapy (21.3%).

Table 4. PPI step-down therapy options and corresponding frequencies of success

<table>
<thead>
<tr>
<th>Step-down method</th>
<th>No. (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinue the PPI and start a histamine$_2$ receptor antagonist (H$_2$RA)</td>
<td>54 (38.3)</td>
</tr>
<tr>
<td>Decrease the PPI dose to a minimal, continuous treatment dose</td>
<td>37 (26.2)</td>
</tr>
<tr>
<td>Discontinue the PPI; no further therapy given</td>
<td>30 (21.3)</td>
</tr>
<tr>
<td>Decrease the PPI dose and start H$_2$RA combination treatment</td>
<td>10 (7.1)</td>
</tr>
<tr>
<td>“Other stepdown plan used”</td>
<td>10 (7.1)</td>
</tr>
</tbody>
</table>

*Denominator for calculations = 141

Discussion
Analyses from the MUE provide interesting and useful clinical information regarding the current use of PPI therapy in the IHS. Internal data derived from this MUE are useful not only in addressing current PPI utilization within the agency but also in guiding efforts to improve provider education and prescribing trends. It is intended that the findings from this study be considered within the current provision of IHS patient care to further optimize both patient and health systems outcomes.

Although a large majority of patients were prescribed a PPI for an approved indication (91.4%), only slightly more than half were reported to receive the correct dose (57.9%). Excessive PPI dosing could potentially amplify significant ADEs while PPI underdosing contributes to wasteful and unnecessary medication expenditures. One possible explanation for the reportedly disproportionate number of patients receiving an incorrect PPI dose may be due to appropriate dose titration. The 2013 American College of Gastroenterology guidelines for the diagnosis and management of GERD recommend patients with a partial...
response to PPI therapy either increase their dose to twice daily therapy or switch to a different PPI. Interestingly, 39.1% of GERD patients treated with omeprazole (the most common PPI) received a daily dose greater than 20 milligrams. Given the FDA-approved omeprazole initial dose for symptomatic GERD is 20 milligrams daily, this could indicate prescriber- or self-imposed dosing titration following an initial lack of full response.

Although not a pre-defined MUE criterion, participating facilities were asked additionally to report on patient eligibility for PPI step-down therapy options selected and success. In eligible patients, discontinuing the PPI and alternating to a H2RA was the most commonly approach to step-down therapy (36.1%). This method was also reported as the most successful (38.3%). Interestingly, nearly one-half (45.5%) of all patients were reported to have successful step-down therapy when the PPI was either decreased to a minimal, continuous dose (e.g., dose reduced by 50%) or discontinued altogether with no further therapy provided. Given their simplicity, the latter two approaches may offer the most convenience for busy IHS clinicians and ultimately result in the broadest success to PPI step-down therapy.

Judicious medication management requires a comprehensive healthcare team approach. By virtue of training and direct access to both patients and medication data, pharmacists are uniquely positioned to address critical medication management gaps and improve therapeutic outcomes. Numerous publications exist documenting the roles, efforts and successes of dedicated pharmacist integration with PPI therapy management. Given the opportunities inherent in the IHS’s self-contained healthcare delivery model, incorporating pharmacists with prescriptive authority or clinical decision support associated with PPI therapies should enhance patient and health systems outcomes.

Major limitations of this study involve a vague articulation

### Table 5. Comparison of NDW and MUE proton pump inhibitor data

<table>
<thead>
<tr>
<th>Measure</th>
<th>MUE result</th>
<th>Numerator/Denominator</th>
<th>NDW result</th>
<th>Numerator/Denominator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female gender</td>
<td>61.7%</td>
<td>574/931</td>
<td>61.7%</td>
<td>99,312/161,062</td>
</tr>
<tr>
<td>Patient age</td>
<td>58.5 years</td>
<td></td>
<td>47% of all patients aged 45-65</td>
<td>496/160,839</td>
</tr>
<tr>
<td>C. difficile-associated diarrhea</td>
<td>&lt;0.01</td>
<td>3/931</td>
<td>0.31%</td>
<td>496/160,839</td>
</tr>
<tr>
<td>Community-acquired pneumonia</td>
<td>4.6%</td>
<td>43/931</td>
<td>4.95%</td>
<td>7,962/160,839</td>
</tr>
<tr>
<td>Bone fractures (hip, wrist, spine)</td>
<td>1.7%</td>
<td>16/931</td>
<td>1.7%</td>
<td>2,728/160,839</td>
</tr>
<tr>
<td>Clopidogrel and PPI (any) concomitant use</td>
<td>5.2%</td>
<td>50/961</td>
<td>2.2%</td>
<td>3,477/160,839</td>
</tr>
</tbody>
</table>

For quality assurance, the MUE results were compared to data from the agency’s internal National Data Warehouse (NDW), an enterprise-wide data warehouse environment for the IHS’s national data repository. The NDW data were initially presented at the February 2014 NTPC meeting however these data were limited to patient demographics (i.e., gender and age), long-term PPI adverse events (i.e., C. difficile-associated diarrhea, community-acquired pneumonia, bone fractures) and clopidogrel and omeprazole or esomeprazole co-administration. When compared, NDW data closely matched the IHS MUE findings with the exception of omeprazole/esomeprazole and clopidogrel concomitant administration (2.2% and 5.2%, respectively). Similarities between the NDW and MUE data, described in Table 5, provide a degree of confidence in the integrity of the MUE results. Furthermore, MUE findings were also paralleled with published results from the VA, a federal agency with a similar healthcare system, on PPI use within their agency7. Comparison of VA study results and the IHS MUE data showed similar demographic data including indication and most common PPI but noted differences (increases) in patients with no documented PPI indication (20.1% and 8.0%, respectively) and patients co-administered PPIs (any) and clopidogrel (33.0% and 6.6%, respectively). The contrasting results may be explained by differences in patient populations, as evidenced by the (mean) age disparity between studies (65.0 years and 58.5 years).

### Conclusion

The overall benefits of PPI therapy and improvement in quality of life greatly outweigh potential risks in most patients. However, patients exposed to PPI therapy without a clinical indication or those receiving a higher dose or longer duration of therapy than needed, are exposed to
unnecessary risks of therapy. Addressing inappropriate use of PPIs not only mitigates potential ADE risk (and associated healthcare utilization costs) but also reduces unnecessary medication expenditures. It is important for clinicians to reassess their patient’s need for continual PPI therapy, weighing the benefits and potential ADEs of therapy at each clinical decision point. Clinical oversight can be accomplished through various means including the integration of healthcare partnerships (e.g., pharmacists) with focus on PPI surveillance or incorporation of a PPI overuse MUE to a facility’s current quality assessment/performance improvement program.

Impact of the research findings. Despite the majority of MUE patients (91.4%) receiving a PPI for an approved indication, only slightly more than half (57.9%) of patients were reported to receive the correct PPI dose.

In patients who were eligible for and initiated on PPI step-down therapy, 67.1% were reported to be successful. Nearly half (45.5%) of all patients were reported as successful when the PPI was either simply decreased to a minimal, continuous dose or discontinued altogether with no further acid-suppressive therapy provided.

Over eighty percent of patients (83.8%) were successful in stepping-down their PPI therapy by either discontinuing their PPI (no further therapy), reducing their PPI dose, or stepping-down their PPI therapy by either discontinuing or alternating to a H2RA.

Acknowledgement. The authors would like to express their appreciation to Dr. Michael Miller, RPh, DrPH, FAPhA for his editorial input during the preparation of this manuscript.

References
17. Plavix (clopidogrel) [prescribing information]. Bridgewater, NJ: Bristol-Myers Squibb; December 2013.


Background:
The IHS National Pharmacy and Therapeutics Committee (NPTC) reviewed cirrhosis and common complications including ascites, hepatic encephalopathy, variceal hemorrhage, spontaneous bacterial peritonitis and hepatorenal syndrome at the February 2015 meeting. Cirrhosis is the eighth leading cause of death in the United States (US) and is a disease that has tremendous impact on the American Indian/Alaska Native (AI/AN) population. Data from 2006 to 2008 showed AI/AN die at a 368% higher rate than other Americans from chronic liver disease and cirrhosis. The mortality disparity rate during that time was 4.7 times higher for AI/AN than for other US ethnicities/races.

Discussion:
MEDICATIONS AND CHRONIC LIVER DISEASE:
Many medications require dosage adjustments in patients with liver disease. Patients with cirrhosis need to be educated on the use of OTC analgesics. Acetaminophen (APAP) and nonsteroidal anti-inflammatory drugs (NSAIDs) can lead to decompensation in patients with compensated cirrhosis or to further decompensation in the already decompensated patient. APAP is an intrinsic hepatotoxin and should be used at therapeutic doses for limited time in patients with cirrhosis. However, a maximum of 2 grams per day is recommended, especially in those with alcoholic cirrhosis. NSAIDs should be avoided in patients with cirrhosis. NSAIDs blunt the response to diuretics in patients with cirrhosis and ascites, as well as, promote renal vasoconstriction leading to acute kidney injury and decreased GFR.

GASTROESOPHAGEAL VARICES:
Variceal hemorrhage is the most common lethal complication of cirrhosis. Varices occur in ~ 50% of patients with cirrhosis. Variceal bleeding, which has a mortality rate of 20% at 6 weeks, ceases spontaneously in up to 40%. If left untreated, late rebleeding occurs in 60% of patients in 1-2 years with a mortality rate of 33%.

Treatment options for primary prophylaxis include nonselective beta blockers (NSBB) or endoscopic variceal ligation (EVL). NSBBs include propranolol and nadolol. Although carvedilol has shown promise in one study, further research is needed before use as primary prophylaxis for varices can be recommended. NSBBs are recommended in both low and high risk patients. EVL is a procedure that can be done at the same time as an EGD. There are few contraindications to performing EVL and a lower incidence of side effects as compared to NSBB use. A 2012 Cochrane review of banding ligation versus beta blockers for primary prevention showed that both NSBB and EVL may be considered for primary prophylaxis in adults with large esophageal varices with high risk for rebleed. NSBB and EVL appear equivalent in prevention with rebleeding rates of 32-33%. The combination of NSBB and EVL had rebleed rates of 14-23% in 2 studies.

ASCITES:
Ascites is both the most common complication of cirrhosis and the most common complication leading to hospitalization. During 10 years of observation, 50% of patients with compensated cirrhosis will develop cirrhosis. Data from 2006 shows those with ascites have a 56% survival rate at 5 years, which is an increase from previous studies.

Treatment of ascites is determined by the cause of fluid retention. First line treatment for ascites includes the following: alcohol cessation if using, sodium restricted diet (2000 mg/day) and diet education, dual diuretics, discontinue NSAIDs if using. Second line treatment includes discontinuing beta blockers, ACE inhibitors, ARBs. Midodrine may be considered if the patient is profoundly hypotensive. Serial therapeutic paracentesis and transjugular intrahepatic portosystemic stent-shunt (TIPS) are also considered second line. For patients who are not candidates for paracentesis, TIPS, or liver transplantation, peritoneovenous shunt is considered third line treatment. Dual diuretic dosing starts with 100mg spironolactone and 40mg furosemide, titrating up every 3 to 5 days maintaining a 100:40 ratio to maximum doses of 400mg/day and 160mg/day respectively. In patients with edema, the goal maximum weight loss is 1 kg/day and in those without edema, 0.5kg/day. The ultimate goal in patients with ascites is to minimize or discontinue the diuretics. Paracentesis is reserved for those patients who do not respond to diuretics and sodium restriction.

SPONTANEOUS BACTERIAL PERITONITIS (SBP):
SBP is an ascitic fluid infection without an evident intra-abdominal surgically treatable source. The mortality rate of greater than 90% has been reduced to about 20% with early diagnosis and treatment. Diagnosis is based on diagnostic paracentesis with ascitic fluid neutrophils > 250/mm³. Ascitic fluid culture is positive in about 40% of cases. The most common organism in SBP is E. coli, 30% of which are resistant to trimethoprim/sulfamethoxazole and 30% resistant to quinolones. Of E. coli resistant to quinolones, 70% of those are also resistant to trimethoprim/sulfamethoxazole. Common gram positive cocci include streptococcus and enterococci. Culture negative SBP, in which the culture is negative but the neutrophils are greater than 250/mm³, is treated as though it is culture positive.

Empirical antibiotic treatment should start immediately after diagnosis is made. The European Association for the Study of the Liver (EASL) guidelines recommend third generation cephalosporins as first line. Quinolones are an acceptable alternative provided the local susceptibility patterns are reasonable. Antibiotics may be switched from IV to oral after 48 hours if the patient is showing clinical improvement. After the neutrophil count drops below 250, typically within 5 to 10 days, the antibiotics can be discontinued.

Prophylaxis should be restricted to those at highest risk for SBP. Ceftriaxone is the antibiotic of choice for GI hemorrhage while oral norfloxacin is recommended for those with low protein count or prior history of SBP. A Cochrane review from 2009 included 13 studies that looked at antibiotics used for SBP and concluded that the current evidence does not demonstrate superiority of 3rd generation cephalosporins, but rather equal efficacy. Further research is needed to determine the efficacy of oral versus intravenous antibiotics as well as to determine length of therapy and efficacy of lower doses versus higher doses of cephalosporins.

**HEPATOrenal SYNDrome (HRS):**
Renal failure in cirrhosis may occur spontaneously or is triggered by events seen in advanced cirrhosis. Prognosis for those with HRS is poor with a survival rate of 50% at 1 month and 20% at 6 months. Liver transplantation provides the best outcome.

HRS treatment requires an inpatient setting for severe acute renal failure. Complications need to be treated early, i.e., screen for sepsis or continue prophylactic antibiotics. Loop diuretics likely will be ineffective, but may be used to maintain urine output and treat central volume overload. Potassium sparing diuretics (spironolactone) are contraindicated as they are high risk for causing hyperkalemia. There is no data on whether or not to continue beta blockers for variceal bleed prophylaxis in these patients. Ascites in patients with HRS should be treated with large volume paracentesis with IV albumin (8g/l of fluid removed). Oral midodrine plus octreotide and albumin has also shown some benefit. In those patients awaiting transplant or with acute, potentially reversible conditions, renal replacement therapy may be recommended.

HRS may be prevented in some patients. EASL guidelines support the use of IV albumin since this has been shown to decrease the incidence of HRS and improve survival. Additionally, norfloxacin 400mg orally daily is suggested to prevent HRS in advanced cirrhosis although further studies are needed.

**HEPATIC ENCEPHALOPATHY (HE):**
Hepatic encephalopathy is an event that defines decompensated cirrhosis. Within 5 years of cirrhosis diagnosis, the risk of first occurrence of HE is 5-25%. Minimal or covert HE occurs in 20-80% of those with cirrhosis. Forty percent of patients will have recurrence of overt HE within 1 year.

Clinical diagnosis of HE is based on two concurrent types of symptoms, impaired mental status and impaired neuromotor function. Because the mental and motor signs do not progress in parallel, it is difficult to stage. HE is mostly a diagnosis of exclusion and should be treated as a continuum. It is classified according to underlying disease, severity of manifestations, time course, and existence of precipitating factors. Only overt hepatic encephalopathy (OHE) is routinely treated.

Treatment should be initiated for patient with altered consciousness. Current drug options for treating HE are nonabsorbable disaccharides (lactulose) and rifaximin. Lactulose is widely recommended for maintaining remission. Rifaximin in addition to lactulose is the best documented agent to maintain remission. Once precipitating factors are removed and liver function and nutritional status have improved, prophylaxis may be discontinued. Lactulose dosing is started with 30ml every 1-2 hours until bowel movement then titrated to achieve 2-3 soft stools per day. No dosage adjustments are required for geriatric patients or renal or hepatic impairment. Rifaximin is dosed at 550mg orally twice a day. It has not been studied in renal impairment and should be used with caution in those with severe hepatic impairment. Major drug interactions include p-glycoprotein/ABCB1 inhibitors, cyclosporine, and warfarin. It may cause C. difficile associated diarrhea.
A Cochrane review of 34 randomized trials in 2004 reviewed the use of nonabsorbable disaccharides (NDs) for HE. Treatment with lactulose or lactitol appeared to reduce risk of no improvement, lowered blood ammonia levels, and showed no statistically significant effect on mortality. Authors concluded there is insufficient evidence to confirm or exclude that nonabsorbable disaccharides have a significant beneficial effect on patients with HE. A meta-analysis published in 2008 compared rifaximin and NDs and found no significant difference in the primary outcome of improvement in HE between the two agents. The authors concluded that rifaximin is not superior to NDs for acute or chronic HE. An open-label trial of lactulose for secondary prevention of HE showed a statistically significant decrease in recurrent episodes of HE in the lactulose group (vs placebo), apparent after 4 months. Finally, rifaximin was studied in a randomized, double-blind, placebo controlled trial for secondary prophylaxis for 6 months. A significant reduction in risk of HE was observed with rifaximin with a NNT of 4 to prevent 1 episode of overt HE. A significant reduction in hospitalization for HE was also noted with a NNT of 9 to prevent 1 hospitalization. More than 90% of all patients in the trial took concomitant lactulose therapy and treatment effects were apparent within 28 days.

Findings
The National Core Formulary (NCF) currently lists propranolol, spironolactone and furosemide. Following the clinical presentation and agency-specific data analyses (procurement and National Data Warehouse), the NPTC added lactulose to the NCF.

If you have any questions regarding this document, please contact the NPTC at IHSNPTC1@ihs.gov. For more information about the NPTC, please visit the NPTC website.

References


Electronic Subscription Available

You can subscribe to The Provider electronically. Any reader can now request that he or she be notified by e-mail when the latest issue of The Provider is available on the Internet. To start your electronic subscription, go to The Provider website (http://www.ihs.gov/Provider). Click on the “subscribe” link; note that the e-mail address from which you are sending this is the e-mail address to which the electronic notifications will be sent. Do not type anything in the subject or message boxes; simply click on “send.” You will receive an e-mail from LISTSERV.IHS.GOV; open this message and follow the instruction to click on the link indicated. You will receive a second e-mail from LISTSERV.IHS.GOV confirming you are subscribed to The Provider listserv.

THE IHS PROVIDER is published monthly by the Indian Health Service Clinical Support Center (CSC). Telephone (602) 364-7777; fax: (602) 364-7788; email:the.provider@ihs.gov. Previous issues of THE PROVIDER (beginning with the 1997 Volume) can be found online at https://www.ihs.gov/provider.

Opinions expressed in articles are those of the authors and do not necessarily reflect those of the Indian Health Service or the Editors.

Circulation: THE PROVIDER (ISSN 1063-4398) is distributed on the CSC website to health care providers working for the IHS and tribal health programs, to medical schools throughout the country, and to health professionals working with or interested in American Indian and Alaska Native health care. If you would like to subscribe, go to https://www.ihs.gov/provider.

Publication of articles: Manuscripts, comments, and letters to the editor are welcome. Items submitted for publication should be no longer than 3000 words in length, typed, double-spaced, and conform to manuscript standards. PC-compatible word processor files are preferred. Manuscripts may be received via e-mail.

Authors should include references. All manuscripts are subject to editorial and peer review. Responsibility for obtaining permission from appropriate tribal authorities and Area Publications Committees to publish manuscripts rests with the author. For those that would like more information, please contact the CSC directly or visit our website at http://www.ihs.gov/csc.