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Infectious Disease [ALERT]

Incisive Commentary and Clinical Abstracts on Current Issues in Infectious Diseases

ABSTRACT & COMMENTARY

Outcomes of Acute Encephalitis in Children

By Hal B. Jenson, MD, FAAP

Dr. Jenson is Professor of Pediatric and Adolescent Medicine, and Dean, Western Michigan University Homer Stryker M.D. School of Medicine, Kalamazoo, MI.

Dr. Jenson reports no financial relationships relevant to this field of study.

SYNOPSIS: In a study of outcomes of children with encephalitis, almost 80% had persistent neurological symptoms on follow-up at least one year later. Abnormal MRI findings and seizures at presentation correlated with lower quality-of-life scores. The presence of seizures at presentation was associated with an ongoing seizure disorder, which was present in 35% of patients.

SOURCE: Rao S, et al. Long-term outcomes and risk factors associated with acute encephalitis in children. *J Pediatr Infect Dis* 2015:1-8.

A retrospective review was conducted at Children's Hospital Colorado of patients 0 to 21 years of age discharged from 2000 to 2010 with a diagnosis of encephalitis. Encephalitis was defined by documented encephalopathy (depressed or altered level of consciousness lasting more than 24 hours, lethargy, or personality change) plus two or more of the following: temperature greater than 38°C, new-onset seizures, so-called central nervous system findings, abnormal EEG findings compatible with encephalitis, abnormal brain computed tomography (CT) or magnetic resonance imaging (MRI) results, and pleocytosis greater than 2 standard deviations above the mean for age.

A structured telephone interview was conducted of parents using the Pediatric Quality of Life Inventory (PedsQL) Generic Core Scales, which is a 23-item scale designed to measure physical and emotional quality of life, and a second questionnaire designed to determine the persistence of neurological symptoms or difficulties with activities of daily living.

Among 114 patients meeting entry criteria, 76 had sufficient hospital data for review. An etiology was identified in 29 cases (38%), of which 93% were infectious. The most common agents were HSV, enterovirus, and influenza. The median age at

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diagnosis was 7 years (IQR, 2-13 years). There were 32 patients (42%) admitted to the intensive care unit (ICU), and four patients (5%) died.

Forty-nine patients were available for follow-up, with a median time to follow-up of 1.3 years. Among these 49 patients, residual neurological deficits were reported in 38 patients (78%), with the most common deficits being psychiatric abnormalities, weakness, behavioral and cognitive deficits, vision problems, and headaches. Seventeen patients (35%) reported ongoing seizures. There were no significant associations between outcomes and pleocytosis, or of outcomes with CT/MRI abnormalities, EEG abnormalities, or neurological deficits present at the time of hospital discharge. Patients admitted to the ICU were more likely to have EEG abnormalities ($P = 0.013$). Seizures at the time of admission were significantly associated with ongoing seizures through follow-up at least one year later (94% vs. 42%; $P = 0.0036$). After removing the effects of age, abnormal MRI results at presentation were associated with lower quality-of-life scores, and the presence of seizures at presentation correlated with an ongoing seizure disorder, which was present in 35% of patients.

■ COMMENTARY

The prognostic factors for children with acute encephalitis are not well-characterized, especially among cases without a specific etiology, which constitute the majority of cases of encephalitis in children. This study, which is exceptional for reporting both short-term and long-term outcomes (of at least one year), shows that there is a high rate, almost 80%, of persistent neurological symptoms in children diagnosed with acute encephalitis. The most common sequelae were psychiatric, behavioral, and cognitive deficits, with the most common physical sequelae being weakness and vision problems.

Lower quality-of-life scores correlated with an abnormal MRI at presentation and seizures at presentation. This suggests that MRI is useful not only in assisting with identifying the etiology of encephalitis, but also provides prognostic information. Seizures at presentation, though not EEG findings, were prognostic for poorer long-term outcomes, with 35% of patients having a persistent seizure disorder. ■

ABSTRACT & COMMENTARY

Tissue Invasion by Malignantly Transformed Cells from *Hymenolepis nana* in a Human Host

By Richard R. Watkins, MD, MS, FACP

Division of Infectious Diseases, Akron General Medical Center, Akron, OH; Associate Professor of Internal Medicine, Northeast Ohio Medical University, Rootstown, OH

Dr. Watkins reports that he has received research support from Forest Laboratories.

SYNOPSIS: The first reported case of human disease caused by parasite-derived cancer cells was discovered in a 41-year-old man with HIV infection; lung, adrenal, and liver nodules; and lymphadenopathy.

SOURCE: Muehlenbachs A, et al. Malignant transformation of *Hymenolepis nana* in a human host. *N Engl J Med* 2015;373:1845-1852.

Hymenolepis nana is the most common human tapeworm, infecting approximately 75 million people. Most infections are asymptomatic and usually limited to the gastrointestinal tract. Muehlenbachs and colleagues report a unique case of extra-intestinal *H. nana* with genomic mutations that were

consistent with malignancy.

The patient was a 41-year-old man diagnosed with HIV infection in 2006 who was nonadherent with antiretroviral therapy (ART). He initially presented with several months of weight loss, fatigue, fever, and cough. His CD4 count was 28/mm^3 and his viral load was 70,000 copies/mL. Stool examination showed *H. nana* eggs and *Blastocystis hominis* cysts. Computed tomography scans showed multiple nodules in the lungs, adrenal glands, and liver, ranging in size from 0.4 to 4.4 cm, as well as diffuse lymphadenopathy. He underwent excisional biopsy of a cervical lymph node and needle biopsy of a lung nodule. Three doses of albendazole were prescribed, and he was restarted on ART. Over the following 4 months, the nodules in the lungs, liver, and adrenals remained stable, but the lymph nodes increased in size. He was diagnosed with histoplasmosis and treated with amphotericin B, but developed renal failure; he declined hemodialysis. Palliative care was started, and he died in May 2013.

The investigators used DNA from the cervical lymph node as well as *H. nana* reference-strain specimens to construct sequencing libraries. Polymerase chain reaction (PCR) assays identified *H. nana* DNA in the specimen, which was confirmed by immunohistochemical studies and in situ hybridization that localized cestode antigen and nucleic acid signals. The DNA from the patient's sequence was found to have three single-nucleotide insertions consistent with a deleterious mutation. Deep sequencing from the lymph node specimen generated 10.2 million reads. When the human sequences were removed, 1.4 million reads mapped onto the *H. nana* reference genome. Furthermore, complex genomic rearrangement and amplification was found in the human sequences, but not in the *H. nana* reference sequences. Finally, insertion-site analysis revealed six insertional mutations, three of which have mammalian homologues associated with malignancy.

■ COMMENTARY

This report is interesting because it apparently shows that malignantly transformed cells derived from a parasite can cause cancer in a human. It is known that infections with certain pathogens (e.g., human papilloma virus, *Schistosoma haematobium*) can lead to the development of cancer in humans, and that transmissible cancer cells circulate in Tasmanian devils. Indeed, it is also understood that in rare cases, cancer cells can be transmitted from human to human, such as with organ transplantation or from mother to fetus. But Muehlenbachs and colleagues present evidence of direct transmission of mutations associated with cancer from *H. nana*, a novel finding. The pathophysiology of the malignant transformation of the tapeworm cells is uncertain. The authors theorize that the patient's compromised immune system allowed the tapeworm to proliferate, resulting in the accumulation of somatic mutations in the *H. nana* stem-cell population.

An unsettling finding from this case is that the patient received albendazole, the drug of choice for tissue-invasive disease. Yet, as the authors mention, the efficacy of albendazole against clonal proliferations of tapeworm stem cells is uncertain, and there is some evidence that it is ineffective. Thus, invasive *H. nana* with cellular proliferations might not be treatable with currently available drugs, and is an area that needs further investigation. It seems plausible that chemotherapy drugs that work in human cancer might also be effective against cancer cells from parasites. Before this hypothesis is explored, the link between human disease and malignant transformation in a parasite needs to be replicated by independent investigators.

[**Editor's Note:** As Dr. Watkins indicates, transmissible cancers have previously been identified, including not only Tasmanian devil facial tumor disease, which is transmitted among the animals by facial biting, but also canine transmissible venereal tumor. Of further interest is that a Nobel Prize in Medicine was awarded to Johannes Fibiger in 1926 for his subsequently refuted "discovery" that the nematode *Spiroptera carcinoma* (now called *Gongylonema neoplasticum*) caused gastric cancer. Although this did not represent a claim of transmissibility of malignant cells but rather a secondary effect of a parasitic infection (such as the association of bladder cancer with *S. haematobium* infection mentioned above), it provides an interesting background anecdote.] ■

GRAND ROUNDS

ID Grand Rounds — Stanford University

By Carlos A. Gomez, MD

Dr. Gomez is Infectious Diseases Fellow, Stanford University Hospital.

Dr. Gomez reports no financial relationships relevant to this field of study.

SYNOPSIS: A 69-year-old male with allogeneic hematopoietic stem cell transplant with a space-occupying lesion of the central nervous system (CNS).

A 69-year-old male with a long-standing history of primary myelodysplastic syndrome (MDS) underwent non-myeloablative allogeneic, matched unrelated donor (MURD), hematopoietic stem cell transplantation (HSCT) in November 2013. Nine months following transplantation, the patient developed idiopathic thrombocytopenia purpura (ITP) that required IVIG administration coupled with high-dose prednisone (80 mg/day). Tacrolimus was discontinued upon ITP diagnosis. Eleven months after transplantation and 2 months after ITP was diagnosed, the patient presented to the outpatient hematology clinic due to high fever (39.5°C), right shoulder pain, pleuritic chest pain, dyspnea, and altered mental status. He was admitted to the hospital for further workup.

At admission, his immunosuppressive and antimicrobial prophylaxis regimen included prednisone (15 mg/daily), mycophenolate mofetil, atovaquone (750 mg three times per week), acyclovir (400 mg TID), and voriconazole (400 mg BID). He was a retired physician living in northern California. He reported active outdoor activities, including short-distance hikes, gardening, and construction at home that started 2 months preceding hospital admission.

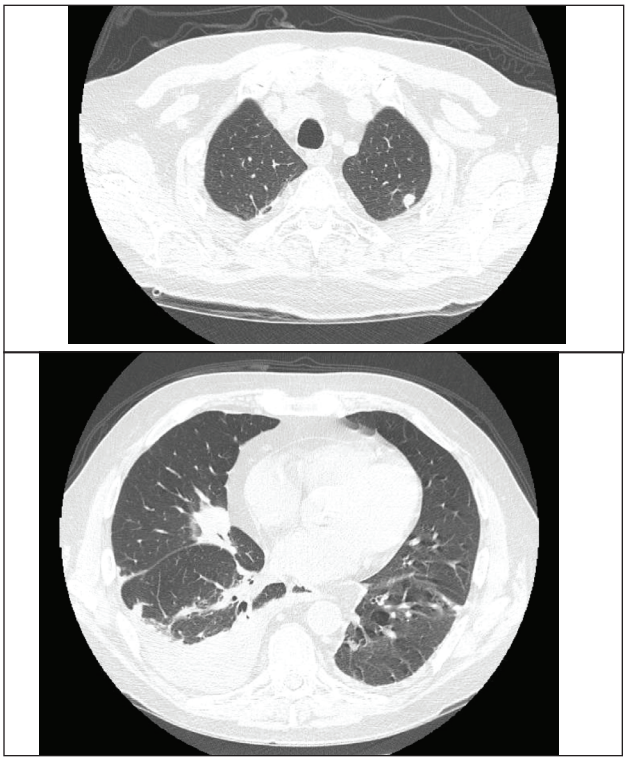
PHYSICAL EXAMINATION

On physical examination, the patient had mild respiratory distress. His temperature was 39.7 °C, blood pressure was 127/68 mmHg, heart rate was 84 beats per minute, and respiratory rate was 20 breaths per minute. His oxygen saturation was 92% at 2 L/min of oxygen by nasal cannula. No oral mucosa lesions were appreciated. Hypoventilation and crackles were noted at the right lung base. Abdominal examination was benign, with no hepatosplenomegaly. He had 2+ lower extremity edema and multiple ecchymosis throughout skin. He appeared drowsy but answered questions appropriately. Cranial nerves examination was intact. No focal neurologic deficit was noted. The rest of the examination was unremarkable.

LAB TESTING AND IMAGING

Laboratory investigation revealed leukopenia (2,100 WBC, 34% neutrophils, 44% lymphocytes); hemoglobin was 9.8 g/dL, and platelet count was 125.000 platelets per microliter of blood. His creatinine was 1.5 mg/dL. Liver function tests were normal. Blood cultures, pneumococcal urine antigen, and legionella urine antigen were negative. Blood cultures were drawn upon admission. Cryptococcal antigen by lateral flow testing, serum *Aspergillus* galactomannan antigen testing, *Coccidioides* immunodiffusion titers, and *Histoplasma* urine antigen were all negative. Initial chest X-ray showed multifocal areas of consolidation, scattered pulmonary nodules, and right-sided pleural effusion. A non-contrast CT of the chest showed multiple solid nodules and areas of alveolar consolidation, along with right pleural effusion. (*See Figure 1.*)

Figure 1: Non-contrast CT of the Thorax Showing Multiple Areas of Solid Nodules, Right Lower and Middle Lobe Consolidation, and Right Pleural Effusion.



CLINICAL COURSE

The patient was admitted to the medical ward. Empirical antibiotic therapy was started with IV vancomycin and cefepime. At day 2 following admission, the patient underwent fiberoptic bronchoscopy with bronchoalveolar lavage (BAL). Bacterial, fungal, and AFB cultures from BAL were non-diagnostic. Direct fluorescent antibody (DFA) testing for *Pneumocystis* was negative. At day 4 of hospital stay, blood cultures turned positive for *Nocardia farcinica*. This finding prompted brain imaging, and MRI of the brain showed multiple areas of rim-enhancing lesions localized across fronto-parietal-temporal and cerebellar areas bilaterally. No

meningeal enhancement or hydrocephalus was noted.

The patient was started on IV trimethoprim-sulfamethoxazole (TMP-SMX), meropenem, and linezolid for empirical *Nocardia* therapy. Once antibiotic susceptibility testing performed by Etest confirmed TMP-SMX susceptibility, the patient was switched to oral TMP-SMX at doses of 2 DS tablets every 8 hours. Two months following hospital admission, the patient remains in good clinical condition. Follow-up brain MRI imaging showed interval improvement in the size of the lesions and overall decreased burden of disease. After 6 months of TMP-SMX therapy, the patient was switched to suppression doses (1 DS tab daily) for chronic secondary prophylaxis against *Nocardia*.

Diagnosis: Disseminated Nocardiosis

DISCUSSION

Here, we present a case of an allogeneic-HSCT recipient with disseminated nocardiosis manifested with bacteremia, pneumonia, and space-occupying lesions in the central nervous system (CNS). Brain abscess is a rare complication following HSCT. The differential diagnosis of space-occupying lesions in the CNS in HSCT patients includes invasive fungal disease (most commonly aspergillosis followed by other filamentous as well as endemic fungi), bacterial brain abscess, *Toxoplasma gondii* encephalitis, *Nocardia* infection, and non-infectious conditions such as infarction or post-transplant lymphoproliferative disorder (PTLD).

Nocardia are filamentous, aerobic, Gram-positive branching rods, appearing weakly acid-fast staining due to the mycolic acid content of their cell wall. The reduced intensity of staining relative to that of mycobacteria is the result of differences in their mycolic acids, with those of *Nocardia* containing only 22-60 carbon atoms, while those of mycobacteria contain 60-80. *Nocardia* is an environmental saprophyte, whose normal habitat includes soil and decaying organic material. The main route of *Nocardia* infection is via the respiratory tract, with potential dissemination to distant sites, especially the CNS. *Nocardia* infection is typically regarded as opportunistic in patients with T-cell mediated deficiency, patients with chronic steroid use, or those under immunosuppression for prevention of organ transplant rejection.

Localized disease manifests most commonly as primary skin infection consisting of sporotrochoid lesions at the site of inoculation, often leading to pyogenic abscess, sinus tract, or destructive disease. In the immunocompromised host, the lung and CNS are commonly affected. In cases of pulmonary disease, chronic productive or nonproductive cough, dyspnea, hemoptysis, fever, and radiographic imaging patterns of consolidation, nodules, or cavitary disease have been described. CNS infection may present as headache, altered mental status, local neurological deficit, or fever. CNS lesions can be insidious in onset or even asymptomatic in the immunocompromised host.

The diagnosis of *Nocardia* infection has been significantly enhanced in the last two decades due to better detection and identification procedures in clinical microbiology. The microbiology laboratory should be notified in advance regarding the suspicion of *Nocardia* infection. Samples collected from lower respiratory tract, aspirates, or biopsy specimens are typically processed for Gram and modified acid-fast stains. Growth of *Nocardia* species usually takes between 3 to 5 days, as demonstrated in our case. In the most recent years, MALDI-TOF (matrix-assisted laser desorption ionization-time-of-flight) has been introduced to expedite *Nocardia* species identification, thus avoiding the need for phenotypic, enzymatic, and 16srRNA gene sequencing testing. Antibiotic susceptibility testing should be performed in all isolates of *Nocardia* following CLSI recommendations (CLSI).

TMP-SMX is the mainstay of treatment; initial combination therapy with other anti-*Nocardia* active agents such as imipenem, meropenem, linezolid, ceftriaxone, or amikacin is recommended in cases of disseminated disease or severe infection involving an immunocompromised host. *Nocardia* speciation and antimicrobial susceptibility testing should guide definitive therapy. There are a paucity of studies available to guide duration of therapy. In cases with deep-seated infection, clinical and radiographic monitoring is recommended to assist determination of the appropriate length of therapy.

The epidemiology of *Nocardia* infection in transplantation has been described in the last two decades. In a large series of SOT patients including 5126 patients, the incidence of *Nocardia* infection was 3.6%, 2.5%, 1.3%, 0.2%, 0.1% in lung, heart, intestinal, kidney, and liver transplant recipients, respectively. In 20% of cases, CNS involvement was identified by brain imaging. CMV disease, high doses of prednisone, and high doses of calcineurin inhibitors (cyclosporine or tacrolimus) were associated with increased risk of *Nocardia* infection. In this large series, 69% of patients developed *Nocardia* infection despite antimicrobial prophylaxis with TMP-SMX; nonetheless, this antimicrobial agent was used as the cornerstone of *Nocardia*

therapy, with a rate of cure of 89%.[1]

A case series from three large academic cancer centers reported an incidence of 0.3% of *Nocardia* infection among allogeneic HSCT patients.[2] The median time onset of *Nocardia* infection following HSCT was 210 days. The most common symptoms at clinical presentation were fever, productive cough, pleuritic chest pain, and weight loss. In 40% of cases, *Nocardia* infection developed despite TMP-SMX prophylaxis. Although the survival rate was high (84%), clinical prognosis was highly determined by the presence of CNS disease.

In conclusion, *Nocardia* infection can present as an opportunistic pathogen in HSCT patients, leading to disseminated disease (most commonly pneumonia and brain abscess), especially in the context of enhanced immunosuppression and absence of TMP-SMX-based antimicrobial prophylaxis. ■

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Ceftazidime-avibactam — Formulary Considerations

By Jamie Kuo, PharmD, Stanford Health Care, CA

Dr. Kuo reports no financial relationships relevant to this field of study.

Ceftazidime-avibactam is a new beta-lactam/beta-lactamase inhibitor combination approved for the treatment of complicated intra-abdominal infections in combination with metronidazole, and complicated urinary tract infections, including pyelonephritis in patients with limited alternative treatment options. The addition of avibactam to ceftazidime extends its spectrum of activity to include organisms that produce Ambler class A and C beta-lactamases, including AmpC, extended spectrum beta-lactamases (ESBLs), and most notably, *Klebsiella pneumoniae* carbapenemases (KPCs).

GENERIC NAME: Ceftazidime-avibactam
TRADE NAME: Avycaz™
U.S. FDA APPROVAL DATE: February 25, 2015

SIMILAR DRUGS

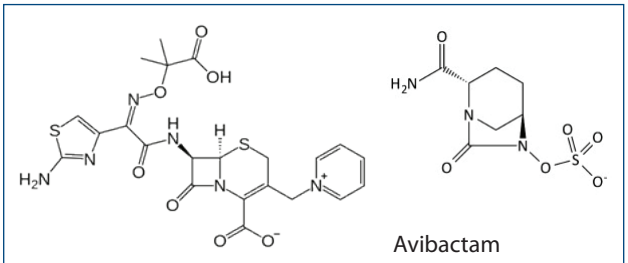
Meropenem, imipenem-cilastatin, doripenem, ceftolozane-tazobactam

INDICATIONS[1]

Treatment of adult patients 18 years or older with the following infections:

- Complicated intra-abdominal infections (cIAI), in combination with metronidazole, caused by *Enterobacter cloacae*, *Escherichia coli*, *Klebsiella oxytoca*, *K. pneumoniae*, *Proteus mirabilis*, *Providencia stuartii*, and *Pseudomonas aeruginosa*.
- Complicated urinary tract infections (cUTI) including pyelonephritis caused by *Citrobacter freundii*, *C. koseri*, *Enterobacter aerogenes*, *E. cloacae*, *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus* spp, and *Pseudomonas aeruginosa*.

PHARMACOLOGY[1,2]



Ceftazidime is a previously FDA-approved, third-generation cephalosporin with broad activity against Gram-negative organisms, including *Pseudomonas aeruginosa*. It is a bactericidal beta-lactam antibiotic that inhibits cell wall synthesis by binding to penicillin-binding proteins. Avibactam is a novel, non-beta-lactam beta-lactamase inhibitor of Ambler classes A and C beta-lactamases through covalent-binding to the enzyme active site. The addition of avibactam preserves ceftazidime activity by inhibiting its degradation by beta-lactamases and confers enhanced activity against Gram-negative bacteria, including ESBL-producing organisms. More importantly, ceftazidime-avibactam is the

CLINICAL TRIALS/EVIDENCE SUMMARY

Trial	Population	Intervention	Efficacy & Safety Results
Vazquez et al.[5] Phase 2, multi-center, prospective, double-blind, randomized study	N = 137 adult patients with cUTI, including pyelonephritis, requiring parenteral antimicrobials	Ceftazidime-avibactam 500 mg/125 mg IV q8h vs Imipenem-cilastatin 500 mg IV q6h Then step down to oral therapy Duration: 7-14 days total	Endpoints at Test of Cure Visit TREATMENT ARMS / N / ME N / ME MR / CE N / CE CR / MITT N / MITT MR Ceftazidime-avibactam / 69 / 27 / 70.4% / 28 / 85.7% / 46 / 67.4% Imipenem-cilastatin / 68 / 35 / 71.4% / 36 / 80.6% / 49 / 63.3% • This study was not statistically powered for non-inferiority. • The most common uropathogen isolated was *E. coli*. • The dose of ceftazidime-avibactam studied is lower than the currently recommended dose. • The most commonly reported adverse events were headache, infusion site reactions, constipation, diarrhea, abdominal pain, and anxiety.
Lucasti et al.[6] Phase 2, multi-center, prospective, double-blind, randomized study	N = 204 hospitalized, adult patients with cIAI requiring surgical intervention	Ceftazidime-avibactam 2.5 g IV q8h + Metronidazole 500 mg IV q8h vs Meropenem 1 g IV q8h Duration: 5-14 days	Endpoints at Test of Cure Visit TREATMENT ARMS / N / ME N / ME CR / CE N / CE CR / MITT N / MITT CR Ceftazidime-avibactam + metronidazole / 102 / 68 / 91.2% / 87 / 92% / 85 / 82.4% Meropenem / 102 / 76 / 93.4% / 90 / 94.4% / 89 / 88.8% • This study was not statistically powered for non-inferiority. • The most common Gram-negative isolated in blood cultures was *E. coli*. • Approximately 50% of patients had appendix-related cIAI. • The most commonly reported adverse events were nausea, vomiting, abdominal pain, pyrexia, wound secretion, cough, increased AST, ALT and/or AlkPhos, increased platelet count, leukocytosis, or hematuria.

cUTI = complicated urinary tract infection; cIAI = complicated intra-abdominal infection; MITT = modified intent-to-treat; ME = microbiologically evaluable; CE = clinically evaluable; MR = favorable microbiological response; CR = favorable clinical response

only beta-lactam/beta-lactamase inhibitor to date to have activity against KPCs. However, ceftazidime-avibactam has limited activity against Ambler class D beta-lactamases (except OXA-48 carbapenemases) and no activity against Ambler class B metallo-beta-lactamases (MBLs). Additionally, ceftazidime-avibactam has minimal activity against *Acinetobacter*, anaerobes, and Gram-positive organisms.

PHARMACOKINETICS & PHARMACODYNAMICS[1-3]

Ceftazidime and avibactam have similar volumes of distribution and half-lives. The volume of distribution of ceftazidime and avibactam is 17 L and 22.2 L, respectively. The half-life of ceftazidime is approximately 3 hours and avibactam is approximately 2.5 hours. Ceftazidime-avibactam dosed at 2.5 g every 8 hours achieves steady-state peak concentrations of ceftazidime and avibactam of 90 and 15 mg/L, respectively. Protein binding is relatively low at less than 10% with ceftazidime and 5.7-8.2% with avibactam. Both are also predominantly excreted renally and removed by hemodialysis. Ceftazidime is minimally metabolized, with 80-90% of the dose being eliminated in urine as unchanged drug. Avibactam is not metabolized, and 97% of the dose is eliminated in urine as unchanged drug.

Similar to the pharmacodynamics of other beta-lactam antibiotics, ceftazidime bactericidal activity is optimized by maximizing the proportion of the time of the dosing interval that the free drug concentration is above the MIC. The suggested pharmacodynamic target of avibactam is the proportion of the time of the dosing interval that the free beta-lactamase inhibitor concentration is above the threshold concentration.

CLINICAL TRIALS/EVIDENCE SUMMARY

• Clinical efficacy and safety of ceftazidime-

	CrCl > 50 mL/min		CrCl 30-50 mL/min*	
Phase 3 cIAI	Ceftazidime-avibactam + metronidazole	Meropenem	Ceftazidime-avibactam + metronidazole	Meropenem
Clinical cure	85%	86%	45%	74%
Mortality	1%	1%	25.8%	8.6%

*Note ceftazidime-avibactam dose in subgroup with CrCl 30-50 mL/min was 33% lower than is currently recommended.

Cost				
	How Supplied	Average Wholesale Price (per vial)	Usual Dose	Cost of Therapy per day
Ceftazidime-avibactam	2.5 g vials	$342	2.5 g q8h	$1026.00
Ceftolozane-tazobactam	1.5 g vials	$99.60	1.5 g q8h	$298.80
Meropenem	1 g vials	$18.48	1 g q8h	$55.44

avibactam is currently limited to Phase 2 studies.
• Results from Phase 3 trials in cUTI and cIAI are completed but have not yet been published. In a Phase 3 cIAI trial, clinical efficacy of ceftazidime-avibactam was decreased in patients with moderate renal impairment (CrCl 30-50 mL/min) compared to patients with normal renal function (CrCl > 50 mL/min).[3]

ADVERSE EFFECTS[3]

• Limited safety data are available at this time, given FDA approval was based on Phase 1 and 2 studies only. Therefore, the manufacturer recommends that ceftazidime-avibactam be reserved for patients who have limited or no alternative treatment options.
• Adverse effects reported at ≥ 10% incidence include nausea, vomiting, constipation, and anxiety.

CONTRAINDICATIONS/WARNINGS/PRECAUTIONS[1,3]

• Serious hypersensitivity to ceftazidime-avibactam, individual components, or other cephalosporins are considered contraindications. Caution is advised in patients with hypersensitivity to penicillins or carbapenems due to potential for cross-reactivity.
• Neurologic toxicity has been reported with ceftazidime, and the risk is increased in patients with impaired renal function. Symptoms include encephalopathy, myoclonus, seizures, or non-convulsive status epilepticus. Dose adjustment is recommended in patients with renal impairment.
• Similar to other antibiotics, prolonged use may result in superinfection, including *Clostridium difficile*-associated diarrhea.
• In a Phase 3 cIAI trial, decreased efficacy was reported in patients with moderate renal impairment (CrCl 30-50 mL/min) compared to patients with normal renal function (CrCl > 50 mL/min). Dose adjustment for renal impairment is recommended (*see dosage and administration section*).

POTENTIAL FOR MEDICATION ERRORS

• Dosing should be stated in total grams rather than grams of individual components to avoid dosing errors.

DRUG INTERACTIONS[1,4]

• Organic anion transporters (OAT) inhibitors (e.g., probenecid) can decrease elimination of avibactam, and their concurrent use with ceftazidime-avibactam should be avoided.

DOSAGE AND ADMINISTRATION[3,4]

Recommended dose/duration:
• Dosing is expressed as total grams of the ceftazidime-avibactam combination in a ratio of 4:1, i.e., 2.5 g is 2 g ceftazidime and 0.5 g avibactam.

Table. Dosing		
Indication	Dose	Duration
cIAI	2.5 g IV every 8 hours in combination with metronidazole	5-14 days
cUTI, including pyelonephritis	2.5 g IV every 8 hours	7-14 days

• Patients with renal impairment should have doses adjusted based on creatinine clearance as calculated by the Cockcroft-Gault equation.

Estimated Creatinine Clearance (mL/min)	Recommended Dose
> 50	2.5 g (2 g/0.5 g) every 8 hours
31-50	1.25 g (1 g/0.25 g) every 8 hours
16-30	0.94 g (0.75 g/0.19 g) every 12 hours
6-15*	0.94 g (0.75 g/0.19 g) every 24 hours
≤ 5*	0.94 g (0.75 g/0.19 g) every 48 hours
*ESRD on HD	Administer after HD on HD days
HD = hemodialysis	

• Both ceftazidime and avibactam are removed by dialysis. Following a 4-hour dialysis session, 55% of the dose was recovered in the dialysate.
• Dose adjustment for hepatic function is not necessary.
Administration instructions:
• Administer as an intermittent intravenous infusion over 2 hours.

CONCLUSIONS

The addition of avibactam to ceftazidime retains ceftazidime's spectrum of activity and has added activity against some ESBL- and KPC-producing pathogens. Expedited FDA approval of ceftazidime-

avibactam was granted based on two small Phase 2 trials and the previously established efficacy and safety of ceftazidime alone. In Phase 2 trials, ceftazidime-avibactam showed similar efficacy to active comparators and appeared to be well-tolerated when used to treat hospitalized adult patients with cUTI and cIAI in combination with metronidazole.

Currently, ceftazidime-avibactam is the only beta-lactam/beta-lactamase inhibitor to have activity against KPCs. In a climate of increasing carbapenem resistance, ceftazidime-avibactam represents an important treatment option in the management of multidrug-resistant Gram-negative infections. With ongoing Phase 3 trials, the precise role of ceftazidime-avibactam remains to be determined and will need to be weighed against the risk of developing drug-resistant bacteria. ■

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ABSTRACT & COMMENTARY

Malaria in Pregnancy — Good News, Bad News, and Opportunity

By Philip R. Fischer, MD, DTM&H

Dr. Fischer is Professor of Pediatrics, Department of Pediatric and Adolescent Medicine, Mayo Clinic, Rochester, MN.

Dr. Fischer reports no financial relationships relevant to this field of study.

SYNOPSIS: With waning natural immunity against malaria, women face increased adverse consequences of malaria infection during pregnancy. As malaria is being conquered, good clinical care of vulnerable individuals is still essential.

SOURCE: Mayor A, Bardaji A, Macete E, et al. Changing trends in *P. falciparum* burden, immunity, and disease in pregnancy. *N Engl J Med* 2015;373:1607-1617.

Dr. Clara Menendez and her colleagues evaluated malaria infection in 1819 Mozambican women who delivered babies during a 10-year period beginning in 2003. Malaria became less common during the decade of the study; during the first two years of the study, 11% had microscopic evidence of malaria at the time of delivery; during the final two years of the study, only 2% were smear-positive at the time of delivery. Antimalarial IgG levels similarly decreased over the decade of the study.

In women who did have malaria, however, parasite densities were nine-fold higher in the blood during the final two years of the study than during the initial two years; parasite densities of infected placentas similarly increased 10-fold during the study years. Infected women had more malaria-associated anemia in recent years than in the earlier years of the study when malaria was more common. During the later years of the study, malaria-infected women had babies who weighed an average of 130 grams less than did babies of malaria-infected women earlier in the study.

■ COMMENTARY

There are significant efforts to overcome malaria in Africa. Women in the current study, for instance, benefitted from the use of insecticide-treated bednets and intermittent preventive anti-malarial treatment. It is exciting to see that efforts to "roll back malaria" are succeeding in some areas with marked decreases in the prevalence of malaria infection.

However, during these years when malaria is less common but not yet eradicated, pregnant women have less anti-malarial immunity and risk having

more severe outcomes of malarial infection — increased parasite density, more anemia, lower birthweight babies. Even after birth, babies continue to suffer adverse effects of their mothers' gestational malaria.[1] It is good news that malaria is less common, but the ongoing bad news is that women who do get malaria during pregnancy now might face even worse outcomes than before.

These data remind us to continue vigilant care of all people, especially pregnant women, in areas where malaria is still transmitted. The improving public health situation leaves people more susceptible to adverse outcomes when they do become infected. Thus, especially in this era of declining malaria prevalence, we must be extremely careful to provide appropriate preventive interventions (bednets, preventive chemotherapy). Similar data from Malawi support targeting women during the beginning weeks of pregnancy.[2] In addition, rapid diagnostic testing of symptomatic individuals and effective early treatment of infected patients are also important. ■

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Infectious Disease [ALERT]

Updates

By Carol A. Kemper, MD, FACP

Borrelia Miyamotoi in My Backyard!

Who Knew?

Salkeld DJ, et al. Disease risk and landscape attributes of tick-borne *Borrelia* pathogens in the San Francisco Bay Area, California. *PLoS ONE* 10 (8), e0134812. Doi:10.1371/journal.pone.0134812.

Reading the local Woodside Almanac (Woodside, CA), my attention was captured by an article describing Lyme-infected ticks found in "all kinds of (local) habitats." But the really interesting part of the article was the observation that *Borrelia miyamotoi*–carrying local ticks were as common in our area as *B. burgdorferi*-infected ticks.

Salkeld and colleagues at the Woods Institute for the Environment at Stanford University examined the prevalence of *Borrelia*-carrying nymphs and ticks at 20 sites within six different San Francisco Bay Area counties, including San Mateo, Santa Clara, Marin, Sonoma, Napa, and Santa Cruz counties. Ticks were collected in May 2012 and May 2013 by dragging a white flannel blankie around various local county and state parks and open space preserves. The number of nymphal ticks and adults collected was recorded every 30 meters. In the immediate vicinity, Palo Alto-exclusive Foothills Park, Wunderlich Park in Woodside (my favorite local county park), and the infamous Windy Hill Preserve (try hiking straight up this 1900-ft elevation- baby on a weekend) made the list. The blanket was dragged through a variety of habitats, through any leaf litter or vegetation, and included coastal live oak forests, coastal redwoods, madrones, blackberries, scrub and coyote brush, and grasslands. Both nymphs and adults were collected, and all *Ixodes pacificus* ticks were tested for *Borrelia* spp.

Ticks were individually tested using quantitative PCR for 16 gene *Borrelia* spp DNA, followed by species-specific hybridization. The overall frequency of infected nymphal and adult ticks was determined, and the density of infected ticks was calculated in 30-meter segments throughout the parks.

Borrelia spp were found in 37/349 (10.6%) nymphs and 22/273 (8.1%) adult ticks. *B. miyamotoi* was found in 3.7% of nymphal ticks (which were found at eight different sites), and 1.8% of adults (found at three different sites). *B. burgdorferi* was observed in 2% of all nymphs, and was found at five sites.

And the site with the highest prevalence of infected ticks? Our very own Windy Hill Preserve, where we locals hike on weekends. But an interesting finding was that not only did tick density vary considerably within the Bay Area, but the infected tick density varied between habitats, even within the same park. While no infected ticks were found in the grassland area of Windy Hill, the nearby Coastal Oak Trail had the highest density of infected ticks (10/100 m^2) of anywhere in the Bay Area. Infected nymphs seemed to be more prevalent in coastal live oak woodlands and semi-arid/scrub areas than other areas.

The taxonomy of *Borrelia* are becoming increasingly complex, with at least 12 different species possibly being associated with Lyme disease — but more is being learned of other species, such as *B. miyamotoi*, which more closely resembles the *B. recurrentis* group of spirochetes. Clinically, the symptoms of

B. miyamotoi infection resemble infection with *Anaplasma phagocytophilum* (previously known as granulocytic Ehrlichiosis), and may be almost as common in certain areas of the country. Dean Winslow, MD, previously summarized the results of a recent retrospective survey (*see* Infectious Disease Alert, *September 2015*) of patients in New England with fever and suspected tick-borne disease, 0.8% of whom had a positive PCR for *B. miyamotoi* DNA. (By comparison, 3.1% were positive for *B. microti* DNA, 1.4% were positive for *A. phagocytophilum* DNA, and 1.7% were positive for *B. burgdorferi* DNA.) Nearly one-fourth required hospitalization, and 96% had fever and severe headache. Interestingly, only 16% of these initially had a positive EIA (using a *B. miyamotoi* recombinant rGlpQ antigen), but 78% of convalescent serum was positive. Ten percent of the patients also had a positive immunoblot to *B. burgdorferi*, suggesting possible co-infection.

Seroprevalence studies for *B. miyamotoi* in our area would be of interest.

Fecal Microbiota Transplantation — Patients Need No Convincing

Drekonja D, et al. Fecal microbiota transplantation for *Clostridium difficile* infection. A systemic review. *Ann Intern Med* 2015;12:630-638; Surawicz CM. Fecal microbiota transplantation: What we know and what we need to know. *Ann Intern Med* 2015;162;662-663.

Relapsing and refractory *Clostridium difficile* infection (CDI) has become a real challenge for clinicians and affected patients alike. Some patients wind up in a seemingly never-ending cycle of illness, gradual improvement, followed by a prolonged vancomycin taper, and eventual relapse. Relapse occurs in 15% to 30% of patients following an initial (successfully treated) episode, and further relapse occurs in more than 50% of those with second or subsequent episodes. Reports of successful resolution of this nasty infection using fecal microbiota transplantation (FMT) has generated enthusiasm. But available studies vary in their approach, their timing, the frequency of treatment (single dose vs. multiple doses over several days), and several guidelines now have been proposed for screening of potential donors. Some recommend FMT for those with two or more episodes, whereas the American College of Gastroenterology suggests FMT can be considered in those with three or more episodes.

These authors performed a systematic review of the available literature related to FMT. Two randomized, controlled trials, 28 case series, and five case reports were identified for a total of 561 FMT subjects. Combining the results of the two randomized clinical trials, 27 of 36 patients treated with FMT had resolution of symptoms (75%). One of these studies administered material via nasogastric (NG) tubes, with successful resolution of symptoms in 81% at 3 months. In contrast, less than 30% of patients in the two comparator arms receiving vancomycin treatment or vancomycin lavage had sustained resolution of symptoms at 3 months. In the first study, FMT was administered following 4-5 days of orally administered vancomycin (500 mg four times daily). Interestingly, 8 of the 43 patients included in this study were enrolled after their first episode of CDI. In the second randomized, controlled study, FMT was administered via NG vs. colonoscopy in 20 patients, with resolution of symptoms in 60% vs. 80% (P = 0.63). FMT was administered 3 days following completion of anti-CDI treatment.

In the various case series, FMT was performed in 480 patients with a history of 3-12 relapses over a 3-27 month period. Although none of these studies included a comparator arm, 85% reportedly remained disease-free following administration of FMT. In addition to these, there were seven smaller non-comparator studies for patients with refractory CDI, all using various methods, with an overall resolution rate of 55%. Symptomatic improvement was observed in 0% to 100%.

A third randomized, controlled trial, not published in time to be included in this analysis, demonstrated successful resolution of symptoms in 90% of patients treated with FMT vs. 26% in a vancomycin-treatment group; the study was halted prematurely because of this substantial difference in favor of FMT.

In conclusion, FMT appears effective in approximately 55% to 90% of patients with relapsing and refractory CDI, and will prove a blessing to those who have been in a miserable cycle of recurrent disease. Observed side effects were minimal and included complaints of cramping, bloating, nausea, transient fever, and dizziness. One patient receiving FMT by an erroneously placed NG tube developed pneumoperitoneum and polymicrobial bacteremia.

Many questions remain, including who, what, and how. Various protocols are used to screen donors, and methods for administration of FMT differ. For those without access to stool, one company is marketing frozen stool from pre-screened healthy donors. I've had several enterprising patients who have tried various approaches, including small home tap water enemas mixed with stool (strained to remove the peas and carrots), to capsules stuffed with a spouse's stool, kept refrigerated, and swallowed

the day following completion of orally administered vancomycin. A couple of patients have tried 10 capsules twice a day for 1-2 days, one of whom relapsed a week later, and tried it again with success. I guess if you can share food and other substances with your husband, his stool is probably OK. While initial reluctance was expressed, patients were quick to embrace this approach following yet another relapse. One of the randomized, controlled trials above indicated that patients were initially squeamish, but when contacted 3 months later, 97% said they would do it again.

It's amazing that such a simple procedure — administration of a small amount of fecal material — can effect such an important change in your bowel flora. But I guess that is how we develop our flora, with ingestion of fecal material from the world around us, bit by bit. As one of my favorite instructors is fond of saying, "Think of the world as covered by a thin layer of feces." ■

CME INSTRUCTIONS

To earn credit for this activity, please follow these instructions:

1. Read and study the activity, using the provided references for further research.
2. Scan the QR code at right or log onto www. AHCMedia.com and click on My Account. *First-time users must register on the site.*
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4. After successfully completing the test, your browser will be automatically directed to the activity evaluation form, which you will submit online.
5. Once the completed evaluation is received, a credit letter will be e-mailed to you instantly.

CME QUESTIONS

1. Malaria during pregnancy:

A. is increasingly common.

B. usually has minimal adverse outcomes.

C. is more severe in women with high levels of antimalarial antibody.

D. leads to maternal anemia, low birthweight, and adverse outcomes in the offspring.

2. Which of the following is correct regarding *Nocardia* species?

A. They are Gram-negative.

B. They are intensely acid fast.

C. They often require 3-5 days before cultures turn positive.

D. Most have become resistant to trimethoprim-sulfamethoxazole.

3. Which of the following is correct regarding ceftazidime-avibactam?

A. Avibactam prevents the renal metabolism of ceftazidime by dehydropeptidases.

B. The combination is active against many KPC-producing *Enterobacteriaceae*.

C. Because most of both components has predominantly hepatobiliary excretion, no dose adjustment is required in the face of renal insufficiency.

D. The combination is always inactive in the presence of ESBL-producing *Enterobacteriaceae*.

CME OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- discuss the diagnosis of infectious diseases;
- explain current data regarding the use of new antibiotics for commonly diagnosed diseases and new uses for traditional drugs;
- discuss the latest information regarding risks, benefits, and cost-effectiveness of new and traditional diagnostic tests; and
- discuss new information regarding how infectious diseases are transmitted and how such information can lead to the development of new therapies.

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