Central Nervous System Infections: Diagnosis and Treatment
Consider a first-line HIV-1 treatment regimen with
THE STRENGTH OF TIVICAY® (dolutegravir)

Indications and Usage for TIVICAY

TIVICAY is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and children aged 12 years and older and weighing at least 40 kg.

The following should be considered prior to initiating treatment with TIVICAY:

- Poor virologic response was observed in subjects treated with TIVICAY 50 mg twice daily with an integrase strand transfer inhibitor (INSTI)-resistance Q148 substitution plus 2 or more additional INSTI-resistance substitutions, including L74I/M, E138A/D/K/T, G140A/S, Y143H/R, E157Q, G163E/K/Q/R/S, or G193E/R.

Proportion (%) of patients achieving HIV-1 RNA <50 copies/mL at Week 48

<table>
<thead>
<tr>
<th></th>
<th>SINGLE</th>
<th></th>
<th>SPRING-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIVICAY 50 mg once daily + ABC/3TC</td>
<td>88% (364/414)</td>
<td>VS</td>
<td>88% (356/403)</td>
</tr>
<tr>
<td>Atripla® (efavirenz/TDF/FTC) once daily</td>
<td>81% (338/419)</td>
<td>VS</td>
<td>86% (347/405)</td>
</tr>
</tbody>
</table>

Discontinuations due to adverse events were 2% for the regimen with TIVICAY vs 10% for Atripla at 48 weeks.

*SINGLE—A randomized, double-blind, active-control trial in treatment-naïve adult patients. At baseline, 32% of patients had HIV-1 RNA >100,000 copies/mL and 53% had CD4+ T-cell counts <350 cells/mm³.

*SPRING-2—A randomized, double-blind, active-control trial in treatment-naïve adult patients. At baseline, 28% of patients had HIV-1 RNA >100,000 copies/mL, 48% had CD4+ T-cell counts <350 cells/mm³, and 39% received ABC/3TC.

Important Safety Information for TIVICAY

Contraindication: Coadministration of TIVICAY with dofetilide (antiarrhythmic) is contraindicated due to the potential for increased dofetilide plasma concentrations and the risk for serious and/or life-threatening events.

Hypersensitivity Reactions

- Hypersensitivity reactions have been reported and were characterized by rash, constitutional findings, and sometimes organ dysfunction, including liver injury. The events were reported in <1% of subjects receiving TIVICAY in Phase 3 clinical trials.
- Discontinue TIVICAY and other suspect agents immediately if signs or symptoms of hypersensitivity reaction develop (including, but not limited to, severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters or peeling of the skin, oral blisters or lesions, conjunctivitis, facial edema, hepatitis, eosinophilia, angioedema, difficulty breathing).
- Monitor clinical status, including liver aminotransferases, and initiate appropriate therapy if hypersensitivity reaction is suspected. Delay in stopping treatment with TIVICAY or other suspect agents after the onset of hypersensitivity may result in a life-threatening reaction. TIVICAY should not be used in patients who have experienced a hypersensitivity reaction to TIVICAY.

Effects on Serum Liver Biochemistries in Patients with Hepatitis B or C Coinfection

- Patients with underlying hepatitis B or C may be at increased risk for worsening or development of transaminase elevations with use of TIVICAY. In some cases the elevations in transaminases were consistent with immune reconstitution syndrome or hepatitis B reactivation particularly in the setting where anti-hepatitis therapy was withdrawn.
- Appropriate laboratory testing prior to initiating therapy and monitoring for hepatotoxicity during therapy with TIVICAY are recommended in patients with underlying hepatic disease such as hepatitis B or C.

Fat Redistribution: Redistribution/accumulation of body fat has been observed in patients receiving antiretroviral therapy.

Immune Reconstitution Syndrome: During the initial phase of treatment, immune reconstitution syndrome can occur, which may necessitate further evaluation and treatment. Autoimmune disorders have been reported to occur in the setting of immune reconstitution; the time to onset is more variable and can occur many months after initiation of treatment.
ABC/3TC = abacavir sulfate/lamivudine; TDF/FTC = tenofovir/emtricitabine.

Poor virologic response was observed in subjects treated with TIVICAY 50 mg twice daily with an integrase strand transfer inhibitor (INSTI)-resistance Q148 substitution plus 2 or more additional INSTI-resistance substitutions, including L74I/M, E138A/D/K/T, G140A/S, Y143H/R, E157Q, G163E/K/Q/R/S, or G193E/R.

The following should be considered prior to initiating treatment with TIVICAY:

- Children aged 12 years and older and weighing at least 40 kg.
- TIVICAY is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and adolescents weighing ≥40 kg.
- TIVICAY is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and adolescents weighing ≥40 kg.

Indications and Usage for TIVICAY

**Hypersensitivity Reactions**

Hypersensitivity reactions have been reported and can occur in the setting of immune reconstitution; the time to onset is more variable and can occur many months after initiation of treatment.

**Important Safety Information for TIVICAY (cont’d)**

**Adverse Reactions:** The most commonly reported (≥2%) adverse reactions of moderate to severe intensity in treatment-naïve adult subjects in any one trial receiving TIVICAY in a combination regimen were insomnia (3%) and headache (2%).

**Drug Interactions:** Coadministration of TIVICAY with drugs that are strong inducers of UGT1A1 and/or CYP3A4 may result in reduced plasma concentrations of dolutegravir and require dose adjustments of TIVICAY.

- TIVICAY should be taken 2 hours before or 6 hours after taking cation-containing antacids or laxatives, sucralfate, oral supplements containing iron or calcium, or buffered medications. Alternatively, TIVICAY and supplements containing calcium or iron can be taken together with food.

- Consult the full Prescribing Information for TIVICAY for more information on potentially significant drug interactions, including clinical comments.

**Pregnancy:** Pregnancy Category B. TIVICAY should be used during pregnancy only if the potential benefit justifies the potential risk. An Antiretroviral Pregnancy Registry has been established.

**Breastfeeding:** Breastfeeding is NOT recommended due to the potential for HIV transmission and the potential for adverse reactions in nursing infants.

**Pediatric Patients:** Safety and efficacy of TIVICAY has not been established in children younger than 12 years old, or weighing <40 kg, or in INSTI-experienced pediatric patients with documented or clinically suspected INSTI resistance.


Please see brief summary of Prescribing Information for TIVICAY on following pages.

Visit www.tivicay.com for more information.
BRIEF SUMMARY

TIVICAY®
(dolutegravir)

The following is a brief summary only; see full prescribing information for complete product information.

CONTRAINDICATIONS

Co-administration of TIVICAY with dofetilide is contraindicated due to the potential for increased dofetilide plasma concentrations and the risk for serious and/or life-threatening events [see Drug Interactions].

WARNINGS AND PRECAUTIONS

Hypersensitivity Reactions: Hypersensitivity reactions have been reported and were characterized by rash, constitutional findings, and sometimes organ dysfunction, including liver injury. The events were reported in <1% of subjects receiving TIVICAY in Phase 3 clinical trials. Discontinue TIVICAY and other suspect agents immediately if signs or symptoms of hypersensitivity reactions develop (including, but not limited to, severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters or peeling of the skin, oral blisters or lesions, conjunctivitis, facial edema, hepatitis, eosinophilia, angioedema, difficulty breathing). Clinical status, including liver aminotransferases, should be monitored and appropriate therapy initiated. Delay in stopping treatment with TIVICAY or other suspect agents after the onset of hypersensitivity may result in a life-threatening reaction. TIVICAY should not be used in patients who have experienced a previous hypersensitivity reaction to TIVICAY.

Effects on Serum Liver Biochemistries in Patients With Hepatitis B or C Co-infection: Patients with underlying hepatitis B or C may be at increased risk for worsening or development of transaminase elevations with use of TIVICAY [see Adverse Reactions]. In some cases the elevations in transaminases were consistent with immune reconstitution syndrome or hepatitis B or C reactivation particularly in the setting where anti-hepatitis therapy was withdrawn. Appropriate laboratory testing prior to initiating therapy and monitoring for hepatotoxicity during therapy with TIVICAY are recommended in patients with underlying hepatic disease such as hepatitis B or C. Fat Redistribution: Redistribution/accumulation of body fat, including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and “cushingoïd appearance” have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established. Immune Reconstitution Syndrome: Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including TIVICAY. During the initial phase of combination antiretroviral treatment, patients whose immune systems respond may develop an inflammatory response to indolent or residual opportunistic infections (such as Mycobacterium avium infection, cytomegalovirus, Pneumocystis jiroveci pneumonia [PCP], or tuberculosis), which may necessitate further evaluation and treatment. Autoimmune disorders (such as Graves’ disease, polyarthalgia, and Guillain-Barré syndrome) have also been reported to occur in the setting of immune reconstitution; however, the time to onset is more variable and can occur many months after initiation of treatment.

ADVERSE REACTIONS

The following lists drug reactions (adverse events assessed as causally related by the investigator or ADRs) are discussed in other sections of the labeling: Hypersensitivity Reactions [see Warnings and Precautions], Effects on Serum Liver Biochemistries in Patients With Hepatitis B or C Co-infection [see Warnings and Precautions], Fat Redistribution [see Warnings and Precautions], Immune Reconstitution Syndrome [see Warnings and Precautions], and Infusion Reactions [see Adverse Reactions].

In a Phase 3 study, subjects with hepatitis B and/or C co-infected were randomized and received either TIVICAY 50 mg once daily or raltegravir 400 mg twice daily with investigator-selected background regimen consisting of up to 2 agents, including at least one fully active agent. At 24 weeks, the rates of adverse events leading to discontinuation were 2% in subjects receiving TIVICAY 50 mg once daily + background regimen and 4% in subjects receiving raltegravir 400 mg twice daily + background regimen. The only treatment-emergent ADR of moderate to severe intensity with ≥2% frequency in either treatment group was diarrhea, 1% (5/354) in subjects receiving TIVICAY 50 mg once daily + background regimen and 2% (6/361) in subjects receiving raltegravir 400 mg twice daily + background regimen.

Table 2. Treatment-Emergent Adverse Drug Reactions of at Least Moderate Intensity (Grades 2 to 4) and ≥2% Frequency in Treatment-Naïve Subjects in SPRING-2 and SINGLE Trials (Week 48 Analysis)

<table>
<thead>
<tr>
<th>ADR</th>
<th>SPRING-2</th>
<th>SINGLE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TIVICAY 50 mg Once Daily + 2 NRTIs (N = 403)</td>
<td>TIVICAY 50 mg + EPZICOM Once Daily (N = 414)</td>
</tr>
<tr>
<td></td>
<td>Raltegravir 400 mg Twice Daily + 2 NRTIs (N = 405)</td>
<td>ATRIPLA Once Daily (N = 419)</td>
</tr>
<tr>
<td>Psychiatric</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal dreams</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Nervous System</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Headache</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Skin and Subcutaneous</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tissue Rashes</td>
<td>0%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Ear and Labyrinth</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vertigo</td>
<td>0%</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

Laboratory Abnormalities: Laboratory abnormalities were generally similar compared with observations with the 50-mg once-daily dose in adult Phase 3 trials. Less Common Adverse Reactions Observed in Treatment-Naïve and Treatment-Experienced Trials. The following ADRs occurred in <2% of treatment-naive or treatment-experienced subjects receiving TIVICAY in a combination regimen in any one trial. These events have been included because of their seriousness and assessment of potential causal relationship: Gastrointestinal Disorders: Abdominal pain, abdominal discomfort, flatulence, upper abdominal pain, vomiting. General Disorders: Fatigue, Hepatobiliary Disorders: Hepatitis. Musculoskeletal Disorders: Arthritis. Renal and Urinary Disorders: Renal impairment. Skin and Subcutaneous Tissue Disorders: Pruritus.

Table 3. Selected Laboratory Abnormalities (Grades 2 to 4) in Treatment-Naïve Subjects in SPRING-2 and SINGLE Trials (Week 48 Analysis)

<table>
<thead>
<tr>
<th>ADR</th>
<th>SPRING-2</th>
<th>SINGLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 2 (≥5.0-5.9 x ULN)</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Grade 3 (≥6.0 x ULN)</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>ACR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 2 (≥5.0-5.9 x ULN)</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Grade 3 (≥6.0 x ULN)</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>Total Bilirubin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 2 (≥1.0-2.5 x ULN)</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Grade 3 (≥2.6-5.0 x ULN)</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

*Includes pooled terms: rash, rash generalized, rash macular, rash maculo-papular, rash pruritic, and drug eruption.

In addition, Grade 1 insomnia was reported by 1% and <1% of subjects receiving TIVICAY and raltegravir, respectively, in SPRING-2; whereas in SINGLE the rates were 7% and 3% for TIVICAY and ATRIPLA, respectively. These events were not treatment limiting. Treatment-Experienced, Integrate Strand Transfer Inhibitor-Naive Subjects: In an international, multicenter, double-blind trial (IN117627, SALINI), 719 HIV-1-infected, antiretroviral treatment-experienced adults were randomized and received either TIVICAY 50 mg once daily or raltegravir 400 mg twice daily with investigator-selected background regimen consisting of up to 2 agents, including at least one fully active agent. At 24 weeks, the rates of adverse events leading to discontinuation were 2% in subjects receiving TIVICAY 50 mg once daily + background regimen and 4% in subjects receiving raltegravir 400 mg twice daily + background regimen. Treatment-Experienced, Integrate Strand Transfer Inhibitor-Experienced Subjects: In a multicenter, open-label, single-arm trial (IN112574, VIKING-3), 183 HIV-1-infected, antiretroviral treatment-experienced adults with virological failure and current or historical evidence of raltegravir and/or elvitegravir resistance received TIVICAY 50 mg twice daily with the current failing background regimen for 7 days and with optimized background therapy from Day 8. The rate of adverse events leading to discontinuation was 3% of subjects at Week 24. Treatment-emergent ADRs in VIKING-3 were generally similar compared with observations with the 50-mg once-daily dose in adult Phase 3 trials. Less Common Adverse Reactions Observed in Treatment-Naïve and Treatment-Experienced Trials. The following ADRs occurred in <2% of treatment-naive or treatment-experienced subjects receiving TIVICAY in a combination regimen in any one trial. These events have been included because of their seriousness and assessment of potential causal relationship: Gastrointestinal Disorders: Abdominal pain, abdominal discomfort, flatulence, upper abdominal pain, vomiting. General Disorders: Fatigue, Hepatobiliary Disorders: Hepatitis. Musculoskeletal Disorders: Arthritis. Renal and Urinary Disorders: Renal impairment. Skin and Subcutaneous Tissue Disorders: Pruritus.

Laboratory Abnormalities: Laboratory abnormalities were generally similar compared with observations with the 50-mg once-daily dose in adult Phase 3 trials. Less Common Adverse Reactions Observed in Treatment-Naïve and Treatment-Experienced Trials. The following ADRs occurred in <2% of treatment-naive or treatment-experienced subjects receiving TIVICAY in a combination regimen in any one trial. These events have been included because of their seriousness and assessment of potential causal relationship: Gastrointestinal Disorders: Abdominal pain, abdominal discomfort, flatulence, upper abdominal pain, vomiting. General Disorders: Fatigue, Hepatobiliary Disorders: Hepatitis. Musculoskeletal Disorders: Arthritis. Renal and Urinary Disorders: Renal impairment. Skin and Subcutaneous Tissue Disorders: Pruritus.

Laboratory Abnormalities: Laboratory abnormalities were generally similar compared with observations with the 50-mg once-daily dose in adult Phase 3 trials. Less Common Adverse Reactions Observed in Treatment-Naïve and Treatment-Experienced Trials. The following ADRs occurred in <2% of treatment-naive or treatment-experienced subjects receiving TIVICAY in a combination regimen in any one trial. These events have been included because of their seriousness and assessment of potential causal relationship: Gastrointestinal Disorders: Abdominal pain, abdominal discomfort, flatulence, upper abdominal pain, vomiting. General Disorders: Fatigue, Hepatobiliary Disorders: Hepatitis. Musculoskeletal Disorders: Arthritis. Renal and Urinary Disorders: Renal impairment. Skin and Subcutaneous Tissue Disorders: Pruritus.
DRUG INTERACTIONS

Refer to Table 5 for established and other potentially significant drug-drug interactions.

Effect of Dolutegravir on the Pharmacokinetics of Other Agents: In vitro, dolutegravir inhibited the renal organic cation transporters, OCT2 (IC50 = 1.93 μM) and multidrug and toxin extension transporter (MATE) 1 (IC50 = 6.34 μM). In vivo, dolutegravir inhibits tubular secretion of creatinine by inhibiting OCT2 and potentially MATE1. Dolutegravir may increase the plasma concentrations of tenofovir and tenofovir disoproxil fumarate, substrates of OCT2 and MATE1, respectively. In vitro, dolutegravir did not inhibit OCT1 (>50 μM) and MATE1 (>5). The following cytochromes: CYP3A4 (IC50 ≤ 2.12 μM) and CYP3A (IC50 = 1.97 μM). However, in vivo, dolutegravir did not alter the plasma concentrations of tenofovir or tenofovir disoproxil fumarate. Coadministration of dolutegravir and other drugs that inhibit these enzymes may increase dolutegravir plasma concentration. Etravirine significantly reduced plasma concentrations of dolutegravir, but the effect of etravirine was mitigated by coadministration of lopinavir/ritonavir or darunavir/ritonavir, and is expected to be mitigated by atazanavir/ritonavir. (Table 5) [see Drug Interactions; Clinical Pharmacology (12.3) of full prescribing information]. Darunavir/ritonavir, lopinavir/ritonavir, ritonavir, tenofovir, boceprevir, telaprevir, primidone, rifabutin, and omeprazole had no clinically significant effect on the pharmacokinetics of dolutegravir. Established and Other Potentially Significant Drug Interactions: Table 5 provides clinical recommendations as a result of drug interactions with Tivicay. [See Dosage and Administration (2) and Clinical Pharmacology (12.3) of full prescribing information.]

Table 5. Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May Be Required Based on Drug Interaction Trials or Predicted Interactions [See Dosage and Administration (2) of full prescribing information]

<table>
<thead>
<tr>
<th>Concomitant Drug Class</th>
<th>Drug Name</th>
<th>Effect on Dolutegravir</th>
<th>and/or Concomitant Drug</th>
<th>Clinical Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-1 Antiviral Agents</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| non-nucleoside reverse transcriptase inhibitor | Etravirine | ↓Dolutegravir | Tivicay should not be used with etravirine without coadministration of darunavir/ritonavir or darunavir/ritonavir, and is expected to be mitigated by atazanavir/ritonavir. [Table 5] [see Drug Interactions; Clinical Pharmacology (12.3) of full prescribing information]. Darunavir/ritonavir, lopinavir/ritonavir, ritonavir, tenofovir, boceprevir, telaprevir, primidone, rifabutin, and omeprazole had no clinically significant effect on the pharmacokinetics of dolutegravir. Established and Other Potentially Significant Drug Interactions: Table 5 provides clinical recommendations as a result of drug interactions with Tivicay. [See Dosage and Administration (2) and Clinical Pharmacology (12.3) of full prescribing information.]
| non-nucleoside reverse transcriptase inhibitor | Etravirine | ↓Dolutegravir | A dose adjustment of Tivicay to 50 mg twice daily is recommended in treatment-naive or treatment-experienced, INSTI-naive patients. Alternative combinations that do not include metabolic inducers should be considered where possible for INSTI-experienced patients with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance.
| non-nucleoside reverse transcriptase inhibitor | Etravirine | ↓Dolutegravir | A dose adjustment of Tivicay to 50 mg twice daily is recommended in treatment-naive or treatment-experienced, INSTI-naive patients. Alternative combinations that do not include metabolic inducers should be considered where possible for INSTI-experienced patients with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance.
| non-nucleoside reverse transcriptase inhibitor | Etravirine | ↓Dolutegravir | A dose adjustment of Tivicay to 50 mg twice daily is recommended in treatment-naive or treatment-experienced, INSTI-naive patients. Alternative combinations that do not include metabolic inducers should be considered where possible for INSTI-experienced patients with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance.
| non-nucleoside reverse transcriptase inhibitor | Etravirine | ↓Dolutegravir | A dose adjustment of Tivicay to 50 mg twice daily is recommended in treatment-naive or treatment-experienced, INSTI-naive patients. Alternative combinations that do not include metabolic inducers should be considered where possible for INSTI-experienced patients with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance.

Table 4. Mean Change From Baseline in Fasted Lipid Values in Treatment-Naive Subjects in SPRING-2 and SINGLE Trials (Week 48 Analysis)

- Subjects on lipid-lowering agents at baseline were excluded from these analyses (19 subjects in each arm in SPRING-2, and in SINGLE: Tivicay n = 27 and Atripla n = 26).
- Forty-nine subjects initiated a lipid-lowering agent post-baseline; their last on-treatment values (prior to starting the agent) were used regardless if they discontinued the agent (SPRING-2: Tivicay n = 5, raltegravir n = 8; SINGLE: Tivicay n = 19 and Atripla: n = 17).

Treatment-Experienced, Integrase Strand Transfer Inhibitor-Naive Subjects: Laboratory abnormalities observed in SAILING were generally similar compared with observations seen in the treatment-naive (SPRING-2 and SINGLE) trials. Treatment-Experienced, Integrase Strand Transfer Inhibitor-Exposed Subjects: The most common treatment-emergent laboratory abnormalities (>5% for Grades 2 to 4 combined) were elevated ALT (8%), AST (6%), cholesterol (8%), hyperglycemia (12%), and lipase (8%). Two percent (3/183) of subjects had a Grade 3 to 4, treatment-emergent hematology laboratory abnormality, with neutropenia (1% [2/183]) being the most frequently reported. Hepatitis B and/or Hepatitis C Virus Co-infection: In Phase 3 trials, subjects with hepatitis B and/or C virus co-infection were permitted to enroll provided that baseline liver chemistry tests did not exceed 5 times the upper limit of normal. Overall, the safety profile in subjects with hepatitis B and/or C virus co-infection was similar to that observed in subjects without hepatitis B or C co-infection, although the rates of ALT and AST abnormalities were higher in the subgroup with hepatitis B and/or C virus co-infection for all treatment groups. Grades 2 to 4 ALT abnormalities in hepatitis B and/or C co-infected compared with HIV mono-infected subjects receiving Tivicay were observed in 16% vs. 2% with the 50-mg once-daily dose and 8% vs. 7% with the 50-mg twice-daily dose. Liver chemistry elevations consistent with immune reconstitution syndrome were observed in some subjects with hepatitis B and/or C at the start of therapy with Tivicay, particularly in the setting where anti-hepatitis therapy was withdrawn (see Warnings and Precautions). Changes in Serum Creatinine: Dolutegravir has been shown to increase serum creatinine due to inhibition of tubular secretion of creatinine without affecting renal glomerular function [see Clinical Pharmacology (12.2) of full prescribing information]. In several studies of up to 24 weeks of treatment and remained stable through 24 to 48 weeks. In treatment-naive subjects, a mean change from baseline of 0.11 mg/dL (range: -0.60 mg/dL to 0.62 mg/dL) was observed after 48 weeks of treatment. Creatinine increases were comparable by background NRTIs and were similar in treatment-experienced subjects. Clinical Trials Experience in Pediatric Subjects: IMPACT F1093 is an ongoing multi-center, open-label, non-comparative trial of approximately 160 HIV-1-infected pediatric subjects aged 6 weeks to less than 18 years, of which 23 treatment-experienced, INSTI-naive subjects aged 12 to less than 18 years were enrolled [see Use in Specific Populations (8.4). Clinical Studies (14.2) of full prescribing information]. The adverse reaction profile was similar to that for adults. Grade 2 ADRs reported in at least 1 subject were rash (n = 1), abdominal pain (n = 1), and diarrhea (n = 1). No Grade 3 or 4 ADRs were reported. The Grade 3 laboratory abnormalities were elevated total bilirubin and lipase reported in 1 subject each. No Grade 4 laboratory abnormalities were reported. The changes in mean serum creatinine were similar to those observed in adults.

Table 3 (continued). Selected Laboratory Abnormalities (Grades 2 to 4) in Treatment-Naive Subjects in SPRING-2 and SINGLE Trials (Week 48 Analysis)

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Preferred Term</th>
<th>SPRING</th>
<th>SINGLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine kinase</td>
<td>Grade 2 (&lt;0.9-3.9 x ULN)</td>
<td>1%</td>
<td>3%</td>
</tr>
<tr>
<td></td>
<td>Grade 3 to 4 (≥10.0 x ULN)</td>
<td>5%</td>
<td>4%</td>
</tr>
<tr>
<td>Hydroxyproton</td>
<td>Grade 2 (1.26-250 mg/dL)</td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td></td>
<td>Grade 3 (&gt;251 mg/dL)</td>
<td>&lt;1%</td>
<td>1%</td>
</tr>
<tr>
<td>Lipase</td>
<td>Grade 2 (1.5-3.0 x ULN)</td>
<td>5%</td>
<td>6%</td>
</tr>
<tr>
<td></td>
<td>Grade 3 &gt;3.0 x ULN)</td>
<td>1%</td>
<td>3%</td>
</tr>
<tr>
<td>Total neutrophils</td>
<td>Grade 2 (&lt;2.05-0.99 x 10^9)</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td></td>
<td>Grade 3 to 4 (&lt;2.0 &lt;0.75 x 10^9)</td>
<td>2%</td>
<td>1%</td>
</tr>
</tbody>
</table>

ULN = Upper limit of normal.
Concomitant Drug Class | Drug Name | Effect on Dolutegravir and/or Concomitant Drug | Clinical Comment
--- | --- | --- | ---
Other Agents | Oxcarbazepine | +Dolutegravir | Co-administration with these metabolic inducers should be avoided because there is insufficient data to make dosing recommendations.
Phenobarbital | +Dolutegravir | | 
Phenytoin | +Dolutegravir | | 
St. John’s wort (Hypericum perforatum) | +Dolutegravir | | 
Medications containing polyvalent cations (e.g., Mg or Al) | +Dolutegravir | | 
Calcium or iron supplements, including multivitamins containing calcium or iron | +Dolutegravir | | 
Oxcarbazepine | +Dolutegravir | | 
Phenobarbital | +Dolutegravir | | 
Phenytoin | +Dolutegravir | | 
St. John’s wort (Hypericum perforatum) | +Dolutegravir | | 
Metformin | +Dolutegravir | | 
Rifampin | +Dolutegravir | | 

a See Clinical Pharmacology (12.3) Table 9 of full prescribing information for magnitude of interaction.
b The lower dolutegravir exposures observed in INSTI-experienced patients with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance [see Microbiology (12.4) of full prescribing information] upon coadministration with potent inducers may result in loss of therapeutic effect and development of resistance to TIVICAY or other coadministered antiretroviral agents.

USE IN SPECIFIC POPULATIONS
Pregnancy: Category B. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, and dolutegravir was shown to cross the placenta in animal studies, this drug should be used during pregnancy only if clearly needed. Antiretroviral Pregnancy Registry: To monitor maternal-fetal outcomes of pregnant women with HIV exposed to TIVICAY and other antiretroviral agents, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263.

Animal Data: TIVICAY showed no evidence of impaired fertility or harm to the fetus in studies performed in rats and rabbits. In pregnant rats, dolutegravir at up to 1,000 mg/kg daily, approximately 27 times the 50-mg twice-daily human clinical exposure based on AUC, from days 6 to 17 of gestation did not elicit maternal toxicity, developmental toxicity, or teratogenicity. In pregnant rabbits, dolutegravir at up to 1,000 mg/kg daily, approximately 0.4 times the 50-mg twice-daily human clinical exposure based on AUC, from days 6 to 18 of gestation did not elicit developmental toxicity or teratogenicity. In rabbits, maternal toxicity (decreased food consumption, scanto/feces/urine, suppressed body weight gain) was observed at 1,000 mg/kg. Nursing Mothers: The Centers for Disease Control and Prevention recommend that HIV-1-infected mothers in the United States not breastfeed their infants to avoid risking postnatal transmission of HIV-1 infection. Studies in lactating rats and their offspring indicate that dolutegravir was present in rat milk. It is not known whether dolutegravir is excreted in human milk. Because of both the potential for HIV transmission and the potential for adverse reactions in nursing infants, mothers should be instructed not to breastfeed if they are receiving TIVICAY. Pediatric Use: TIVICAY is not recommended in pediatric patients younger than 12 years or weighing less than 40 kg.

Safety and efficacy of TIVICAY have not been established in pediatric patients who are INSTI-experienced with documented or clinically suspected resistance to other INSTIs (raltegravir, elvitegravir). The safety, virologic, and immunologic responses in subjects who received TIVICAY were evaluated in 23 treatment-experienced, INSTI-naive, HIV-1–infected subjects aged 12 to less than 18 years in an open-label, multicenter, dose-finding clinical trial, IMPACT P1093 [see Adverse Reactions, and Clinical Pharmacology (12.3) and Clinical Studies (14.2) of full prescribing information]. Pharmacokinetic parameters, evaluated in 9 subjects weighing ≥40 kg receiving 50 mg daily and 1 subject (weighing 37 kg) receiving 25 mg once daily, were similar to adults receiving 50 mg once daily. See Dosage and Administration (2.2) of full prescribing information for dosing recommendations for pediatric patients aged 12 years and older and weighing at least 40 kg. Frequency, type, and severity of adverse drug reactions in pediatric subjects were comparable to those observed in adults [see Adverse Reactions]. Geriatric Use: Clinical trials of TIVICAY did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects. In general, caution should be exercised in the administration of TIVICAY in elderly patients reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy [see Clinical Pharmacology (12.3) of full prescribing information]. Hepatic Impairment: No clinically important pharmacokinetic differences between subjects with moderate hepatic impairment and matching healthy subjects were observed. No dosage adjustment is necessary for patients with mild to moderate hepatic impairment (Child-Pugh Score A or B). The effect of severe hepatic impairment (Child-Pugh Score C) on the pharmacokinetics of dolutegravir has not been studied. Therefore, TIVICAY is not recommended for use in patients with severe hepatic impairment [see Clinical Pharmacology (12.3) of full prescribing information]. Renal Impairment: Dolutegravir plasma concentrations were decreased in subjects with severe renal impairment compared with those in matched healthy controls. However, no dosage adjustment is necessary for treatment-naïve or treatment-experienced and INSTI-naive patients with mild, moderate, or severe renal impairment or for INSTI-experienced patients with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance [see Microbiology (12.4) of full prescribing information] with severe renal impairment, as the decrease in dolutegravir concentrations may result in loss of therapeutic effect and development of resistance to TIVICAY or other coadministered antiretroviral agents [see Clinical Pharmacology (12.3) of full prescribing information]. Dolutegravir has not been studied in patients on dialysis.

OVERDOSAGE
Limited experience with single higher doses (up to 250 mg in healthy subjects) revealed no specific symptoms or signs apart from those listed as adverse reactions. There is no known specific treatment for overdose with TIVICAY. If overdose occurs, the patient should be monitored and standard supportive treatment applied as required. As dolutegravir is highly bound to plasma proteins, it is unlikely that it will be significantly removed by dialysis.

NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis: In two-year carcinogenicity animal studies conducted with dolutegravir, mice received up to 500 mg/kg, and rats up to 50 mg/kg. No significant increases in the incidence of drug-related neoplasms were observed in either group at the highest doses tested. In mice, AUC exposures were approximately 14-fold higher than those in humans at the recommended dose of 50 mg twice daily. In rats, dolutegravir AUC exposures were 10-fold and 15-fold higher in males and females, respectively, than those in humans at the recommended dose of 50 mg twice daily. Mutagenesis: Dolutegravir was not genotoxic in the bacterial reverse mutation assay, mouse lymphoma assay, or in the in vivo rodent micronucleus assay. Impairment of Fertility: In a study conducted in rats, there were no effects on mating or fertility with dolutegravir up to 1,000 mg/kg/day. This dose is associated with an exposure that is approximately 24 times higher than the exposure in humans at the recommended dose of 50 mg twice daily.

PATIENT COUNSELING INFORMATION
Advise the patient to read the FDA-approved patient labeling (Patient Information). Manufactured for: by: GlaxoSmithKline Research Triangle Park, NC 27709 Research Triangle Park, NC 27709 TCV:2BRS Revised: May 2014 TIVICAY and EPZC059 are registered trademarks of VIIV Healthcare. The other brands listed are trademarks of their respective owners and are not trademarks of VIIV Healthcare. The makers of these brands are not affiliated with and do not endorse VIIV Healthcare or its products. ©2014 VIIV Healthcare group of companies. All rights reserved. Printed in USA. DGV213R0 June 2014
Central Nervous System Infections: Diagnosis and Treatment

STATEMENT OF EDITORIAL PURPOSE

The Hospital Physician Infectious Diseases Board Review Manual is a study guide for fellows and practicing physicians preparing for board examinations in infectious diseases. Each manual reviews a topic essential to current practice in the subspecialty of infectious diseases.

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Central Nervous System Infections: Diagnosis and Treatment

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Central Nervous System Infections: Diagnosis and Treatment

Alfredo J. Mena Lora, MD, and Jeremy D. Young, MD, MPH

INTRODUCTION

Infections involving the central nervous system (CNS) are an important cause of morbidity and mortality worldwide. The anatomy of the CNS is complex, and certain physiologic characteristics, such as the blood-brain barrier, play a vital role both in the pathophysiology and therapeutic interventions of these conditions. Many pathogens can infect the CNS, including bacteria, viruses, fungi, mycobacteria, and parasites. These pathogens can cause a variety of infectious syndromes, including meningitis, encephalitis, and pyogenic abscess formations, among many others. Many of these syndromes can be mimicked by noninfectious causes such as neoplasms and rheumatologic diseases, adding levels of complexity in the approach to these cases. However, the clinical presentation, physical examination, radiographic findings, and epidemiology can often help narrow the differential diagnosis. The rapid recognition and management of CNS infections is often critical to achieving favorable outcomes, particularly for pyogenic bacterial infections.

In 2009, more than 88,199 cases of meningococcal meningitis were reported in 14 African countries. With 5352 deaths reported, the 2009 epidemic season was one of the worst recorded.1 Meanwhile, the incidence of meningococcal disease in the United States has been in a steady 20-year decline, with less than 1000 cases reported each year.2 Meningococcal meningitis highlights facts that pertain to all CNS infections: the risk of a given pathogen is influenced by vaccination status, geographic region, epidemiologic exposures, co-morbidities, and the immune status of the host. It is imperative for clinicians to understand the key concepts involving CNS infections in order to promptly initiate appropriate empiric antimicrobial therapy.

CASE PRESENTATION

CASE PATIENT 1

A 64-year-old man with no previous medical history presents to the emergency department (ED) complaining of headache, which began acutely and is severe in intensity. The patient also reports subjective fevers, chills, and a stiff neck. On examination, he is febrile with a temperature of 101.4°F.
The physical exam also reveals photophobia and nuchal rigidity. The patient has no evidence of delirium or altered consciousness. No focal neurologic deficits are present.

- What is the appropriate initial approach to suspected meningitis?

**BACTERIAL MENINGITIS**

Acute meningitis is clinically defined as a syndrome characterized by the onset of meningeal symptoms over the course of hours and up to several days. It can be caused by a variety of viral, bacterial, and parasitic agents. Acute bacterial meningitis is a medical emergency requiring a prompt diagnosis and empiric treatment. In the pre-antibiotic era, nearly all cases of bacterial meningitis led to death. Poor outcomes are associated with greater burden of microorganisms in cerebrospinal fluid (CSF), and therefore the prompt administration of appropriate antimicrobial agents—with adequate dosing—is one of the cornerstones of management. The proper initial empiric regimens vary based on epidemiologic risk factors (Table 1), with β-lactams playing a key role in most combinations. It is common for clinicians to encounter patients who report a history of allergy to β-lactams, with some estimates suggesting an allergy prevalence of approximately 10% in the general population. Thus, clinicians must also know how to approach severe infections and life-threatening conditions with appropriate alternative therapies, when indicated.

The advent of effective antimicrobials and vaccines for certain pathogens has dramatically decreased the morbidity associated with, and the incidence of, bacterial meningitis. Potent antimicrobials introduced in the 1930s and 1940s drastically changed meningitis from an untreatable condition to one that is potentially curable. Despite the use of modern therapeutics, the case fatality rate for meningitis remains high, with some studies reporting rates as high as 25%. Effective vaccines against *Streptococcus pneumoniae* and *Haemophilus influenzae* type B dramatically decreased the incidence of this disease, particularly in the pediatric popula-

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**Table 1. Risk Factors, Pathogens, and Empiric Antibiotics for Bacterial Meningitis**

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Pathogens</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≤ 50</td>
<td><em>Streptococcus pneumoniae</em></td>
<td>Ceftriaxone 2 g IV every 12 hr Vancomycin 25–30mg/kg loading dose then 15–20 mg/kg every 12 hr</td>
</tr>
<tr>
<td></td>
<td><em>Neisseria meningitidis</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Haemophilus influenzae</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Streptococcus agalactiae</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &gt; 50</td>
<td><em>Streptococcus pneumoniae</em></td>
<td>Ampicillin 2 g IV every 4 hr</td>
</tr>
<tr>
<td></td>
<td><em>Listeria monocytogenes</em></td>
<td>Ceftriaxone 2 g IV every 12 hr Vancomycin load then 15–20 mg/kg every 12 hr</td>
</tr>
<tr>
<td></td>
<td><em>Haemophilus influenzae</em></td>
<td></td>
</tr>
<tr>
<td>Recent neurosurgery</td>
<td><em>Pseudomonas and other gram-negative bacilli</em></td>
<td>Cefepime 2 g IV every 8 hr Vancomycin load then 15–20 mg/kg every 12 hr</td>
</tr>
<tr>
<td></td>
<td><em>Staphylococcus aureus</em></td>
<td></td>
</tr>
<tr>
<td>Immunocompromised</td>
<td><em>Listeria monocytogenes</em></td>
<td>Ampicillin 2 g IV every 4 hr</td>
</tr>
<tr>
<td></td>
<td><em>Streptococcus pneumoniae</em></td>
<td>Ceftriaxone 2 g IV every 12 hr Vancomycin load then 20 mg/kg every 12 hr</td>
</tr>
<tr>
<td></td>
<td><em>Mycobacteria</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Fungal pathogens</em></td>
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</tr>
</tbody>
</table>

IV = intravenously.
Despite this decline, case fatality rates have remained relatively unchanged. After a dramatic decline in the proportion of cases caused by *H. influenzae* after the introduction of effective vaccination, the rank order of the remaining causative pathogens has remained relatively unchanged despite vaccination programs against *S. pneumoniae*.3,8

**Causative Pathogens**

Epidemiologic risk factors and common causative agents play an important role in decision-making when choosing empirical antimicrobials. The most common pathogens associated with community-acquired bacterial meningitis are *S. pneumoniae*, *Neisseria meningitidis*, *Streptococcus agalactiae*, and *H. influenzae* (Table 1).8,9 *S. pneumoniae* remains the most common pathogen in adults, while *S. agalactiae* is the most common etiology of bacterial meningitis in patients younger than 2 years.3,8 Nosocomial meningitis is typically associated with neurosurgical procedures, and pathogens can depend on the location and type of procedure as well as the timing of the infection after the inciting event. The most common pathogens associated with nosocomial meningitis include gram-negative bacilli, *Staphylococcus aureus*, coagulase-negative staphylococci, *Propionibacterium acnes*, and other skin commensals.10 Predicting causative agents in immunocompromised hosts can be a challenge, as these patients can present with uncommon presentations of common pathogens as well as with presentations of truly uncommon pathogens.

**Initial Evaluation**

The initial approach to patients with suspected bacterial meningitis includes an immediate diagnostic evaluation and emergent antimicrobial therapy along with adjunctive anti-inflammatory agents, when indicated. Blood cultures should be obtained and a lumbar puncture should be performed as soon as feasible.5 The classic triad of fever, nuchal rigidity, and altered mentation is present in about 44% of cases, but at least 2 of these symptoms, along with headache, are present in most cases. Thus, at the initial stages of evaluation the differential diagnosis remains wide. This wide diagnosis, combined with the potential for post-lumbar puncture herniation due to increased intracranial pressure, has prompted physicians to obtain CNS imaging prior to performing lumbar puncture.

**CASE 1 CONTINUED**

The clinical findings are concerning for acute bacterial meningitis. As you discuss the case with the ED physician, you recommend obtaining a lumbar puncture as the next diagnostic step. Your colleague requests your opinion regarding the need for computed tomography (CT) imaging prior to performing a lumbar puncture.

- **When should clinicians obtain imaging prior to performing a lumbar puncture?**

A prospective study with 301 adult cases of suspected meningitis identified clinical features that can be used to identify patients who are unlikely to have abnormal cranial imaging.11 Based on the results of this study, imaging should be performed before lumbar puncture in patients with new-onset seizures, immunocompromised status, altered mentation, or presence of signs or physical exam findings that are suspicious for space-occupying lesions, such as papilledema.5 Imaging remains a common diagnostic adjunct, as these indications for imaging are present in approximately 45% of patients with bacterial meningitis.11
CASE 1 CONTINUED

You discuss the next diagnostic approach with the emergency physician. The patient does not meet any of the indications for imaging, and thus performing a lumbar puncture and sending CSF for analysis is appropriate at this time. The emergency physician is now preparing to perform the lumbar puncture. As he obtains all necessary equipment and places orders for the appropriate tests, he requests further guidance in selection of the appropriate empiric antimicrobial regimen.

• What is the appropriate empiric management of suspected acute bacterial meningitis?

Management

The initial empiric antimicrobial regimen depends on the clinical characteristics and epidemiologic risk factors of any given case. For adults younger than 50 years of age, an intravenous third-generation cephalosporin combined with vancomycin are the empiric agents of choice. Patients older than 50 years of age are at risk for Listeria, and for this reason high-dose ampicillin should be added. This agent should also be included if other risk factors for Listeria are present, such as alcoholism or altered immune status. In the setting of recent neurosurgical procedures, use of a β-lactam with activity against Pseudomonas, such as cefepime or ceftazidime, is recommended along with vancomycin. Important factors in choosing empiric therapy include: consideration of the appropriate spectrum to cover the most likely pathogens; knowledge of institutional antibiograms and local susceptibility patterns; the use of bactericidal therapy; and administration of antibiotics that penetrate the blood-brain barrier. Always remember to use the appropriate dosing of antimicrobials when treating infections of the CNS (Table 1).

CASE 1 CONTINUED

After discussing the appropriate regimen, you are informed that the patient has a severe β-lactam allergy. The patient reports that the allergy was severe and required intubation at a previous admission. He wants to “stay far away from anything that has penicillin,” and is refusing desensitization for this reason.

• What are some appropriate empiric alternatives for patients with a severe β-lactam allergy?

A β-lactam allergy can limit the number of antimicrobial choices available for empiric treatment. Though a history of β-lactam allergy is commonly reported, approximately 90% of these patients are not truly allergic and could safely receive β-lactams. Reported allergies often lead to patients receiving unnecessarily broad-spectrum or less effective antibiotics as alternatives. Thus, it is important to obtain a thorough history to assess if indeed the reported allergy is a true β-lactam allergy.

Alternatives to β-lactams for coverage of the most common pathogens include moxifloxacin and chloramphenicol. Trimethoprim-sulfamethoxazole can be used for empiric Listeria coverage when indicated. It may be useful to consult an allergist, as desensitization may be optimal later during the treatment course in order to use β-lactams for pathogen-specific therapy.

• Should dexamethasone be added to empiric antimicrobials in the treatment of suspected meningitis in the developed world?

Inflammation from bacterial meningitis can lead to significant complications, such as hearing loss
and other neurologic sequelae. Many studies have evaluated the effects of adjunctive dexamethasone therapy in the treatment of bacterial meningitis, with randomized prospective trials demonstrating reduced mortality and morbidity in patients receiving dexamethasone.\textsuperscript{12,13} This benefit is mostly seen in patients with meningitis caused by \textit{S. pneumoniae}.\textsuperscript{5,9,12} Thus, expert consensus and guidelines from major societies recommend the use of corticosteroids, which are to be administered before or with the first dose of antimicrobials. Once the pathogen has been identified, dexamethasone is to be continued for 4 days for pneumococcal meningitis. Otherwise, this medication should be stopped.\textsuperscript{5}

**CASE 1 CONTINUED**

A lumbar puncture is performed and empiric agents started. Analysis of the CSF reveals 456 white blood cells (WBCs)/μL with 77% neutrophils. The CSF protein is elevated at 224 mg/dL and CSF glucose is 65 mg/dL. Serum glucose is within normal limits. Small gram-positive rods are found on Gram stain.

- **What is the likely pathogen and how should the regimen be modified for pathogen-directed therapy?**

The likely pathogen is \textit{Listeria monocytogenes}. It is the third most common cause of bacterial meningitis overall, with most patients being older than age 50 or otherwise immunocompromised.\textsuperscript{14} When \textit{Listeria} is the etiology, the empiric antimicrobial agent of choice is high-dose ampicillin, but synergistic gentamicin should be added when this pathogen has been identified. In the setting of β-lactam allergy, high-dose trimethoprim-sulfamethoxazole is the alternative agent of choice.\textsuperscript{15}

Once the diagnosis is obtained and pathogen-specific therapy has been initiated, antimicrobials should be continued along with supportive care. Repeating a lumbar puncture may be warranted when clinical improvement is delayed, but is not typically necessary. This is usually considered at 48 hours, with cultures expected to be negative within 24 hours of therapy.

**CASE 1 CONTINUED**

Vancomycin is discontinued. There is no role for corticosteroids for \textit{Listeria} meningitis, so this is discontinued as well. After discussing these changes with the primary team, you receive a call from the head of the ED nursing staff. She is inquiring about the indications for post-exposure prophylaxis of other patients in the ED and staff, as well as close contacts of the patient in the community.

- **What is the role of prophylaxis and isolation in cases of acute bacterial community-acquired meningitis?**

Antibiotic prophylaxis is only required for close contacts of patients with \textit{N. meningitidis} or occasionally \textit{H. influenzae} if there are unvaccinated children in the home. Close contacts are defined as individuals who frequently sleep and eat in the same dwelling with the patient. Health care workers who have contact with secretions, such as during intubation, should be treated as well.\textsuperscript{16} Post-exposure prophylaxis for meningitis is described in Table 2.\textsuperscript{17} The most common agents used for prophylaxis of those exposed to meningococcus include ciprofloxacin and rifampin.

**Outcomes**

Outcomes for bacterial meningitis can be poor, with case fatality rates as high as 25% despite
antibiotics. Many patients have long-term neurologic sequelae, such as hearing loss and focal neurologic deficits, even with the appropriate use of adjunctive corticosteroids.

**Case Learning Objectives**

In preparation for your boards, you must know well the empiric agents for meningitis. Knowing the second-line agents is important, as patients may have contraindications or allergies to first-line therapies. An important point to know for the boards is the use of trimethoprim-sulfamethoxazole for *L. monocytogenes* meningitis in persons with a β-lactam allergy. You should recognize the possible pathogen on Gram stain and be able to tailor therapy based on this information.

**CASE PATIENT 2**

**Initial Presentation and History**

A 37-year-old man with a history of latent tuberculosis (TB) is brought to the ED by his family members for evaluation of altered mental status. The patient was in his usual state of health until about 1 week prior to presentation. Family members noted decreased appetite and activity. He works at a supermarket, and has missed work for the past 2 days due to headache. On the morning of presentation, family members found the patient lying in bed, confused and unresponsive. He was breathing but not answering questions nor responding to his name. He has no known past medical history other than latent TB, diagnosed 6 months ago at a routine pre-employment health visit. He migrated from Mexico about 15 years prior. The patient was prescribed isoniazid by his primary care physician, but was unable to fill this prescription due to loss of insurance after he became unemployed shortly after his medical appointment. He did not seek medical attention after finding new employment.

**Evaluation and Management**

On initial evaluation in the ED, the patient is febrile to 100.8°F. Vital signs are otherwise unremarkable. He is not responsive to questions. The neurological exam is notable for drowsiness and inability to follow commands. Cranial nerve examination is notable for diplopia, consistent with a palsy of the sixth cranial nerve. He withdraws all extremities to painful stimuli. No other deficits are noted. A CT scan of the head is performed and reveals no abnormalities. Lumbar puncture is performed and CSF is reported to have 503 WBCs/µL with 48% neutrophils, 42% lymphocytes, 8% monocytes, and 1% eosinophils. The CSF glucose level is 31 mg/dL and serum glucose is 105 mg/dL.

Empiric ceftriaxone, vancomycin, and acyclovir are started to treat the most common bacterial and viral pathogens, and the patient is admitted for further management. Cultures from CSF and

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**Table 2. Post-Exposure Prophylaxis for Meningitis**

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Contact</th>
<th>Prophylaxis</th>
</tr>
</thead>
</table>
| *Neisseria meningitidis* | Intimate contacts at household or day care  
Health care workers with contact with secretions | One dose of ciprofloxacin 500 mg by mouth  
or  
4 doses of rifampin 600 mg by mouth every 12 hr |
| *Haemophilus influenzae* | Unvaccinated household contacts < 4 years old  
Unvaccinated day care contacts < 2 years old | Rifampin 20 mg/kg daily × 4 days                |
a broad viral panel, including herpes simplex virus (HSV) and varicella-zoster virus, are sent. Magnetic resonance imaging (MRI) of the brain is reported to show intense and dense enhancement in the subarachnoid space and basal structures concerning for basilar pachymeningitis, with small areas of infarction and evolving hydrocephalus (Figure 1). The infectious diseases service is consulted for further recommendations.

- **What pathogens should be suspected in this case and what changes to the empiric regimen are recommended?**

This patient has a basilar meningitis, is a migrant from an endemic region, and is known to have untreated latent TB. Though he was prescribed isoniazid for latent TB, he was unable to start therapy. His CSF has a lymphocytic-predominant pleocytosis and low glucose, and thus suspicion for TB meningitis should be high and empiric antitubercular therapy would be appropriate. The diagnosis of CNS TB can be difficult, and a significant delay in initiating therapy can be fatal. Thus, empiric treatment with antitubercular agents should be started immediately upon suspicion for TB.²⁸

**CNS TUBERCULOSIS**

**Clinical Manifestations**

It is estimated that TB affects approximately one third of the world population.¹⁹ Once a host is infected with TB, bacillemia occurs which may allow the pathogen to seed distant organs. CNS TB is rare, representing approximately 1% of all cases of active infection.²⁰ CNS manifestations include meningitis, tuberculomas, and spinal tuberculosis.²¹ The presentation can be similar to acute bacterial meningitis, but is often more subacute. Headache, fever, and nuchal rigidity can be present in up to 80% of cases. TB meningitis commonly involves basilar structures, and thus cranial nerve palsies can be present in up to 50% of cases (Table 3).²⁸ A basilar meningitis with vasculitis and infarction are highly suggestive radiographic findings, and should lead the clinician to suspect TB meningitis.

**CASE 2 CONTINUED**

Rifampin, isoniazid, pyrazinamide, and ethambutol are added empirically based on your recommendations. On the second day of hospitalization, no pathogens are found on Gram stain and cultures remain negative for bacterial and fungal pathogens. Other negative tests include serum cryptococcal antigen and HIV antibody test. Antibacterial agents are stopped, while antitubercular agents are continued. The primary team plans to perform a repeat lumber puncture and is requesting guidance on further laboratory testing of CSF.

**Diagnostic Approach**

CSF should be sent for acid-fast staining and cultures. The sensitivity of acid-fast bacilli (AFB)
in CSF can be as high as 80%, though this is dependent on the quantity of CSF fluid sent to the lab and the type of CNS TB present.\textsuperscript{20–22} AFB are less likely to be found in patients with tuberculomas, as compared to those with TB meningitis. Obtaining large volumes of CSF from lumbar punctures and repeated serial sampling of CSF may increase the diagnostic yield.\textsuperscript{20} Imaging may be helpful to characterize disease location and burden, but it may be difficult to differentiate these findings from other illnesses, such as cryptococcal meningitis.

• **What is the role for molecular diagnostics?**

Nucleic acid amplification testing (NAAT) may be useful to confirm TB, but the negative predictive value is not adequate to rule out this diagnosis, particularly if there is a high pre-test probability. The sensitivity of NAAT is variable, but is approximately 50%, with a specificity of 97%, giving molecular diagnostic testing an excellent positive predictive value. Despite these limitations, there is expert consensus that CSF should be sent for molecular analysis as well as cultures when there is a high suspicion of TB.\textsuperscript{20} Recent studies have shown that centrifuged CSF samples tested with Xpert MTB/RIF molecular testing can have a sensitivity as high as 80%.\textsuperscript{23} Molecular diagnostics for extrapulmonary TB may play a key role in the future, but more data is needed to further define the operating characteristics and standardize the use of such testing.

• **Should a CSF sample be sent for measurement of adenosine deaminase?**

Adenosine deaminase (ADA) has been used in the diagnosis of pleural effusions and pleural TB for decades. This test has been limited by its lack of specificity and sensitivity, which by some estimates is less than 45% in pleural disease.\textsuperscript{24} The utility of ADA in CSF for diagnosis of TB meningitis is minimal due to these same limitations. Multiple conditions can elevate ADA, including other infections and malignancies, giving this test a very poor specificity. Due to these limitations, measurement of ADA in CSF is not generally recommended in the evaluation of patients with possible CNS TB.\textsuperscript{20}

• **How is TB meningitis treated?**

**Treatment**

The initial therapy for TB meningitis follows the same principles as pulmonary TB. An initial empiric regimen of 4 drugs is used for the first 2 months of therapy, and 2 active drugs are continued thereafter. The optimal duration of therapy is unknown, but most experts recommend at least 9 to 12 months total (Table 4).\textsuperscript{20,25}

• **What is the role of dexamethasone as adjunctive therapy?**

Dexamethasone has been used as adjunctive therapy in the treatment of CNS TB for over 50 years.\textsuperscript{18} Throughout this time, evidence has ac-

<table>
<thead>
<tr>
<th>Table 3. Clinical Manifestations of CNS Tuberculosis</th>
</tr>
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<tbody>
<tr>
<td>Unrelenting headache</td>
</tr>
<tr>
<td>Cranial nerve palsies (CN VI most common)</td>
</tr>
<tr>
<td>Fever</td>
</tr>
<tr>
<td>Lethargy</td>
</tr>
<tr>
<td>Confusion</td>
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<tr>
<td>Seizures</td>
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<tr>
<td>Personality changes</td>
</tr>
<tr>
<td>Irritability</td>
</tr>
<tr>
<td>Nuchal rigidity</td>
</tr>
</tbody>
</table>


Cumulated to support its use. Though prospective, randomized trials are few, multiple studies have shown reduced morbidity and mortality with adjunctive corticosteroids for TB meningitis.\textsuperscript{18,20,25} The true mechanism of how dexamethasone reduces morbidity and mortality is unclear, but it is believed that the anti-inflammatory effects from this agent reduce inflammation and vasogenic cerebral edema, similar to its benefits for pneumococcal disease. Guidelines from major societies in the United States and the United Kingdom support the use of steroids in cases of TB meningitis.\textsuperscript{20,25}

**Outcomes**

Outcomes for CNS TB are poor overall, with some case series reporting case fatality rates of 25% to 50%.\textsuperscript{26,27} Damage to brain structures can be extensive, with vasculitis and subsequent infarction causing further areas of damage. The degree of alteration in consciousness, as measured in the Glasgow Coma Scale, is a strong predictor of poor outcomes.\textsuperscript{21,27} The case patient presented with profound confusion, and his alteration in consciousness worsened throughout his admission. He eventually progressed to a vegetative state and family members withdrew care.

**Case Learning Objectives**

The main learning objectives for this case include the prompt recognition of cases at risk for disseminated TB and CNS involvement, particularly those from endemic regions or with a history of untreated latent TB. Severe hypoglycemia should be recognized as a common and suggestive finding in CNS TB, and the utility of molecular diagnostics should be understood. The role of dexamethasone in the treatment of TB meningitis is a key topic as well.

**CASE PATIENT 3**

**Initial Presentation and History**

A 59-year-old man with a history of diabetes and renal transplantation presents to the ED with headache, fever, and neck pain. He reports being in his usual state of health until approximately 8 days ago. He then became ill, with the sudden onset of nausea, vomiting, and abdominal discomfort. His symptoms progressed, and he also developed headache and neck pain 48 hours ago. He reports a febrile episode at home overnight and presents for further evaluation. He underwent renal transplantation 3 years ago due to a history of poorly controlled diabetes and diabetic nephropathy. The patient migrated from Honduras 30 years ago and travels frequently to visit his family.

**Evaluation and Management**

On examination, vital signs are notable for a temperature of 100.8°F. The patient is drowsy but responding to questions appropriately and is alert to person, place, and time. The physical exam is notable for neck stiffness and mild, diffuse tender-
ness to palpation in the abdomen. The initial workup includes basic labs and blood cultures. A CT of the head is reported as normal. Labs are notable for a peripheral leukocytosis to 15,000 WBCs/μL that is neutrophil predominant and unchanged peripheral eosinophilia to 16%. Lumbar puncture is performed and CSF analysis shows a pleocytosis, with 355 WBCs/μL, 88% neutrophils, 6% lymphocytes, 4% monocytes, and 2% eosinophils.

Empiric antimicrobials are started for bacterial meningitis. On hospital day 2, blood cultures and Gram stain from CSF are growing gram-negative rods. *Escherichia coli* is eventually identified in the CSF, while blood cultures are positive for *Klebsiella pneumoniae*, *E. coli*, and *Proteus mirabilis*.

- What is the most likely etiology of *E. coli* meningitis and polymicrobial gram-negative bacteremia in this patient?

**STRONGYLOIDES INFECTIONS IN IMMUNCOMPROMISED HOSTS**

This immunocompromised host presented with meningitis and bacteremia caused by multiple species of gram-negative bacilli. Though he has lived in the United States, he was born in, and travels frequently to, an endemic region for *Strongyloides stercoralis*. His workup also demonstrated eosinophilia, supporting this presumptive diagnosis.

*Strongyloides stercoralis* is an intestinal nematode which can live its entire life cycle within the host, which can lead to persistent infection via this autoinfective cycle. It is prevalent in tropical and subtropical regions worldwide, with an estimated disease burden between 30 to 100 million. Immunocompromised hosts may develop a variety of manifestations and can develop the dreaded hyperinfection syndrome.

The life cycle of *Strongyloides* starts with transcutaneous penetration by the filariform larvae (Figure 2). This pathogen then migrates to the lung and subsequently ascends the tracheobronchial tree, is swallowed by the host, then enters the gastrointestinal tract. At this point, further reproduction occurs, with organisms penetrating the perianal skin or intestinal mucosa. The clinical spectrum of strongyloidiasis follows this cycle, and includes acute and chronic strongyloidiasis, disseminated strongyloidiasis, and the hyperinfection syndrome. Acute infection refers to the initial stages, where a local reaction at the site of dermal entry and tracheal irritation with the passage of the parasite from lung to the gastrointestinal tract can occur. The pathophysiology of chronic strongyloidiasis results from replication in the gastrointestinal tract, which can be asymptomatic or manifest with signs and symptoms such as bloating and diarrhea. Hyperinfection refers to an acceleration in the life cycle of *Strongyloides*, where penetration of the

![Figure 2](image-url)
nematode through the mucosa occurs at a much faster rate and with a larger pathogen load. This can subsequently cause enteric bacteria to migrate to the blood, causing bacteremia and metastatic infections, including to the CNS. *Strongyloides* hyperinfection syndrome also can cause protein-losing enteropathy and pneumonitis.\(^{30}\)

Immunocompromised hosts are at higher risk of developing the hyperinfection syndrome. This condition has been seen in patients on corticosteroids, azathioprine, cyclophosphamide, methotrexate, and even chemotherapeutic agents such as vinca alkaloids, Adriamycin, ifosfamide, and melphalan. Interestingly, patients receiving cyclosporine rarely develop hyperinfection. The use of cyclosporine in renal transplants became widespread after the 1990s, at which time case reports of hyperinfection in renal transplant recipients decreased.\(^{31}\) Experimental data shows that cyclosporine may have anthelmintic effects on *Strongyloides stercoralis*, which may provide an explanation for this observation.\(^{32}\) As immunosuppressants become more widely used in organ transplantation and in the treatment of rheumatologic diseases, clinicians must understand how to effectively diagnose and manage this disease, and must recognize which patients to screen prior to transplant and other immunocompromising states.

• **Who should be screened for *Strongyloides***?

Patients who should be tested for *Strongyloides* include: those born in or who travel to endemic regions, who have or are about to receive solid organ transplants, those treated with corticosteroids or immunosuppressants, or those with HTLV-1 infection or hematologic malignancies including leukemias and lymphomas.\(^{28,30,31}\) It may be prudent to test symptomatic or minimally symptomatic patients with persistent peripheral or unexplained eosinophilia with recent or remote travel histories to endemic areas as well.\(^{30}\) HTLV-1 infection highly predisposes individuals to strongyloidiasis, and recurrent or severe infection should prompt testing for this underlying viral infection.

**CASE 3 CONTINUED**

Antimicrobials are tailored based on cultures to cover all pathogens in blood and CSF. The patient is now afebrile and with significant clinical improvement. The presumptive diagnosis of *Strongyloides* hyperinfection syndrome is discussed with the primary team. They request guidance on further testing to potentially establish this as the definitive diagnosis.

• **What test would most likely establish the diagnosis?**

Obtaining a definitive diagnosis for *Strongyloides* infection can be difficult. In chronic strongyloidiasis, the sensitivity of stool studies can reach 50%. It is believed that sensitivity may be higher in those with hyperinfection. Serologic tests can be useful, particularly in patients who are critically ill for whom quick diagnostic methods would be most useful. Some studies have shown a sensitivity of up to 90% for serologic tests, though false-positives can occur if other parasitic infections are present.\(^{33,34}\) Certainly, the specificity of serologic testing is not ideal. Thus, obtaining combined stool and blood samples would be the best diagnostic approach, with blood enzyme-linked immunosorbent assay (ELISA) testing the most likely test to establish the diagnosis.

**CASE 3 CONTINUED**

Samples from stool and blood are sent. The patient has improved and the primary team is pre-
paring him for discharge, with a central catheter in place to continue his parenteral antimicrobials. The blood ELISA test for *Strongyloides* is reported positive. Stool testing remains negative. The primary team requests guidance on interpretation of these results and further therapeutic interventions.

- **What is the next therapeutic intervention in this patient?**

The stool test is not sufficiently sensitive to rule out infection and, given the high pre-test probability of strongyloidiasis, the positive ELISA test confirms the diagnosis. The drug of choice for treatment of *Strongyloides* infection is ivermectin. The recommended therapy is 200 µg/kg/day orally for 2 days, or giving each dose 2 weeks apart instead of on consecutive days. Albendazole can be used as an alternative agent as well. In cases of hyperinfection syndrome, treating the bacterial infections, such as bacteremia or meningitis, is key. Reduction of immunosuppression, as is feasible, along with anthelminthic therapy should be pursued.

### Outcomes and Conclusion

Mortality for hyperinfection syndrome remains high, given the wide range of bacterial infectious complications that arise from this syndrome. Strongyloidiasis is common worldwide, but remains an underestimated threat in many developed countries. With the widespread use of immunosuppressants and organ transplants, clinicians must be able to recognize those at risk and appropriately diagnose and treat *Strongyloides*.

### Case Learning Objectives

Learning objectives for this case are to identify polymicrobial bacteremia with enteric pathogens and metastatic complications such as meningitis as a possible sign of *Strongyloides* hyperinfection in immunocompromised hosts with epidemiologic risk factors. The diagnosis and treatment are fairly straightforward, and understanding the sensitivity of the different tests is useful for both boards and clinical practice.

### CASE PATIENT 4

A 70-year-old man with a history of hypertension presents to the ED after the sudden onset of left hand weakness. This weakness started earlier in the morning and progressed quickly to complete weakness of the affected extremity. He called an ambulance and was brought to the ED for evaluation. He has a history of hypertension and benign prostatic hypertrophy and reports multiple past sinus infections. In the ED, a grand mal seizure is witnessed. Head CT scan reveals a 2.1-cm ring-enhancing lesion in the right frontal lobe with significant surrounding vasogenic edema (Figure 3). Levetiracetam is started and the patient is admitted for further workup.
• What are the most likely causative pathogens?

The case describes a patient with a history of sinus infections who developed headache and neurologic deficits. Imaging demonstrated a new ring-enhancing lesion on CT imaging, indicating that the patient is likely to have a brain abscess. The estimated incidence of brain abscess ranges from 0.4 to 0.9 cases per 100,000 population. Understanding the underlying pathophysiology of brain abscess can help elucidate the likely source of infection and pathogen(s), and thus can help guide the clinician in choosing appropriate empiric therapy.

BRAIN ABSCESS
Pathophysiology and Causative Organisms

Like many other infectious syndromes, the etiology and pathophysiology of a brain abscess is highly dependent on underlying comorbidities, including the immune status of the patient. Abscesses evolve from an area of localized cerebritis into a lesion with a necrotic and purulent center. This inflammatory process can cause symptoms in the surrounding cerebral anatomical structures. Headache, fever, seizures, and neurologic deficits can ensue. As the inflammatory reaction evolves, the lesion encapsulates, causing the distinctive ring-enhancement on imaging. Brain abscess can be caused by a variety of bacterial, parasitic, and fungal pathogens, which can enter the CNS via exogenous or endogenous routes. Exogenous infections typically result from the direct inoculation of the CNS due to trauma or an invasive procedure. Cases of endogenous brain abscess are often due to hematogenous seeding from bacteremia or contiguous infections from nearby anatomical structures. Common infections that can lead to brain abscess formations include otitis media, sinusitis, and maxillofacial infections. It is estimated that as many as 20% of brain abscesses can be cryptogenic, with no known cause identified. Performing a thorough history and examination to identify predisposing factors and epidemiologic exposures for the brain abscess is imperative, as they will guide empiric management (Table 5).

CASE 4 CONTINUED

The patient is admitted to the neurosurgical unit for further management and the infectious diseases service is consulted for an evaluation. His history of sinus infections and the location and characteristics of the lesion suggest a brain abscess from a contiguous source as the cause. The primary team is requesting assistance in selecting proper empiric antimicrobial agents.

• What is the proper empiric antimicrobial regimen for a suspected pyogenic brain abscess?

The immediate initiation of empiric antimicrobials is a cornerstone of therapy, as delaying the start of appropriate, high-dose antibiotics is associated with increased morbidity and mortality. Some studies show as much as a 50% increase in mortality risk per day of delay in starting these antimicrobials. Urgent neurosurgical evaluation is important as well, as a delay in drainage—if indicated—is also associated with poor outcomes. The empiric agents of choice are based on predisposing factors of the individual patient (Table 5). Regimens tend to be broad, as brain abscesses are often polymicrobial, including anaerobes. Advances in molecular diagnostics via sequencing of PCR-amplified 16S rDNA have proven useful in obtaining microbiologic diagnosis, and have also increased the number of identified agents in cere-
bral abscesses. Empiric agents should provide adequate antibacterial coverage.

- **What is the role for surgical intervention in this patient?**

  The management of brain abscess is often a combination of medical and surgical intervention. The standard of care 2 decades ago involved complete resection of the lesion in all patients. However, further studies and advances in neurosurgical techniques have changed this approach. Surgical management now involves stereotactic aspiration of the purulent center, which is performed for diagnostic and therapeutic purposes. While neurosurgical evaluation is likely indicated in every case, the decision to intervene surgically should be individualized. Studies have shown success in medical management of small brain abscess measuring less than 2.5 cm. This approach is also advocated in stable patients who have multiple small abscesses. Antimicrobial therapy alone would be an appropriate initial therapeutic option for this patient given the size of the abscess and potential morbidity and mortality associated with neurosurgical drainage or resection.

**Outcomes**

Major advances in medical therapeutics and surgical interventions have had a dramatic impact on morbidity and mortality caused by brain abscess. A systematic review of data published over the past 60 years demonstrated a decrease in the case fatality rate from 40% to 10%, and an increase in full recovery rates from 33% to 70%. Despite these advances, this condition still carries high morbidity.
ity and mortality. It is imperative for clinicians to understand the basic concepts of this disease in order to ensure the prompt initiation of appropriate antimicrobial therapy and know the basic principles regarding neurosurgical evaluation and intervention. The patient described in this case was treated successfully with medical management alone.

Case Learning Objectives

Key objectives from this case include selecting the proper empiric antimicrobials, based on the likely source of the brain abscess. Identifying patients who can be successfully treated with medical management alone—those with lesions smaller than 2.5 cm—is an important concept for board review.

**CASE PATIENT 5**

A 27-year-old man presents for evaluation of fever, headache, stiff neck, and vomiting. His symptoms first started 6 days ago. His headache is located in the frontotemporal region, has gradu-

ally worsened over the past 4 days, and is now 9/10 in intensity. He returned from a 1-month trip to Southeast Asia 4½ weeks prior to the onset of symptoms. On physical examination, the patient is neurologically intact. An initial workup reveals no peripheral leukocytosis. CT of the head is normal. Lumbar puncture is performed, and CSF analysis shows 320 WBCs/µL, of which 51% are neutrophils, 31% lymphocytes, 15% eosinophils, and 4% monocytes. Empiric antimicrobials are started for acute bacterial meningitis and the patient is admitted for further workup.

On his second day of admission, Gram stain and cultures from CSF are reported negative. CSF studies are reported negative for viral PCR, including HSV-1 and HSV-2, mycobacteria, and fungi. HIV antibody testing is negative. The primary team consults you for further evaluation.

> **Based on the epidemiologic risk factors, clinical presentation, and CSF fluid analysis, what is the likely pathogen involved in this case?**

This case describes a young healthy adult with recent travel who presented with eosinophilic meningitis. The differential diagnosis for eosinophilic meningitis is wide, and includes infectious and noninfectious causes (Table 6). His travel to Southeast Asia and his symptoms are concerning for *Angiostrongylus* infection. Human angiostrongyliasis is caused by *Angiostrongylus cantonensis*, a nematode present in rats.44

**ANGIOSTRONGYLIASIS**

**Epidemiology**

*Angiostrongylus cantonensis* was first discovered in the lungs of rats in the Guangzhou province of China in the 1930s, and the first case of human disease was described by the 1940s.44 It

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**Table 6. Causes of Eosinophilic Meningitis**

<table>
<thead>
<tr>
<th>Infectious</th>
<th>Noninfectious</th>
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<tbody>
<tr>
<td><em>Angiostrongylus cantonensis</em></td>
<td>Malignancy</td>
</tr>
<tr>
<td>Gnathostoma spinigerum</td>
<td>Glioblastoma</td>
</tr>
<tr>
<td>Paragonimus spp</td>
<td>Hodgkin disease</td>
</tr>
<tr>
<td>Strongyloides stercoralis</td>
<td>Non-Hodgkin lymphoma</td>
</tr>
<tr>
<td>Toxocara canis</td>
<td>Acute leukemia</td>
</tr>
<tr>
<td>Loa Loa</td>
<td>Meningeal carcinomatosis</td>
</tr>
<tr>
<td>Toxoplasma gondii</td>
<td>Medications</td>
</tr>
<tr>
<td>Taenia solium</td>
<td>Contrast/myelography</td>
</tr>
<tr>
<td>Coccidioides immitis</td>
<td>Ibuprofen</td>
</tr>
<tr>
<td>Schistosoma japonicum</td>
<td>Ciprofloxacin</td>
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<tr>
<td>Fasciola hepatica</td>
<td>Vancomycin</td>
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<tr>
<td>Trichinella spiralis</td>
<td>Gentamicin</td>
</tr>
<tr>
<td></td>
<td>Ventriculoperitoneal shunts</td>
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<td></td>
<td>Neurosurgical prosthetic devices</td>
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remains a rare disease, with only a few thousand cases reported in the literature. However, with outbreaks and cases reported in returning travelers, infectious diseases clinicians must be able to identify this disease.\textsuperscript{45,46} Eosinophilic meningitis is defined as a CSF pleocytosis with at least 10% eosinophils.\textsuperscript{47} Of the few infectious causes of eosinophilic meningitis, \textit{Angiostrongylus} is the most common.\textsuperscript{44,46} \textit{Angiostrongylus} infections have been reported in the South Pacific, Asia, Australia, and the Caribbean.\textsuperscript{47} U.S. states have reported endemic \textit{Angiostrongylus} infections as well, including Hawaii and Louisiana.

**Pathophysiology**

The rat is the definitive host, with snails, mollusks, prawns and crabs as intermediaries.\textsuperscript{44} Infection in humans is acquired orally, after infected intermediate hosts or contaminated vegetables are ingested. After ingestion, the larvae cause an initial gastroenteritis. Larva subsequently enter the bloodstream and are highly neurotropic (Figure 4).\textsuperscript{44,47}

**Clinical Manifestations**

The most common reported signs and symptoms of \textit{Angiostrongylus} meningitis include headache, vomiting, fever, nausea, somnolence, vomiting, and abdominal pain.\textsuperscript{44,45} Frontotemporal headaches seem to be a cardinal sign, present in up to 90\% of cases.\textsuperscript{46} Other symptoms are nonspecific, and can include myalgias, weakness, and hyperesthesia. The incubation period can be as long as 35 days.\textsuperscript{44}

**An Important Possibility: Baylisascaris**

When suspecting infectious eosinophilic meningitis in the United States, \textit{Baylisascaris procyonis} should always be in the differential diagnosis. This pathogen completes its life cycle in raccoons, with humans as accidental hosts.\textsuperscript{48} Raccoons infected with \textit{Baylisascaris} are common in many geographic regions of the continental United States, including the Middle Atlantic, Midwest, and the Northeast. Cases have been reported in California, Oregon, New York, Pennsylvania, Illinois, Michigan, and Minnesota.\textsuperscript{48} Given this wide geographic

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**Figure 4.** Life cycle of \textit{Angiostrongylus cantonensis}. CNS = central nervous system.
distribution, it is important for infectious disease clinicians to have this pathogen on the differential for all cases of eosinophilic meningitis. The diagnosis of *Baylisascaris* can be challenging, and usually involves serologic testing or identification of larvae on biopsy.\(^\text{48}\) Ophthalmologic evaluation can be useful, as this tissue can be involved and larvae can be identified in these samples.

**CASE 5 CONTINUED**

The concern for *Angiostrongylus* in this case of eosinophilic meningitis is discussed with the primary team. The team informs you that they are planning to repeat his lumbar puncture and request recommendations for further diagnostic testing.

- **What is the diagnostic approach for *Angiostrongylus* infection?**

**Diagnosis**

Making a definitive diagnosis of *Angiostrongylus* meningitis can be difficult. A definitive diagnosis can be made by finding the organisms in the CSF, but this is rarely possible. By some estimates, larvae in CSF can be found in less than 10% of cases.\(^\text{46}\) Though *Angiostrongylus*-specific antibodies from CSF or serum are sensitive and specific, these tests are not readily available and specimens may need to be sent to labs abroad. A presumptive diagnosis based on clinical features and epidemiologic risk factors, such as travel or known exposure to intermediate hosts, is important in order to start empiric therapy. Serologic or PCR diagnosis may be useful in the setting of outbreaks.

- **What is treatment for *Angiostrongylus* infection?**

**Treatment**

Supportive care is key for those infected with *Angiostrongylus*. Some experts advise against the use of antiparasitic agents, due to the fear of paradoxical worsening of the inflammatory process as larvae die in the CNS.\(^\text{44,46}\) Evidence supporting the use of antiparasitic agents and steroids has been evolving in the past decade and a half. A prospective, randomized, double-blind placebo-controlled trial of 66 cases in Thailand showed decreased symptoms without adverse effects for those treated with albendazole.\(^\text{49}\) Similarly, mebendazole plus prednisolone appears to be safe and efficacious.\(^\text{50}\) A randomized, controlled study and a Cochrane review of the literature reported quicker resolution of symptoms for patients treated with adjunctive corticosteroids.\(^\text{51,52}\)

**Case Learning Objectives**

Clinicians must be aware of common infectious and noninfectious causes of eosinophilic meningitis. Identifying common risk factors, such as travel to endemic areas and consumption of unwashed fresh produce or raw snails and mollusks, are important clues that can lead to the diagnosis of angiostrongyliasis. Although this condition is rare, it can occur in common destinations for North American travelers, such as the Caribbean and Hawaii. Eosinophilic meningitis, combined with epidemiologic risk factors and a specific exposure history, can lead you to the correct diagnosis of *A. cantonensis* infection.

**CASE PATIENT 6**

A 48-year-old woman presents to the ED via ambulance for evaluation of new right-sided weakness and new-onset seizure. She reports that the weakness started suddenly this morning. Family members then witnessed a seizure before the ambulance arrived. The patient has no known medical
problems. She was born in Mexico and goes back to visit relatives once a year.

On examination, vitals are unremarkable. Neurologic exam is remarkable for right-sided weakness in both the upper and lower extremities. CT imaging is immediately performed, and reveals a rim-enhancing lesion in the left frontal lobe with significant surrounding vasogenic edema, and there is a second lesion in the occipital region that is calcified (Figure 5). The patient is admitted to the hospital for further workup.

• Based on the epidemiologic risk factors, clinical presentation, and imaging findings, what is the likely diagnosis in this case?

This 48-year-old woman with prior medical history presents with new-onset seizures and CT imaging demonstrating multiple ring-enhancing lesions, including a calcified lesion in the occipital region. The patient is from a region endemic for neurocysticercosis (NCC), which is the most likely diagnosis.

NEUROCYSTICERCOYSIS

Epidemiology

Cysticercosis is a major public health concern in many low-income populations. The World Health Organization considers it a neglected tropical disease, a group of bacterial, protozoan, and viral illnesses with high prevalence in low-income countries.53 With an estimated 1.7 to 3 million people thought to have seizures due to NCC, it is the most common cause of epilepsy worldwide. NCC is common in Central and South America, the Caribbean, and Southeast Asia, and, in some of these high prevalence regions, NCC can account for up to 50% of all cases of epilepsy.54,55 In developed nations, it is frequently diagnosed in migrant populations from endemic areas.

Pathophysiology

Cysticercosis is an infection with the larval form of Taenia solium, a cestode worm also known as “pork tapeworm” which resides in the small intestine of humans. Humans are the definitive host, while intermediate hosts are usually free roaming pigs. These intermediate hosts ingest the larval form. Ova hatch and invade the intestines of the intermediate host. Infective embryos subsequently migrate to the blood stream and larval cysts eventually are present in any tissue supplied by blood, such as muscle or brain. Humans acquire the parasite by ingesting the ova, usually from undercooked meat. Cysts evaginate in the upper small intestine, attach to the mucosa, and develop into adult tapeworms. Mature tapeworms can grow to be several meters long, residing in the gastrointestinal tract and liberating ova or segments of terminal proglot-
tids in human feces. Intermediate and definitive hosts alike become infected by eating tapeworm eggs in the feces of a human infected with a tapeworm. Cysticercosis develops from fecal-oral transmission from hosts infected with the tapeworm (Figure 6). After ingestion of the oncospheres, they are carried via the bloodstream to various organs. Viable cysts form after 2 to 3 months, in a distribution that generally follows areas of blood flow to the brain. Cysts can be within the brain tissue (parenchymal) or in the subarachnoid spaces, ventricles, and spine (extraparenchymal). Cysts can be present along a spectrum that includes viable cysts, degenerating cysts, and calcified cysts.\[^{53-56}\]

Viable cysts represent the initial stage, when there is no inflammation present. An inflammatory response begins and a granuloma forms around the cyst. This inflammatory phase causes a variety of changes and inflammatory reactions surrounding the cyst. These are considered degenerating cysts, as inflammation starts and subsequently winds down. Depending on the location, size, and degree of edema, seizures may occur during this phase. Finally, the granuloma and cysts hyalinize and calcify as the inflammatory reaction resolves. Signs and symptoms of NCC depend on the disease burden, as well as the location, stage of the cysts, and degree of inflammation (Table 7).

**CASE 6 CONTINUED**

The patient is admitted to the neurosurgical unit for close monitoring and further management. Antiepileptic agents are started and the infectious diseases service is called for further recommendations. The team believes NCC is the most likely diagnosis, but would like to make a definitive diagnosis. They request recommendations on further testing for the diagnosis of NCC.

- **What further testing can be ordered to support the diagnosis of NCC?**

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**Figure 6.** Life cycle of *Taenia solium*. GI = gastrointestinal.
The diagnosis of NCC often depends on obtaining epidemiologic, serologic, and imaging data that adds to the likelihood of NCC as the cause of the constellation of symptoms in a particular case. Diagnostic criteria can be helpful but have not been validated in large trials. Brain biopsy is not routinely performed, but histologic demonstration of the parasite from a biopsy of an affected brain or spinal cord lesion would provide a definitive diagnosis. When histology is not feasible, diagnosis rests on a combination of imaging and serology along with the appropriate epidemiologic risk factors.

Imaging
In cases with appropriate epidemiologic risk factors, diagnosis can be done solely via imaging. MRI is superior to CT imaging to visualize cysts located in deep brain anatomical structures, and can be more useful to define the cyst and determine its stage. However, CT imaging can best detect calcifications. CT imaging is considered the best initial imaging test, while MRI should be performed to better assess the extent of disease. Based on radiographic characteristics, imaging can be described as diagnostic, probable, or consistent with NCC. Cysts that are round, 1 to 2 cm in diameter, and have smooth walls and a central opacity representing the scolex are diagnostic in the right clinical setting. For variations beyond this classic radiographic finding, data from serology can be helpful to support the diagnosis.

Serology
The 2 serologic tests for cysticercosis are the enzyme-linked immunoelectrotransfer blot (EITB) and ELISA. EITB is very specific for exposure and disease, and there is wide experience with this test. It is the recommended test by experts at the Centers for Disease Control and Prevention. ELISA tests have been developed and are specific for active viable infection, but this assay is not highly sensitive. Public health officials should be notified, as cysticercosis is a reportable disease in several states.

CASE 6 CONTINUED
The EITB test for Taenia is sent and an MRI of the brain is ordered to better characterize the lesions and assess the burden of disease. The MRI is able to better differentiate the lesion, which is now described as having a small central radiopaque area, consistent with a scolex. The laboratory calls and reports that the EITB is positive. There is enough evidence to support the diagnosis of NCC. The neurosurgical team is considering further surgical and medical treatment options and requests your opinion on therapeutic interventions.

- What is the role of anthelmintic agents in the management of NCC?

Treatment
Treatment modalities for NCC depend on the clinical manifestations, the location, number, size, and...
stage of the cysts. Management of NCC involves a medical-surgical approach, particularly for treatment of complications such as seizures, edema, intracranial hypertension, and hydrocephalus.\textsuperscript{53} NCC rarely presents as a neurosurgical emergency, but evaluation for possible surgical management is warranted, particularly when anatomic complications such as hydrocephalus are present.\textsuperscript{53,55,59}

Our knowledge of medical management for NCC has evolved dramatically in the past 15 years. Whether to use anthelmintic therapy depends greatly on the stage of the cysts. Calcified cysts do not benefit from anthelmintic treatment, as the parasite is already deceased. It was initially thought that anthelmintic therapy was deleterious, as it could promote inflammation and worsen symptoms, but recent studies have changed this paradigm.\textsuperscript{53} Anthelmintic therapy is now indicated for viable, noncalcified cysts.\textsuperscript{55} Anthelmintic agents recommended for use in NCC include albendazole and praziquantel. Studies have shown that albendazole is more effective than praziquantel, and a recent randomized trial reported that combination therapy with both agents was more effective than either agent alone, suggesting that this may be the correct approach.\textsuperscript{60}

**What is the role of corticosteroids in the management of NCC?**

Corticosteroids play a key role in the management of NCC. They are used to reduce inflammation caused by anthelmintic therapy as well as the inflammation present during the natural course of the illness, thus reducing complications such as seizures.\textsuperscript{53,55,59} Corticosteroids should always be used when anthelmintic therapy is prescribed. When anthelmintic therapy is not indicated, corticosteroids may still be helpful in combination with antiepileptic drugs, as studies have shown this approach to decrease the number of seizures compared to antiepileptic drugs alone.\textsuperscript{61}

**CASE 6 CONTINUED**

After controlling the inflammatory response with corticosteroids and proper management of epilepsy with antiepileptic agents, the patient has no further seizures and slowly regains motor function of her right side. Albendazole therapy is initiated and surgery deferred. The patient is discharged to a rehabilitation facility and is able to return to work 12 weeks later.

**Preventive Measures**

Cure rates for NCC are low and morbidity can be high due to the long-term burden of epilepsy. Thus, an important intervention whenever a case of NCC is diagnosed is to attempt preventive measures for family members and close contacts. When traveling to endemic regions, persons should avoid foods that might be contaminated by human feces. Those who work in the food industry must be educated in good hand-washing practices. Stool examinations for *Taenia* may be useful for persons from highly endemic regions.

**Case Learning Objectives**

Key objectives from this case include identifying NCC in patients with typical findings on imaging and appropriate epidemiologic risk factors. Understanding the role of corticosteroids, antiepileptic agents, anthelmintic agents, and surgery in the management of NCC is important.

**BOARD REVIEW QUESTIONS**

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