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Incisive Commentary and Clinical Abstracts on Current Issues in Infectious Diseases

ABSTRACT & COMMENTARY

Broad Spectrum Antibiotic Use in Infancy Sets Table for Early Childhood Obesity

Use of narrow spectrum antibiotics not associated with later obesity

By Philip R. Fischer, MD, DTM&H, and Roma Bhatia, BS,

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Ms. Bhatia is a medical student at the Mayo Clinic.

Dr. Fischer and Ms. Bhatia report no financial relationships in this field of study

SOURCE: Bailey LC, et al. Association of antibiotics in infancy with early childhood obesity. *JAMA Pediatr* published online September 29, 2014, doi:10.1001/jamapediatrics.2014.1539.

From 2001 to 2013, Bailey and colleagues studied 65,480 children in a primary care network affiliated with Children's Hospital of Pennsylvania that covered urban and suburban parts of Pennsylvania, New Jersey, and Delaware. Premature and small for gestational age babies were excluded from the study, as were infants who did not have follow up between 12-59 months and infants in whom BMI was unable to be assessed.

Medical records were analyzed and the use of antibacterial medications during the first two years of life was documented; antifungal and antiviral agents were not studied. Penicillin and amoxicillin were considered to be "narrow spectrum" agents while broad spectrum antibiotics consisted of other systemic antibacterial medications. Obesity was defined as a body mass index (BMI) of greater than the 95th percentile for age and sex. Potentially confounding factors were also evaluated, and careful multivariate analyses were undertaken.

Sixty-nine percent of children received antibiotic treat-

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ment during the first two years of life; 15% were obese at 4 years of age. Children were more likely to develop obesity during early childhood (24-59 months of age) if they received multiple courses of broad spectrum antibiotics (rate ratio, RR, 1.16 if four or more courses). Earlier broad-spectrum antibiotic use was also associated with more obesity (RR 1.11 for use at 0-5 months of age, 1.09 at 6-11 months). The use of narrow spectrum antibiotics (penicillin, amoxicillin) was not associated with later obesity.

Other factors such as male gender, Hispanic ethnicity, pubic insurance coverage, asthma, and steroid use were also significantly associated with development of obesity. The link between broad spectrum antibiotic use and obesity, however, was independent of these other factors.

COMMENTARY

Obesity is a problem of public health importance with 17% of US children and adolescents being overweight or obese.[1] In Bailey's large study described here, 69% of children received antibiotics during the first two years of life — an average of 2.3 antibiotic courses per child with 62% of children getting penicillin or amoxicillin at least once and 41% receiving a broad spectrum antibiotic at least once. It is likely that alterations in antibiotic use might decrease the risk of obesity.

During the first three years of life, the pattern of intestinal flora develops; by three years of age, the microbiome has assumed adult patterns.[2] The establishment of the microbiome is likely fragile as it evolves during the early years of life. The resulting microbiome then affects energy metabolism and growth.[3]

In mice, early antibiotic use alters the microbiome and leads to alterations in short-chain fatty acids and affects lipid and cholesterol metabolism.[4] In obese adults, antibiotic use alters the microbiome and changes insulin sensitivity.[5] Thus, antibiotics can alter the intestinal microbiome at any age, but alterations in early life seem particularly important.

However, the etiologic relationships between the microbiome and obesity are not completely clear. In obese adults, microbiome patterns are associated with increased energy harvest.[6] The new data provided by Bailey suggest that antibiotic-induced alterations in microbiome patterns at an early age might predispose to increased weight gain. Ten percent of Bailey's subjects were already obese by two years of age, and it could be that obesity itself predisposes to risky microbiomes.

Of course, there are also other pediatric health-related reasons for avoiding unnecessary use of microbiome-altering broad spectrum antibiotics. Antibiotic use in the first year of life has been associated with a 2.9 fold increase in the risk of developing inflammatory bowel disease,[7] and the risk appears to be twice that much when the antibiotics are effective against anaerobic organisms.[8]

As well noted by Bailey and colleagues, childhood obesity is multifactorial. Other illnesses and social factors contribute to obesity. Nonetheless, we now have clear data that practical interventions might moderate the risk of obesity — antibiotics should indeed be used judiciously during infancy, and narrower spectrum antibiotics should be used when broader coverage is not clearly necessary. ■

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Treating Latent Tuberculosis Infection: Is It Time to Retire Isoniazid?

By Richard R. Watkins, MD, MS, FACP

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Dr. Watkins reports no financial relationships in this field of study

SYNOPSIS: A meta-analysis that included 53 studies found treatment regimens for latent tuberculosis containing rifamycins had improved efficacy and lower toxicity compared to isoniazid.

SOURCE: Stagg HR, et al. Treatment of latent tuberculosis infection: A network meta-analysis. *Ann Intern Med* 2014;161: 419-428.

Latent tuberculosis infection (LTBI) is a common reason for referral to infectious disease specialists. For the past few decades the standard therapy in the United States has been isoniazid for 9 months. While generally safe and effective, many patients are unable or unwilling to comply with this lengthy regimen. Thus, it is necessary to offer effective and low toxic regimens for the shortest time available to optimize compliance rates. Stagg and colleagues aimed to provide an up-to-date recommendation based on randomized, controlled clinical trials for the relative efficacies and adverse event profiles of different LTBI treatment regimens.

The study was a meta-analysis of randomized, controlled clinical trials that used a network approach, which the authors stated is a better method than conventional meta-analyses because it allows indirect comparisons of regimens and produces better inferences of relative efficiency. The two main endpoints were hepatotoxicity and development of active TB. Regimens were grouped as follows: all rifampicin regimens; isoniazid regimens 3 to 4 months in duration, 6 months in duration, 9 months in duration, or 12 months or more in duration; isoniazid-rifampicin regimens 3 to 4 months in duration; all rifampicin plus pyrazinamide regimens; and all rifampicin-isoniazid-pyrazinamide regimens. The main adverse event of interest was hepatotoxicity of grade 3 or higher, but all types and severity of adverse events were recorded. The quality of the studies was determined by using the Cochrane Collaboration's tool for evaluating study bias.

Of 1,516 studies identified, 53 with 133,992 subjects met the inclusion criteria for the network meta-analysis. All of the tested regimens except isoniazid-rifampicin had a favorable odds ratio (OR) <1.0 compared to no treatment. Six regimens were efficacious compared to placebo: isoniazid for 6 months (OR 0.64; 95% confidence interval [CI], 0.48 to 0.83), isoniazid for 12 months or longer (OR 0.52; CI, 0.41 to 0.66), rifampicin for 3 to 4 months (OR 0.41; CI, 0.18 to 0.86), rifampicin-isoniazid for 3-4 months (OR 0.52; CI, 0.34 to 0.79), pyrazinamide-isoniazid-rifampicin (OR 0.34; CI, 0.18 to 0.62), and rifampin-pyrazinamide (OR 0.55; CI 0.33 to 0.92). The rifabutin-isoniazid regimen had a wide confidence that crossed 1, as did isoniazid for 9 months. Rifampicin-only and rifapentine-isoniazid regimens had lower rates of hepatotoxicity than isoniazid-only for 6 months or longer. Furthermore, rifampicin-isoniazid regimens had lower hepatotoxicity versus isoniazid-only therapy when the latter was given for 12 to 72 months. There was also good evidence that regimens containing pyrazinamide had higher rates of hepatotoxicity. Immunosuppression, HIV status and TB incidence did not affect the incidence of hepatotoxicity. Other serious adverse events were rare across all the studies. Rifampicin-pyrazinamide regimens had the highest risk for gastrointestinal adverse events, while rifampicin containing regimens had the highest risk for central nervous system adverse events. Five toxicity-related deaths were reported which were all due to severe hepatitis from isoniazid.

COMMENTARY

A large body of evidence has accumulated over the last few decades for treating LTBI. The present study critically analyzed these data and reported two main findings:

(1) 3 to 4 months of rifampicin monotherapy was

effective in preventing the development of active TB and had a low incidence of hepatotoxicity compared to isoniazid, and;
(2) pyrazinamide, while effective, has an unacceptably high risk-to-benefit ratio.

Thus, rifampicin seems to have the optimal balance of effectiveness and tolerability. While important, neither of the two results is novel or unexpected as previous studies have come to the same conclusions. Indeed, the clear benefits associated with rifampicin monotherapy raises the question of why 9 months of isoniazid therapy remains the standard of care for LTBI in North America. Compliance with this regimen is fair at best and isoniazid-associated hepatotoxicity, while rare, can be fatal. Shorter course therapy also has the potential advantage of using fewer health care resources and perhaps lowering costs. Further economic analyses comparing standard therapy (i.e. isoniazid) versus shorter course rifamycin therapy will help to clarify this issue. Moreover, results of an ongoing trial comparing the efficacy of 4 months of rifampicin to 9 months of isoniazid and another evaluating 3 months of self-administered isoniazid-rifapentine will add to the available evidence.
One frequent criticism of meta-analyses is that they can make comparisons between studies that are too dissimilar to be meaningful, e.g. apples to oranges. Indeed, it has been said that a meta-analysis is to an analysis what meta-physics is to physics. The interesting approach Stagg and colleagues took was to use mixed-treatment comparisons, also known as Bayesian network meta-analysis. This method allows for comparisons of different regimens when no trials directly compare them and provides an intelligent guess of the expected outcome if a trial was performed. Of course, such an estimate is not as high quality or authoritative as a direct trial. Given the multitude of studies on the treatment of LTBI, it is challenging for clinicians to compare the different treatment regimens. With the present study, Stagg and colleagues have brought considerable clarity to the issue.

Should the medical community retire isoniazid for 9 months as the standard therapy for LTBI? Based on current evidence the answer is "yes." It will be interesting to see if authorities like governmental and professional organizations switch their focus to short-course rifamycin-based regimens and author new clinical guidelines that reflect this shifting paradigm. ■

ID Grand Rounds — Stanford: Female, 52, with Fever and Progressive Weakness

By Joanna K. Nelson MD, Fellow, Division of Infectious Diseases, Stanford University

Dr. Nelson reports no financial relationships in this field of study

A 52-year-old woman with no significant past medical history presented to Stanford Hospital in July, 2014, with fever and progressive weakness. She had been in her usual state of health until the day prior to admission, when she began to feel fatigued with subjective fevers and "restless legs."

The following day, she had progressive lower extremity weakness such that by evening she was unable to get out of bed. On presentation to the Emergency Department, she complained, in addition to the symptoms noted above, of diffuse headache and mild neck stiffness of two days duration. She denied chills, rigors, nausea, vomiting, rash, diarrhea, dysuria, bowel or bladder incontinence, or paresthesias. Her past medical history was significant only for hyperlipidemia. She was not on any medications, and denied toxic ingestions. She lived in Fresno County, California, and had no significant travel history. She was an avid outdoors-woman, participating in golf, swimming, hiking, and running on a regular basis. She reported occasional interactions with mosquitos but no known bites. She had no other significant exposures.

PHYSICAL EXAM: On initial presentation, her temperature was 38.8 degrees Celsius, heart rate was 90 beats per minute, blood pressure was 132/86, respiratory rate was 16 breaths per minute, and oxygen saturation was 96% on room air. She was

a fatigued but nontoxic appearing female. She had shotty cervical lymphadenopathy, but no appreciable meningismus. Her neurologic exam was notable for markedly reduced lower extremity strength with 2/5 strength on right lower extremity and 1/5 on left lower extremity. Her sensation to touch was intact. Patellar reflexes were absent bilaterally. The remainder of her physical exam was normal.

LAB TESTS/CLINICAL MANAGEMENT:
Laboratory values revealed a normal WBC at 4.9/mm3, hemoglobin 11.3 gm/dl, platelets 178,000/mm3. Her serum creatinine was 0.8 mg/dL and liver function tests were within normal limits. Examination of cerebrospinal fluid (CSF) revealed 0 RBC, 323 WBC/mm3 (84% lymphs, 11% neutrophils, 5% mononuclear cells), glucose 80 mg/dL, and protein 84 mg/dL. CSF Gram stain examination was negative and bacterial culture showed no growth. MRI of the thoracic and lumbar spines showed focal signal abnormality from the conus to T7 vertebra suggestive of an inflammatory process. Electromyography showed decreased motor amplitudes with preserved sensory response and no significant denervation suggestive of central process such as myelitis.

Further workup revealed the following tests to be negative: serum HIV antibody, CSF cryptococcal antigen, serum and CSF Treponemal pallidum screen, CSF coccidioidomycosis immunodiffusion, and CSF HSV PCR. Serum West Nile virus IgM antibody by EIA was positive at 1.26 (normal <0.89), IgG was negative. CSF West Nile virus IgM was inconclusive.

The patient was diagnosed with acute flaccid paralysis secondary to West Nile virus. She was treated with supportive care in addition to administration of intravenous immunoglobulin (IVIG) at a dose of 500 mg/kg IV daily for 4 days. Her weakness remained stable throughout her hospital stay, and she was ultimately discharged to a rehabilitation facility.

DISCUSSION

West Nile virus is a flavivirus transmitted by Culex mosquitoes. It is the most frequently identified arboviral disease in the United States. Most cases occur during the months of August and September. The majority of patients are asymptomatic when infected, but 20-40% will go on to develop symptoms, usually manifested as a flu-like syndrome. Less than 1% will develop more serious neuroinvasive disease, which can manifest as meningitis, encephalitis, flaccid paralysis or any combination of these three entities.[1]

Acute flaccid paralysis occurs due to selective damage of anterior horn cells. The paralysis usually progresses quickly and plateaus within hours.[1] Unlike Guillain-Barré syndrome, in West Nile poliomyelitis-like illness there is generally minimal to no sensory loss.[2] There is minimal data regarding the long term outcome of WNV poliomyelitis-like illness; however, follow up of patients involved in a previous outbreak suggest that about one third have complete recovery, one third have partial recovery, and one third have no improvement.[3]

Treatment largely consists of supportive care. There are case reports and case series describing improved outcomes in some patients after the administration of IVIG.[4,5] IVIG has been shown in mouse models of neuroinvasive West Nile virus to be beneficial if administered early in the course.[6] In addition, there are case reports of clinical improvement in immunocompromised patients after IVIG administration.[7] Overall, more rigorous controlled trials are needed to draw any conclusions on the benefits of any adjunctive therapies.

DIAGNOSIS: West Nile virus infection with flaccid paralysis.

ACKNOWLEDGEMENTS: Dr. Brian Blackburn and Dr. Gina Suh also participated in the care of this patient. ■

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Dalbavancin — Formulary Considerations

By Emily Mui, PharmD, Stanford University

Dr. Mui reports no financial relationships in this field of study.

Dalbavancin is a lipoglycopeptide antibiotic for intravenous administration with activity against Gram-positive organisms, including methicillin resistant *Staphylococcus aureus* that is distinguished by its extraordinarily long serum half-life that allows once weekly dosing.

GENERIC NAME: Dalbavancin

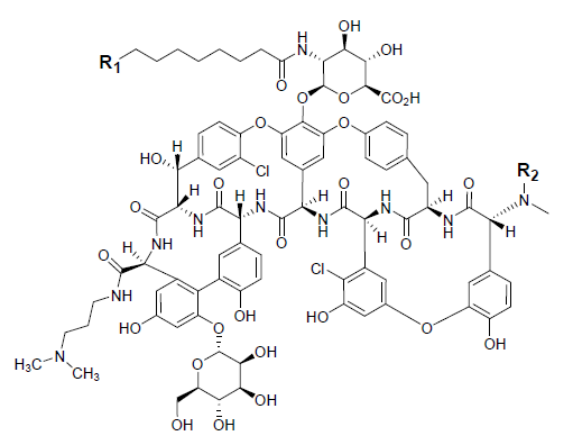
TRADE NAME IN U.S. Dalvance™

U.S. FDA APPROVAL DATE: May 23, 2014

SIMILAR APPROVED DRUGS: Televancin, like dalbavancin, is a lipoglycopeptide. Both are related to the glycopeptide antibiotic, vancomycin.

U.S. FDA- APPROVED INDICATIONS
Treatment of adult patients with acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible isolates of the following gram-positive microorganisms: *Staphylococcus aureus* (including methicillin-susceptible and methicillin-resistant strains), *Streptococcus pyogenes*, *Streptococcus agalactiae* and *Streptococcus anginosus* group (including *S. anginosus*, *S. intermedius*, *S. constellatus*).

STRUCTURE AND PHARMACOLOGY



The presence of the long fatty acid chain correlates with an extended serum half-life and, by interacting with the lipid cell membrane, improves antibacterial activity. The 3-3-dimethylaminopropyl amide substituent also enhances antibacterial activity.

This lipoglycopeptide, like vancomycin, interferes with cell wall synthesis by binding to the D-alanyl-D alanine terminus of the stem pentapeptide in nascent cell wall peptidoglycan, thus preventing cross-linking. Dalbavancin is bactericidal in vitro against *S. aureus* and *S. pyogenes* at clinically relevant concentrations. It is active in vitro against vancomycin-intermediate *S. aureus* (VISA), but not against vancomycin-resistant *S. aureus* nor against vancomycin-resistant Enterococcus faecium (VRE) caused by vanA. It does have activity against the much less common VRE carrying vanB.

The antibacterial activity of dalbavancin is concentration-dependent with AUC/MIC being the optimal correlate.

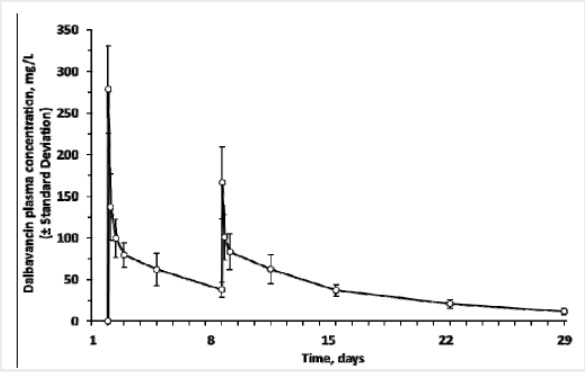
PHARMACOKINETICS
Pharmacokinetic parameters following a single 1,000mg intravenous dose of dalbavancin:

Parameter	Single 1,000mg dose
Cmax (mg/L)	287 (13.9)
AUC 0-24 (mgxh/L)	3,185 (12.8)
AUC 0-day7	11,160 (41.1)
AUC 0-inf	23,443 (40.9)
Terminal t ½ (h)	346 (16.5)
CL (L/h)	0.0513 (46.8)

Dalbavancin AUC 0-24h and Cmax both increase proportionally to dose following single IV dalbavancin doses ranging from 140mg to 1500mg, indicating linear pharmacokinetics. No apparent accumulation of dalbavancin was observed following multiple IV infusions administered once weekly for up to 8 weeks with 1000mg on Day 1, followed by up to seven weekly 700mg doses in healthy adults with normal renal function (*see table on top of next page*).

DISTRIBUTION: Reversibly bound to plasma protein (~93%) with a volume of distribution reported to be 9.75 – 15.7 L in adults.

METABOLISM: Not a substrate, inhibitor or inducer of CYP450 isoenzyme. Minor metabolite of dalbavancin (hydroxyl-dalbavancin) has been observed in the urine of healthy subjects, but not in human plasma.



EXCRETION:
• 20% excreted in feces through 70 days post dose
• 33% excreted in urine as unchanged dalbavancin through 42 days post dose
• 12% excreted in urine as metabolite through 42 days post dose

RENAL IMPAIRMENT:
• The pharmacokinetics of dalbavancin were evaluated in 28 subjects with varying degrees of renal impairment and in 15 matched control subjects with normal renal function. Following a single dose of 500mg or 1000mg dalbavancin, the mean plasma clearance was reduced 11%, 35%, and 47% in subjects with mild (CrCL 50-79mL/min), moderate (30-49 mL/min), and severe (<30mL/min) renal function. No dosage adjustment necessary for patients with CrCL > 30 ML/min or patients receiving hemodialysis. The recommended 2-dose regimen for dalbavancin in patients with severe renal impairment who are not receiving regularly scheduled hemodialysis 750mg followed by one week later 375mg.
• Dalbavancin PK parameters in subjects with end-stage renal disease receiving regularly scheduled hemodialysis (3x/week) are similar to those observed in subjects with mild to moderate renal impairment. Less than 6% of an administered dose is removed after three hours of hemodialysis, thus no dosage adjustment is recommended of patients receiving regularly schedule hemodialysis, and dalbavancin may be administered without regards to timing of hemodialysis.

HEPATIC IMPAIRMENT:
• The PK of dalbavancin were evaluated in 17 subjects with mild, moderate, severe hepatic impairment (Child-Pugh class A, B or C) and compared to those with nine matched healthy subjects with normal hepatic function. The mean AUC was unchanged in subjects with mild hepatic impairment compared to subjects with normal hepatic function; however the mean AUC 0-336 hours decreased 28% and 31% in subjects with moderate and severe hepatic impairment respectively, compared to those with normal hepatic function. The manufacturers do not recommend a dosage adjustment for mild hepatic impairment, but caution should be exercised when prescribing dalbavancin in patients with moderate and severe haptic function.

CLINICAL TRIALS/EVIDENCE SUMMARY
In both DISCOVER 1 and 2, patients with ABSSI were randomized to receive 2 intravenous doses of dalbavancin (1000 mg on day 1 and 500 mg on day 8) or to receive vancomycin 1000 mg or 15 mg/kg every 12 hours with an option to switch to orally administered linezolid after 3 days. The primary endpoint in each trial was the cessation of increase in size of the lesion at 48-72 hours and absence of fever. In DISCOVER 1, this endpoint was achieved in 83.3% of dalbavancin and 81.8% of vancomycin/linezolid recipient. In DISCOVER 2, the primary endpoint was achieved in 76.8% of dalbavancin and 78.3% of vancomycin/linezolid patients.

See Clinical Response Rates in ABSSSI Trials at 48-72 hours after initiation of therapy in table below.

	Dalbavancin	Vancomycin + Linezolid	Difference (95% CI)
DISCOVER 1	240/288 (83.9%)	233/285 (81.8%)	1.5% (-4.6, 7.9)
DISCOVER 2	285/371 (76.8%)	288/268 (78.3%)	-1.5% (-7.6, 4.6)

See secondary endpoints in these two ABSSSI trials evaluated the percentage of ITT patients achieving a 20% or greater reduction in lesion area from baseline at 48-72 hours after initiation of therapy in table below.

	Dalbavancin	Vancomycin + Linezolid	Difference (95% CI)
DISCOVER 1	259/288 (89.9%)	259/285 (90.5%)	-1.0% (-5.7, 4.0)
DISCOVER 2	325/371 (87.6%)	316/368(85.9%)	1.7 (-3.2, 6.7)

Secondary endpoint evaluated the clinical success rate at follow-up visit occurring between day 26–30. Clinical success at this visit was defined as having a decrease in lesion size (both length and width measurement), temperature of 37.6 C or lower, meeting pre-specified criteria for local signs: purulent discharge and drainage absent or mild and improved from baseline, heat/warmth & fluctuating absent, swelling/induration & tenderness to palpitation absent or mild.

	Dalvance	Vancomycin/Linezolid (n/N) (%)	Difference (95% CI)
DISCOVER 1			
ITT	241/288 (83.7%)	251/285 (88.1%)	-4.4% (-10.1, 1.4)
CE	212/226(93.8%)	220/229 (96.1%)	-2.3% (-6.6, 2.0)
DISCOVER 2			
ITT	327/371 (88.1%)	311/368 (84.5%)	3.6% (-1.3, 8.7)
CE	283/294 (96.3%)	257/272 (94.5%)	1.8%, (-1.8, 5.6)

ADVERSE EFFECTS: Serious adverse reactions occurred in 109/1778 (6.1%) of patients treated with dalbavancin and 80/1224 (6.5%) of patients treated with comparator. Dalbavancin was discontinued in 53/1778 (3%) patients and the comparator was discontinued due to an adverse reaction in 35/1224 (2.8%) patients.

	Dalbavancin (n=1778)	Comparator (n=1224)
Nausea	98 (5.5)	78 (6.4)
Vomiting	50 (2.8)	37 (3)
Diarrhea	79 (4.4)	72 (5.9)
Headache	83 (4.7)	59 (4.8)
Rash	48 (2.7)	30 (2.4)
Pruritus	38 (2.1)	41 (3.3)

The following selected adverse reactions were reported in dalbavancin patients at a rate of <2% in clinical trials:
• Blood and lymphatic system disorders: anemia, hemorrhagic anemia, leucopenia, neutropenia, thrombocytopenia, petechiae, eosinophilia, thrombocytosis
• Gastrointestinal disorders: GI hemorrhage, melena, hematochezia, abdominal pain
• Infusion related reactions
• Hepatobiliary disorders: Hepatotoxicity, hepatic transaminase increase, blood alkaline phosphatase increased, INR increased.
• Among patients with normal baseline ALT levels, more dalbavancin than comparator-treated patients had post-baseline ALT elevations greater than 3 times the upper limit of normal (ULN), 12 (0.8%) vs 2 (0.2%), respectively including three subjects with post-baseline ALT values greater than 10 times ULN.
• 8/12 patients related with dalbavancin and one comparator patient had underlying conditions which could affect liver enzymes, including chronic viral hepatitis and a history of alcohol abuse.
• One dalbavancin treated patient in a phase 1 trial had post-baseline ALT elevations greater than 20 times ULN.
• ALT elevations were reversible in all subjects.
• No comparator-treated subject with normal baseline transaminase had post-baseline ALT elevations greater than 10 times ULN
• Anaphylacotid reactions
• Clostridium difficile, oral candidiasis, vulvovaginal mycotic infection
• Vascular disorders: flushing, phlebitis, wound hemorrhage, spontaneous hematoma

CONTRAINDICATIONS/WARNINGS/PRECAUTIONS:
• Contraindicated in patients with known hypersensitivity to dalbavancin. No data available on cross-reactivity between dalbavancin and other glycopeptides, including vancomycin.
• Infusion related reactions- dalbavancin must be infused over 30 minutes to minimize risk of infusion-related reactions. Rapid infusion can cause reactions that resemble "Red-Man Syndrome", including flushing of upper body, urticarial, pruritus, and/or rash. Stopping or slowing the infusion may result in cessation of these reactions.
• In phase 2/3 trials, more dalbavancin treated subjects than comparator-treated subjects with normal baseline transaminase levels had post-baseline ALT elevations greater than 3 times the upper limit of normal. Overall, the abnormal LFT tests were reported with similar frequency in the dalbavancin and comparator arms.

USE IN SPECIAL POPULATIONS
• Pregnancy – category C
• There is a lack of well-controlled studies with

dalbavancin in pregnant women. In rat and rabbit studies, there was no evidence of embryo or fetal toxicity found at doses of 15mg/kg/day (1.2 and 0.7 times the human dose based on exposure, respectively). Delayed fetal maturation was seen in rats at doses of 45mg/kg/day (3.5 times the human dose based on exposure).

• Nursing mothers – dalbavancin is excreted in the milk of lactating rats, however it is unknown whether or not dalbavancin or its metabolite is excreted in human milk.

• Pediatric use –safety and efficacy not established

DRUG INTERACTIONS

• No clinical drug-drug interaction studies have been conducted with Dalbavancin. There is minimal potential for drug-drug interaction between dalbavancin and cytochrome P450 substrates, inhibitors, or inducers.

• No known food-drug interactions

DOSAGE AND ADMINISTRATION

CrCL >30 mL/min:	1000mg followed one week later by 500mg
CrCL <30 mL/min:	750mg followed one week later by 375mg
Hemodialysis:	No dose adjustment

COST

Agent	Unit	AWP Cost per Unit	Cost per Day	Cost per week	Cost per month
Vancomycin	1g vial	$4.41	$8.82	$61.74	$246.96
	1g Frozen Bag	$27.64	$55.28	$386.96	$1,547.84
Ceftaroline	600mg vial	$75.81	$151.62	$1,061.34	$4,245.36
Linezolid	600mg IV solution	$167.35	$334.70	$2,342.90	$9,371.60
	600mg tablet	$162.69	$325.38	$2,277.66	$9,110.64
Daptomycin	500mg vial	$425.66	$425.66	$2,979.62	$11,918.48
Dalbavancin	500mg vial	$1,490.00	-	$2,980.00	$7,450.00
Tedizolid	200mg vial	$282.00	$282.00	$1,974.00	$7,896.00
	200mg tablet	$354	$354	$2,478.00	$9,912.00

CONCLUSIONS

Dalbavancin is a new once weekly antimicrobial FDA for the treatment of adult patients with acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible isolates of the following gram-positive microorganisms: *Staphylococcus aureus* (including methicillin-susceptible and methicillin-resistant strains), *Streptococcus pyogenes*, *Streptococcus agalactiae* and *Streptococcus anginosus* group (including *S. anginosus*, *S. intermedius*, *S. constellatus*). Dalbavancin appears to be well tolerated, although patients in clinical trials of serious skin infections have been shown to develop serum aminotransferase elevations while on therapy. The acquisition cost of Dalbavancin is considerably more expensive than other broad-spectrum gram-positive agents; however its once weekly administration may offer savings of resources in the outpatient setting. ■

REFERENCES

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2. Zhanel GG, Calic D, Schweizer F et al. New Lipoglycopeptides A comparative review of dalbavancin, Ortivancin and Telavancin. *Drugs* 2010; 70 (7): 859-886
3. Boucher HW, Wilcox M, Talbot GH, et al. Once-Weekly Dalbavancin versus Daily Conventional Therapy for Skin Infection. *N Engl J Med* 2014;370:2169-79.

Infectious Disease [ALERT]

Updates

By Carol A. Kemper, MD, FACP

Failure of treatment: *M. genitalium* and macrolides

Declining rates of response to standard treatment for non-gonococcal urethritis (NGU) may prompt changes in accepted treatment strategies. Current

Salado Rasmussen K, et al. Mycoplasma genitalium testing pattern and macrolide resistance: A Danish Nationwide retrospective survey. *CID* 2014;59:24-30.

Manhart, LE. Diagnostic and resistance testing for Mycoplasma genitalium: What will it take? *CID* July 2014; 59:31-32.

guidelines recommend the use of either single dose azithromycin 1 gram or doxycycline 100 mg twice daily x 7 days for patients with NGU, as defined by mucupurulent or purulent urethral discharge or a urethral swab with > 5 white blood cells per HPF in the absence of gonorrhea; or a positive nucleic acid amplification test (NAAT) for *Chlamydia trachomatis* (CT), *Mycoplasma genitalium* (MG), *Ureaplasma urealyticum* biovar 2 (UU) or *Trichomanas vaginalis* (TV). However, rates of response to these standard first-line regimens are declining, especially those infections due to *M. genitalium*. Response rates to single dose azithromycin in 3 recent U.S. studies ranged from a high of 77% in New Orleans to as low as 40% in Seattle. While there remains a significant debate regarding the potential of *Mycoplasma genitalium* to cause symptomatic infection in both men and women, it is apparent that current treatment protocols do not adequately cover this organism and that many failures of treatment for symptomatic urethritis are likely due to *M. genitalium*. Doxycycline is also now widely ineffective against this organism.

Unlike the United States, testing for *M. genitalium* has been performed on a routine basis in Denmark since 2003, allowing a retrospective epidemiologic analysis and survey of resistance patterns. From 2006 to 2010, a total of 31, 600 specimens from 28,958 persons were submitted for testing for *M. genitalium* by PCR. The number of positive specimens increased from 3858 in 2006 to 7,361 in 2010 — with an observed increase of 2.4% to 3.8% in women, and an increase of 7.9% to 10.3% in men during this period.

More than half of the specimens were submitted by general practitioners, with positive results in 5.7% of specimens, and 40% of the patients were men. In contrast, gynecologists submitted one-third of the specimens, most of whom were women, and rates of infection were lower at 2.0%. STD clinics tested 11% of the patients, with 10.4% being positive.

Beginning in 2007, specimens were tested for macrolide resistance using a rapid pyrosequence assay testing for mutations in the 23S rRNA gene. Macrolide resistance was detected in 38% of specimens — but was highest in patients being seen at STD clinics (43%). It is anticipated that newer CDC STD guidelines will provide, for the first time, recommendations on testing for *M. genitalium* — although many of the commercially available tests have not yet been approved by the FDA, and resistance testing is not incorporated.

PET-CT for fever of unknown origin

Gafter-Gvili A, et al. FDG-PET/CT for the diagnosis of patients with fever of unknown origin. *QJM* September 9th, 2014. Advance Access.

FUO remains often — by definition — a puzzle. While I love a good puzzle as much as the next ID doc, I especially enjoy one I can solve. When discussing the work up with patients and their families, I often liken it to peeling an onion — take away one layer, and then another, until the problem is finally revealed. But the process can be frustrating and stressful for patients and their families, with prolonged work ups and multiple studies. Now, consider adding one more study for use in the work up of FUO. PET/CT scanning may help to target and characterize an area of inflammation, infection, or malignancy.
These authors performed a 4-year retrospective analysis of the utility of FDG — PET/CT scanning in patients hospitalized for the evaluation of FUO at the Rabin Medical Center in Tel Aviv. From 2008 to 2012, PET/CT scan was performed in 112 adults (> 18 years of age) with FUO. FUO was defined as fever lasting 3 or more weeks without a diagnosis following a minimum one-week work up (either inpatient or outpatient). Patients with HIV infection and neutropenia were excluded from study. All of the patients underwent a standard battery of tests, including cell counts, chemistries, sed rates, blood cultures and various serologies, but specific studies, including CT scans, MRIs, echocardiograms, etc. were at the discretion of the treating physicians.

PET/CT scans were considered positive when they led to the confirmation or localization of a disease process, either by culture or pathology. A negative study was defined as one in which no disease process was identified, and the fever resolved without a diagnosis, and the patient remained well for the next 6 months of follow up.

Nearly three-fourths (74%) of the patients received a final diagnosis, which included infection (43%), non-infectious inflammatory disease (16%), malignancy (14%) or other (2%). FUO resolved in 20% of patients without a diagnosis and the patients remained afebrile for 6 months of follow-up. Six patients (5%) died with fever and no diagnosis.

PET Scans in 69 patients were abnormal — and were useful in helping to solve the diagnosis in 52 patients (true-positives). Abnormal scans in the remaining 17 patients were considered falsely-positive, either because no disease was identified and

the fever resolved with no sequelae for the next 6 months; or because an alternate diagnosis was made, and the scan proved non-contributory. PET scans were negative in 43 of the cases. Based on these findings, the sensitivity of PET scanning in the work up of FUO was 72% and specificity was 57%. Overall, PET scanning was felt to be useful in 66% of cases. Of those scans that were true-positives, 31 infections were diagnosed (60%), including pneumonia (in 7 cases), endovascular infections, including infections of aortic graft material, femoral graft material, endocarditis, infected pacemakers x 2, infected stents x 2); but also included hepatic abscess, septic arthritis, occult osteomyelitis, occult pyelonephritis, epidural abscess, as well as one case each of CMV colitis, TB and nocardia. Fourteen of the true-positive PET scans led to diagnosis of malignancy (meaning that PETs were useful in diagnosing 14 of 15 cases of malignancy), including 9 cases of lymphoma, 2 cases of non-Hodgkin's lymphoma, 2 cases of lung cancer, and a sarcoma. Nine of these cases presented an initial diagnosis of malignancy, and six were relapses of an earlier malignancy.

Twenty-three scans were considered true negatives — but 6 cases were eventually diagnosed with infections based on other means, including three cases of Q fever, 2 cases of mononucleosis, and one case of urosepsis — but the scans were considered true negatives because PET scanning would not be considered useful in these conditions.

While these results are limited to patients hospitalized for FUO, and only retrospective in design, this is the largest collection of FUO patients studied to date. These data are consistent with other studies of PET scanning as a diagnostic tool — although the authors believe that FDG PET/CT may be more useful than PET alone — and the addition of FDG contrast may provide even better results. When considering the next step in your FUO work up, it is best to keep in mind that PET scanning remains inherently limited by the anatomic nature of its results — and is therefore not useful in certain infections, like those based on serologic results, or inflammatory disorders, such as vasculitis. But I can immediately see the utility, especially in patients with occult graft infection, where nuclear studies have been negative. ■

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CME QUESTIONS

1. Which of the following is correct?

A. The risk of obesity prior to 60 months of age was increased in children who had received multiple courses of broad spectrum antibiotics in infancy.

B. Receipt of penicillin in infancy was not associated with an increased risk of obesity.

C. Receipt of amoxicillin in infancy was not associated with an increased risk of obesity.

D. All of the above.

2. Which of the following is correct with regard to the treatment of latent tuberculosis?

A. Rifampin monotherapy for 3-4 months is effective in prevention of active tuberculosis.

B. Rifampin monotherapy for 3-4 months has an unacceptably high rate of hepatotoxicity.

C. Pyrazinamide has the lowest rate of toxicity among the drugs analyzed.

D. Compared to rifampin, isoniazid has a lower rate of hepatotoxicity.

3. Which of the following is correct?

A. West Nile virus is transmitted by Aedes mosquitoes.

B. West Nile virus may cause a polio-like syndrome as a result of infection of anterior horn cells.

C. West Nile virus infection always causes symptomatic central nervous system disease.

D. Sensory loss is commonly seen in patients with central nervous system infection due to West Nile Virus.

TIPPING POINT

"I've thought often about it. I wish we had put a [CDC response] team like this on the ground the day the [index Ebola] patient was diagnosed. That might have prevented [the nurse's] infection, but we will do that from this day onward." CDC Chief **Tom Frieden,** 10/14/14

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 latent 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