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Infectious Disease [ALERT]

Incisive Commentary and Clinical Abstracts on Current Issues in Infectious Diseases

ABSTRACT & COMMENTARY

Combination Therapy With Daptomycin Plus Beta-Lactam Antibiotics in MSSA Bacteremia

By Dean L. Winslow, MD, FACP, FIDSA, FPIDS

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

SYNOPSIS: In a retrospective cohort study of 350 patients, the combination of a beta-lactam antibiotic plus daptomycin was not superior to beta-lactam monotherapy in patients with bacteremia due to methicillin-susceptible *Staphylococcus aureus*.

SOURCE: Grillo S, Cuervo G, Carratala J, et al. Impact of β-lactam and daptomycin combination therapy on clinical outcomes in methicillin-susceptible *Staphylococcus aureus* bacteremia: A propensity score-matched analysis. *Clin Infect Dis* 2019;69:1480-1488.

Researchers at a university hospital in Spain conducted a retrospective cohort study of 514 patients with methicillin-susceptible *Staphylococcus aureus* (MSSA) bacteremia. After excluding 164 patients who died in the first 48 hours in the hospital or who were treated with antibiotic combinations other than beta-lactam/daptomycin, 350 patients were evaluable. Investigators performed a 1:2 matched propensity score analysis and analyzed the data using Cox regression analysis. One hundred thirty-six patients received a beta-lactam antibiotic plus daptomycin and 214 patients received beta-lactam monotherapy. Patients who received beta-lactam plus daptomycin therapy had higher Pitt scores (a prognostic score) and persistent bacteremia more often than beta-lactam monotherapy patients. In the raw analysis, the researchers found no differences in mortality rates between the two groups. After propensity score matching,

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investigators identified no significant differences between the beta-lactam/daptomycin (110 patients) and beta-lactam monotherapy (168 patients) groups for all-cause mortality rates at seven days (8.18% vs. 7.74%; P = 1.000), 30 days (17.3% vs. 16.1%; P = .922), and 90 days (22.7% vs. 23.2%; P = 1.000). This was true even in a subanalysis of patients who had a high-risk infection source and in a subgroup excluding vascular catheter-related bacteremia.

[While infection due to methicillin-resistant *S. aureus* gets a lot more attention, morbidity and mortality from infection due to MSSA remains very high despite treatment with antibiotics.]

■ COMMENTARY

While infection due to methicillin-resistant *S. aureus* (MRSA) gets a lot more attention, morbidity and mortality from infection due to MSSA remains very high despite treatment with various antibiotics with potent in vitro activity against MSSA. Over the years, we have tried many different antibiotic combinations to improve outcomes in MSSA bacteremia (including endocarditis). It was quite popular in the 1970s and 1980s to treat MSSA bacteremia with a beta-lactam antibiotic plus aminoglycoside. This seemed to make sense, since cell wall active antibiotics and aminoglycosides often demonstrate in vitro bactericidal synergy. Although studies showed that beta-lactam/aminoglycoside combination treatment caused more rapid clearance of bacteremia, this was at the cost of significant nephrotoxicity, and it did not reduce mortality.[1]

It was also popular for many years to treat *S. aureus* bacteremia with a beta-lactam plus rifampin based on the observation that beta-lactam/rifampin combinations often appeared synergistic in "checkerboard" studies where only minimum inhibitory concentrations (MICs) (not minimum bactericidal concentrations [MBCs]) were examined. However, rifampin not only has numerous problematic interactions with other drugs, but it actually antagonizes the bactericidal action of cell wall active antibiotics in vitro, delays clearance of bacteremia, and may even increase mortality in Staph. bacteremia.[2]

I remember being excited by reading a paper published in 2011 that showed that daptomycin in combination with ceftaroline (and possibly other beta-lactam antibiotics) often was effective salvage therapy in MRSA bacteremia.[3] Because beta-lactams and daptomycin exert their bactericidal effects against *S. aureus* by different mechanisms of action, it was reasonable to examine beta-lactam plus daptomycin in MSSA bacteremia. My simplistic explanation of why MSSA remains so difficult to treat (despite antibiotics with excellent in vitro activity) is that it is an incredibly virulent pathogen, as evidenced by its tissue invasiveness and propensity to cause metastatic infection, even in healthy hosts. ■

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ABSTRACT & COMMENTARY

Colonization With *Clostridioides difficile* Frequently Leads to a Misdiagnosis of Healthcare-Associated Infection

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

SYNOPSIS: A prospective cohort study from a single institution found 27% of patients diagnosed with healthcare-associated *C. difficile* infection were colonized with the same isolate on admission.

SOURCE: Gonzalez-Orta M, Saldana C, Ng-Wong Y, et al. Are many patients diagnosed with healthcare-associated *Clostridioides difficile* infections colonized with the infecting strain on admission? *Clin Infect Dis* 2019;69:1801-1804.

The diagnosis of *Clostridioides difficile* infection (CDI) has important consequences for both patients and healthcare institutions. Emerging evidence suggests many cases of CDI currently classified as healthcare-associated are actually colonized with *C. difficile* on admission. However, previous studies have not used molecular typing to compare relatedness between admission and infecting strains. Therefore, Gonzalez-Orta and colleagues used whole-genome sequencing (WGS) analysis to compare strains of *C. difficile* taken on admission to those from patients diagnosed with CDI.

The study was conducted at the Veterans Administration Medical Center in Cleveland. Inclusion criteria were an anticipated length of stay of at least two days, no diagnosis of CDI in the preceding eight months, and no diarrhea at the time of enrollment. Patients who consented had perirectal swabs collected at the time of admission, which were plated on selective media. Stools that tested positive for *C. difficile* toxin genes by polymerase chain reaction (PCR) were collected from the microbiology laboratory and then cultured for toxigenic *C. difficile* using a sensitive broth enrichment method. An enzyme immunoassay (EIA) for toxin also was performed. The researchers defined healthcare-associated CDI as the presence of diarrhea (three or more unformed stools in 24 hours) and a positive PCR assay. For patients who had positive perirectal cultures on admission and a diagnosis of CDI, WGS was performed to ascertain the relatedness of the admission and CDI isolates. The investigators recognized the possibility that colonized patients might have been diagnosed with CDI even if they developed diarrhea from noninfectious causes, so they reviewed the medical records to find out if there were other explanations for the diarrhea.

[The investigators recognized the possibility that colonized patients might have been diagnosed with *Clostridioides difficile* infection even if they developed diarrhea from noninfectious causes.]

There were 480 patients who enrolled in the study. Of these, 68 (14%) had a positive perirectal swab for toxigenic *C. difficile* on admission, of which 25 (37%) were detected by the broth enrichment method. During the follow-up period, eight of the 68 (12%) with positive admission rectal swab cultures were diagnosed with CDI, compared to five of 412 (1%) with negative admission cultures (P = 0.0001). Of the eight positive patients, six met the investigational criteria for healthcare-associated CDI (HA-CDI). Three out of the 11 episodes (27%) of HA-CDI occurred in patients who had a positive admission perirectal swab culture for a genetically related strain. Furthermore, four of the eight patients diagnosed with CDI who had a positive admission perirectal swab culture also had a positive EIA for stool toxin.

■ COMMENTARY

This is an interesting, although small, study that found a significant proportion (27%) of patients diagnosed with CDI were colonized with the infecting strain on admission. Thus, standard infection control practices (e.g., contact isolation) will not be effective in reducing infections in these patients. This supports the notion that better CDI testing stewardship is needed so that patients with colonization are not falsely diagnosed as having HA-CDI, which carries important ramifications for both the patient and healthcare institutions. For example, patients may receive unnecessary treatment for an infection they do not have, and the diagnosis of CDI will become a permanent part of their medical record, while the healthcare institution suffers due to a publicly reported inaccurate quality measure. Moreover, the study by Gonzalez-Orta and colleagues reminds clinicians that not all nosocomial diarrhea is due to CDI, and providers should carefully consider other potential etiologies (e.g., medications, including antidepressants, antihypertensives, antibiotics, and stool softeners; enteral feedings; and underlying illness).[1]

The study has some limitations. First, the number of CDI cases was small. Second, the study was conducted at a single institution with a population that was primarily male (95%), had a high rate of hospitalization in the preceding year (44%), and had a high frequency of recent antibiotic use (63%). These characteristics limit the generalizability of the findings to other settings and patient populations. Third, because only one *C. difficile* isolate was cultured from each perirectal swab, it is possible that additional patients carried the same admission and CDI strains. Similarly, the possibility exists that the infecting strain was present on admission but not detected at that time. Finally, the authors did not provide details about how they ascertained whether a patient with *C. difficile* colonization had true CDI.

Another take-home point from the study is that it reinforces the usefulness of WGS in helping to solve contemporary clinical dilemmas. Further applications of WGS undoubtedly will be found that will aid in antibiotic stewardship and infection-control efforts. A recent report of WGS used in a cluster of linezolid- and vancomycin-resistant enterococcal infections in transplant recipients when standard microbiology practices proved unreliable highlights the usefulness of this emerging technology.[2] ■

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ABSTRACT & COMMENTARY

Uninfected Children Exposed Prenatally to HIV Exhibit Language Delays

By Micaela A. Witte and Philip R. Fischer, MD, DTM&H

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Ms. Witte and Dr. Fischer report no financial relationships relevant to this field of study.

SYNOPSIS: In South Africa, uninfected children exposed to human immunodeficiency virus (HIV) exhibit delays in receptive and expressive language at 24 months compared to non-HIV-exposed children.

SOURCE: Wedderburn CJ, Yeung S, Rehman AM, et al. Neurodevelopment of HIV-exposed uninfected children in South Africa: Outcomes from an observational birth cohort study. *Lancet Child Adolesc Health* 2019;3:803-813.

Each year, 1.4 million children are born to mothers infected with HIV. Fortunately, because of the use of antiretroviral therapy (ART), many of these children are not infected, creating an entirely new worldwide population of 14.8 million children exposed to but uninfected by HIV. Although previous research has shown that infected children born to HIV-infected mothers show signs

of developmental delay, few studies have examined uninfected children exposed to HIV.

Thus, Wedderburn and colleagues studied 248 uninfected children born to HIV-infected mothers and compared them with 895 children born to HIV-uninfected mothers in South Africa to determine whether these children showed signs of developmental delay. Mothers were consented at 20-28 weeks gestation and followed throughout their pregnancies. HIV-infected mothers were treated with ART from the time of their diagnosis. After birth, the children born to HIV-infected mothers were started on ART, and all children were tested for HIV infection at six-month increments. At six months, a subset of 260 children (61 born to infected mothers and 199 born to uninfected mothers) were tested with the culturally appropriate and well-validated Bayley Scales of Infant and Toddler Development, third edition (BSID-III). At 24 months, 732 of the children (168 born to infected mothers and 564 born to uninfected mothers) were tested again with the BSID-III.

At six months, there was no significant difference between the children born to infected mothers and the children born to uninfected mothers in any of the BSID-III subscales. However, at 24 months, the children born to infected mothers showed significantly lower receptive language and expressive language sub-scores compared to the children born to uninfected mothers after adjusting for potential confounding variables (i.e., maternal age, maternal education, maternal depression, maternal tobacco exposure, gestational age, breastfeeding). Specifically, 14% of children born to infected mothers showed signs of receptive language delay compared to only 7% of children born to uninfected mothers. Similarly, 11% of children born to infected mothers displayed signs of expressive language delay compared to only 6% of children born to uninfected mothers. There were no significant differences in the cognition, gross motor, and fine motor sub-scores.

In addition, an exploratory analysis showed that children born to infected mothers with a CD4 cell count of 500 cells per µL or less had lower receptive and expressive language scores than children born to uninfected mothers. There was no significant difference in these sub-scores between children born to infected mothers with a CD4 cell count greater than 500 cells per µL and children born to uninfected mothers.

In summary, the team in South Africa found that HIV/ART exposure was predictive of receptive and expressive language delay at 24 months. This delay also was associated with an infected mother's CD4 cell count of 500 cells per µL or less.

■ COMMENTARY

In 1994, Connor and colleagues found that treating HIV-infected pregnant women with ART reduced the risk of HIV transmission to their children.[1] Since that time, the use of ART has expanded greatly, with 76% of HIV-infected mothers in middle- and low-income countries receiving ART in 2016. Largely because of this pronounced ART use, maternal to infant transmission of HIV has fallen to less than 5% in these countries.[2]

[The effectiveness of antiretroviral therapy in the prevention of HIV transmission has created a growing population of HIV-exposed, uninfected children who have yet to be truly evaluated.]

The effectiveness of ART in the prevention of HIV transmission has created a growing population of HIV-exposed, uninfected children who have yet to be truly evaluated. The work by Wedderburn and colleagues begins to uncover some of the unique characteristics of this population. Specifically, like children infected with HIV perinatally, HIV-exposed, uninfected children show deficits in language development.[3] Thus, HIV infection alone may not fully explain the language delays exhibited by HIV-infected children. More importantly, there may be something about early exposure to HIV that explains this delayed development.

Wedderburn and colleagues hypothesized that this relationship between perinatal HIV exposure and language delay may be associated with maternal immunosuppression, since mothers with a CD4 cell count of 500 cells per µL or less had children with the most pronounced language delays. It is thought that this immunosuppression, or the toxicity of ART itself, may affect neurodevelopment in utero. A recent study conducted by Lauda and colleagues found that HIV-exposed, uninfected children had almost twice as many infection-related hospitalizations in the first two years of life as children not exposed to HIV. This gives added support to the notion that there are consequences

to the immunosuppression experienced by these children.[4]

It also is possible that being raised in a family affected by HIV affects language development. A recent meta-analysis conducted by Madigan and colleagues examined the relationship between the language learning environment and language development outcomes. Results showed a strong positive association between sensitive responsiveness, or caregivers' ability to attune to and foster child language, and language outcomes. The warmth, or the positive nature of mother-child interactions, also was associated with better language development.[5]

[The degree to which HIV, antiretroviral therapy, and the mother-child interaction contribute to language delay is not yet clear.]

In a commentary on these findings about the effect of a child's language learning environment, Heidi Feldman suggested that there may be three other important aspects of the language learning environment that affect language development. Specifically, she stated based on prior research that the quantity of child-directed speech, the quality of the language presented, and the nature of the interactions are extremely important for language development.[6] It is through environmental components that children are able to reach their full language potential.

Caregiver illness may negatively affect the language-learning environment. In a recent study conducted by Bell and colleagues, chronic maternal illness was associated with impaired language development in both daughters and sons. Furthermore, for each year that a child was exposed to a mother's chronic condition, the risk of language delay increased.[7] There is something about having a chronically ill mother that impairs the language learning environment.

In the study conducted by Wedderburn and colleagues, the sickest mothers (i.e., the mothers with the lowest CD4 cell counts) had the children with the most pronounced language delays. It is possible that these mothers' chronic illness impaired their ability to provide the best language-learning environment. However, the degree to which HIV, ART, and the mother-child interaction contribute to language delay is not yet clear. Future research should fully elucidate the cause-and-effect relationships between HIV exposure and language developmental delay with a focus on improving the language environment. ■

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ABSTRACT & COMMENTARY

Fatal Bacteremia Due to Fecal Microbiota Transplantation

By Stan Deresinski, MD, FACP, FIDSA

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

SYNOPSIS: Two patients developed bacteremia due to an extended-spectrum beta-lactamase producing *Escherichia coli* that had been transmitted to them via stool transplantation.

SOURCE: DeFilipp Z, Bloom PP, Torres Soto M, et al. Drug-resistant *E. coli* bacteremia transmitted by fecal microbiota transplant. *N Engl J Med* 2019 Oct 30. doi: 10.1056/NEJMoa1910437. [Epub ahead of print].

A 69-year-old man with cirrhosis due to chronic hepatitis C virus infection received fecal microbiota transplantation (FMT) oral capsules upon enrolling in an open-label trial to assess its role in prevention of hepatic encephalopathy, for which he also received rifaximin. He developed fever and a pulmonary infiltrate 17 days after his last FMT dose and was given levofloxacin, which was changed to piperacillin-tazobactam when blood cultures yielded aerobic Gram-negative bacilli. A further therapeutic change was made to carbapenem therapy when the organism was found to be an extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli*, and the infection resolved.

A 73-year-old man with myelodysplastic syndrome was admitted for receipt of an allogeneic hematopoietic stem cell transplant (allo-HCT) from an unrelated HLA-mismatched donor after reduced intensity conditioning. He was given two doses of cyclophosphamide, followed by ongoing sirolimus and mycophenolate mofetil as prophylaxis against graft-versus-host disease and also received antibacterial prophylaxis with cefpodoxime. He received multiple doses of FMT oral capsules as part of a study of its effects in allo-HCT. Five days after receipt of his transplant and eight days after receipt of his last FMT capsule, at which time his absolute neutrophil count was 0/mm^3, he became febrile. Blood drawn for culture yielded an ESBL-producing *E. coli*. He worsened and died despite treatment with meropenem.

Both patients had received FMT capsules from the same lot, and ESBL-positive *E. coli* was detected in each of these lots. Although screening of donor stool for the presence of ESBL-producing *E. coli* was initiated prior to these cases in January 2019, these lots had been prepared before that time and did not undergo such screening. Isolates from the implicated lot and those from the patients were found to be essentially identical by whole genome sequencing.

■ COMMENTARY

Gram-negative bacteremia has been reported rarely as a complication of FMT. In fact, recent evidence indicates that, when used in the management of patients with recurrent *Clostridioides difficile* infection (CDI), FMT appears to protect from bloodstream infection.[1]

The two patients described here received FMT for reasons other than recurrent CDI, and both had disease states that predispose to bacteremia. One of the patients, who was treated in the setting of allogeneic stem cell transplantation and profound neutropenia, died as a consequence of bloodstream infection, despite having received appropriate antibiotic therapy.

If nothing else, this report illustrates the critical importance of extensive screening of donor stool before its clinical use. ■

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ABSTRACT & COMMENTARY

Recurrent *Clostridioides difficile* Infection: Better Outcomes With Fecal Microbiota Transplantation Than With Antibiotics

By Stan Deresinski, MD, FACP, FIDSA

Clinical Professor of Medicine, Stanford University

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

SYNOPSIS: Relative to vancomycin or metronidazole treatment of recurrent *Clostridioides difficile* infection, treatment with fecal microbiota transplantation is associated with a reduced risk of bloodstream infection, shorter hospital length of stay, and improved survival.

SOURCE: Ianiro G, Murri R, Sciumè GD, et al. Incidence of bloodstream infections, length of hospital stay, and survival in patients with recurrent *Clostridioides difficile* infection treated with fecal microbiota transplantation or antibiotics: A prospective cohort study. *Ann Intern Med* 2019 Nov 5. doi: 10.7326/M18-3635. [Epub ahead of print].

In a prospective observational cohort study with subset propensity matching, Ianiro and colleagues examined the incidence and outcomes of bloodstream infection (BSI) in patients with recurrent *Clostridioides difficile* infection (CDI) treated with fecal microbiota transplant (FMT) compared to those treated with antibiotics.

[*Clostridioides difficile* infection is known to be associated with an increased risk of bloodstream infection, likely as the result of disruption of the colonic epithelial barrier allowing bacterial translocation.]

The entire cohort consisted of 290 patients: 181 received antibiotic therapy (mostly vancomycin or metronidazole) and 109 received FMT. BSI infection occurred in 40 (22.1%) of the antibiotic recipients and five (4.6%) of the FMT recipients. Of the 45 BSI, 14 were due to *Candida* spp.

Because of significant baseline differences in the two groups, a propensity cohort analysis with 1:1 matching with 57 pairs was performed. In this cohort, BSI within 90 days occurred in 15 (26%) and two (4%) in the antibiotic and FMT group, respectively (95% confidence interval [CI] for the difference, 10% to 35%). FMT also was associated with a shorter mean length of stay (13.4 days vs. 27.8 days). Overall survival within 90 days was 89% in the FMT group and 58% in the antibiotic group (95% CI for the difference, 16% to 47%).

■ COMMENTARY

CDI is known to be associated with an increased risk of BSI, likely as the result of disruption of the colonic epithelial barrier allowing bacterial translocation. It has been suggested that further alteration of the intestinal flora by therapeutic administration of vancomycin may contribute additionally to the risk of bacterial translocation. In contrast, restoring a more normal fecal flora may be protective against pathogen entry into the bloodstream.

This study indicates that in patients with recurrent CDI, treatment with FMT is associated with a reduced incidence of BSI, shorter length of stay, and reduced mortality relative to treatment with vancomycin or metronidazole. If confirmed, most of us will have to change our current practice. ■

ABSTRACT & COMMENTARY

Antimicrobial Susceptibility Testing in Cystic Fibrosis — An Unfortunate Failure

By Stan Deresinski, MD, FACP, FIDSA

Clinical Professor of Medicine, Stanford University

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

SYNOPSIS: The results of antimicrobial susceptibility testing of respiratory isolates from patients with cystic fibrosis failed to predict outcomes of antibiotic therapy.

SOURCE: Somayaji R, Parkins MD, Shah A, et al; Antimicrobial Resistance in Cystic Fibrosis International Working Group. Antimicrobial susceptibility testing (AST) and associated clinical outcomes in individuals with cystic fibrosis: A systematic review. *J Cyst Fibros* 2019;18: 236-243.

Somayaji and colleagues, on behalf of the Antimicrobial Resistance in Cystic Fibrosis International Working Group, examined the ability of antimicrobial susceptibility testing to predict the results of antibiotic therapy in patients with cystic fibrosis (CF), as well as whether this predictive value was affected by the testing method. They identified 20 studies that met their criteria, most of which dealt with *Pseudomonas aeruginosa*. Thirteen of the studies dealt with the treatment of pulmonary exacerbations and the rest with maintenance therapy.

Of the 16 studies addressing the overall issue of the predictive value of susceptibility testing regardless of the method used, 13 found no benefit. Four studies addressed the methodology question, and none found evidence of a positive effect. The methods evaluated included bactericidal combination (as many as four agents at once) antibiograms as well as the testing of organisms growing as biofilm.

■ COMMENTARY

This analysis indicates that in vitro antimicrobial susceptibility testing fails to provide guidance to the clinician regarding antibiotic therapy of pulmonary infections in patients with CF. A large retrospective study in children with CF that was published too recently to be included in this analysis involved 6,451 pulmonary exacerbations, for which 2,518 susceptibility tests were performed. Similarly, this study failed to detect the benefit of such testing.[1] It should be recognized that the study by Somayaji and colleagues was largely confined to infections with *P. aeruginosa*, and the results may not apply to, e.g., *Staphylococcus aureus* infections.

Several reasons may account for these findings.[2] These include the frequent polymicrobial nature of the infections, the presence of heteroresistance, the presence of persisters, the growth in biofilm, and the segregated growth within microenvironments. Additionally, the administration of antibiotics by inhalation further confounds the issue. The results reviewed here are consistent with the admonition by Waters and colleagues that the best guide for the clinician is the clinical response, not the in vitro susceptibility results. When the latter indicates resistance to the administered antibiotic but the patient is clinically improved, the susceptibility results should be ignored. ■

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Infectious Disease [ALERT]

Updates

By Carol A. Kemper, MD, FACP

Intestinal Yeast Revisited — With a New Angle

SOURCE: Malik F, Wickremesinghe P, Saverimuttu J. Case report and literature review of auto-brewery syndrome: Probably an underdiagnosed medical condition. *BMJ Open Gastroenterol* 2019;6:e000325.

Although auto-brewery syndrome (ABS) may be a little-recognized medical condition, it has provided a theoretical defense for cases of driving under the influence (DUI). ABS occurs when selected yeasts and fungi in the small intestine and cecum ferment carbohydrates to alcohol, leading to occult intoxication. While some yeast naturally colonize the colon of healthy individuals, certain strains of *Candida* and *Saccharomyces cerevisiae* (brewer's yeast) can abnormally colonize the small intestine and cecum, where they can convert carbohydrates to endogenous alcohol. In an earlier study of teetotalers in the Middle East, researchers detected low levels of blood alcohol in some individuals simply from endogenous gut production. Patients with disturbances in gut flora from prior antibiotic use or inflammatory bowel disease may be more likely to develop ABS.

The authors report the saga of a previously healthy 46-year-old man whose life was virtually ruined by ABS. He had been arrested for DUI, had several traumatic falls when inebriated (including an intracerebral hemorrhage), despite protestations that he had not been drinking, and ended up being cared for in a nursing facility. He claimed he had been fine until he was treated with three weeks of Keflex for a traumatic injury, after which he developed intermittent periods of confusion, mental

deterioration, aggression, and depression. Blood alcohol levels were measured at various times from 50 to 400 mg/dL.

During an investigation by curious physicians, his blood alcohol level was observed to increase by ~57 mg/dL following a carbohydrate challenge. Both *S. cerevisiae* and *Saccharomyces boulardii* were isolated in stool cultures; cultures obtained from the upper small gut and cecum grew *C. albicans* and *C. parapsilosis*. He was treated sequentially with a carbohydrate-free diet, fluconazole 150 mg daily for 14 days, nystatin three times daily for 10 days, and then increasing doses of itraconazole, without much success. He then received micafungin 150 mg daily for six weeks — and it worked. Carbohydrates were re-introduced gradually into his diet, he received probiotics, and resumed a fairly normal, inebriate-free life.

To establish the diagnosis, the authors suggest standardization of the procedures, with a standardized carbohydrate challenge, e.g., 200 g glucose, following overnight fasting, with serial blood alcohol levels obtained between 0 to 24 hours. Delayed blood draws may be necessary since some yeasts are slow fermenters.

Patients feasibly could monitor their own blood alcohol levels using an over-the-counter breathalyzer — although these devices require regular calibration with fresh reagents and careful maintenance or they may provide false readings. A recent *New York Times* exposé suggested that many professional breathalyzers are not properly calibrated or maintained and are potentially inaccurate.

Preemptive Steroids for TB/HIV Treatment

SOURCE: Meintjes G, Stek C, Blumenthal L, et al. Prednisone for the prevention of paradoxical tuberculosis-associated IRIS. *N Engl J Med* 2018;379:1915-1925.

Immune reconstitution inflammatory syndrome (IRIS) during tuberculosis (TB) treatment occurs in 18-54% of HIV-infected patients and carries significant morbidity, frequently resulting in high-dose steroid use and prolonged hospitalization. Despite the survival benefit of antiretroviral therapy (ART), earlier initiation of HIV medications has been shown to significantly increase the risk of IRIS in patients being treated for TB. Patients with newly diagnosed TB and HIV infection, therefore, often are started on TB medications first, with delayed initiation of ART for one to two months, depending on their CD4 count.

This research team examined whether the addition of modest doses of prednisone for four weeks could reduce the risk of TB IRIS in patients who had started TB treatment within 30 days and who were just beginning ART. A total of 240 patients were randomly assigned to receive ART plus prednisone 40 mg daily for two weeks and then 20 mg daily for two weeks, or ART plus identical-looking placebo.

[Despite the survival benefit of antiretroviral therapy, earlier initiation of HIV medications has been shown to significantly increase the risk of IRIS in patients being treated for TB.]

Most patients were male (60%); their median CD4 count was 49 cells per microliter (range, 24-86 cells per microliter), and their median viral load was 5.5 logs. Patients had received anti-tuberculous medications for a median of 17 days before beginning ART. Patients with uncontrolled diabetes, Kaposi sarcoma, neurological or pericardial TB, or those who received non-standard TB therapy were excluded.

The preemptive addition of prednisone when beginning ART therapy reduced the risk of TB-associated IRIS by ~30%. IRIS symptoms occurred in 32.5% of those in the prednisone group compared to 46.7% of the placebo group (relative risk [RR] 0.7, P = 0.03). Open label steroids were prescribed for IRIS signs and/or symptoms in 13% of the prednisone group vs. 28.3% of the placebo group. Hospitalization was required in 14% of the prednisone group vs. 22.5% of the placebo group. Nine patients died, including five in the prednisone group. Interestingly, the risk of invasive bacterial infection and AIDS-defining infection was not dissimilar between the two groups (11 patients in the prednisone group vs. 18 patients in the placebo group, P = NS). The onset of IRIS symptoms was similar between the two groups, occurring within a median of 10 days in the prednisone group and eight days in the placebo group.

Modest doses of preemptive steroids administered for four weeks in patients being treated for TB, along with their ART therapy, reduced the risk of IRIS by about 30%, and fewer such patients required high-dose glucocorticoids to control IRIS symptoms. Side effects were minimal, and

investigators did not observe an increased risk of invasive bacterial infection or AIDS-related infections. The dose of prednisone used for preemptive therapy was fairly low compared to that recommended for actual treatment of IRIS symptoms (1 to 1.5 mg/kg body weight) — and was not dose-adjusted for concurrent use with rifampin (which may have further lowered the prednisone dose).

Fluoroquinolone for Exposure to Drug-Resistant Tuberculosis

SOURCE: Malik AA, Fuad J, Siddiqui S, et al. TB preventive therapy for individuals exposed to drug-resistant tuberculosis: Feasibility and safety of a community-based delivery of fluoroquinolone-containing preventive regimen. *Clin Infect Dis* 2019 Jun 12. pii: ciz502. doi: 10.1093/cid/ciz502. [Epub ahead of print].

For household contacts of persons with drug-resistant tuberculosis (DR-TB), the risk of acquiring tuberculosis (TB) is approximately 20-47%, and the risk of developing active TB disease may be as high as 10-20%. As a result, in 2018, the World Health Organization recommended that high-risk contacts of persons with DR-TB receive preemptive treatment for TB.

In Karachi, Pakistan, at least 400 cases of DR-TB occur annually. The authors of this study prospectively examined the use of oral fluoroquinolone therapy in high-risk household contacts of such patients. From 2016 to 2017, researchers contacted 800 contacts from 100 households of patients with DR-TB for evaluation and possible study participation. Only household contacts of patients with DR-TB were considered (including those with fluoroquinolone-resistant strains, but not those with extensively drug-resistant TB).

Community health workers evaluated household contacts within two to four weeks of the index case enrollment in a treatment facility. A total of 737 household contacts were screened, 11 of whom were already being treated for TB, and three were found to have active TB. Those who were eligible for study treatment included all children younger than 5 years of age; any child between 5 and 17 years of age with a positive skin test or HIV, diabetes, or malnutrition; or any adult 18 years of age or older with diabetes, HIV, or malnutrition.

[In 2018, the World Health Organization recommended that high-risk contacts of persons with DR-TB receive preemptive treatment for TB.]

Two-hundred fifteen contacts were eligible for study; 172 initiated therapy and 121 completed the course of treatment (70.3% completion rate). Participants received one of four different regimens for six months, including either levofloxacin (weight-based, maximum dose 1,000 mg daily) plus either ethambutol or ethionamide, or moxifloxacin (weight-based, maximum dose 400 mg daily) plus either ethambutol or ethionamide. During the study, researchers monitored the participants every two months by either a telephone call or home visit, and then for a year following the completion of treatment. About 20% reported one or more side effects from the medications, and dose-limiting side effects were the main reason for premature treatment discontinuation. Side effects were less frequent with the combination fluoroquinolone plus ethambutol compared to the combination of fluoroquinolone plus ethionamide (14.2% vs. 33.5%, respectively).

This completion rate of 70.3% for six months of preventive TB therapy is tremendous — and for those who completed therapy, 96% completed 12 months of additional follow-up. (For each study visit, the participants received a small stipend ~$6 US for travel time and expenses.) None of the household contacts developed TB disease during study or the 12 months of follow-up. The authors recommended the combination of fluoroquinolone plus ethambutol for chemoprophylaxis of high-risk household contacts of DR-TB, since it seemed to be tolerated better. ■

CME INSTRUCTIONS

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CME QUESTIONS

1. Which of the following statements is true?

a. HIV-uninfected children exposed prenatally to HIV uniformly have normal speech development.

b. HIV-infected children exposed prenatally to HIV uniformly have normal speech development.

c. HIV-uninfected children exposed prenatally to HIV usually have delays in speech development by 6 months of age.

d. HIV-uninfected children exposed prenatally to HIV have an increased risk of delays in speech development at 24 months of age.

2. Which of the following is correct regarding the study by Ianiro and colleagues evaluating the outcomes of treatment of a recurrent *Clostridioides difficile* infection?

a. Relative to antibiotic treatment, treatment with fecal microbiota transplant is associated with an increased incidence of bloodstream infection.

b. Relative to antibiotic treatment, treatment with fecal microbiota transplant is associated with a shorter in-hospital length of stay.

c. Relative to antibiotic treatment, treatment with fecal microbiota transplant is associated with increased mortality.

d. Relative to antibiotic treatment, treatment with fecal microbiota transplant is associated with an increased risk of subsequent recurrence of *C. difficile* infection.

3. Which of the following is correct regarding the findings of Gonzalez-Orta and colleagues?

a. Forty-one percent of patients were found to be colonized with toxigenic *Clostridioides difficile* at the time of hospital admission.

b. Twelve percent of patients without colonization on admission subsequently developed *C. difficile* infection.

c. Twelve percent of patients colonized on admission subsequently developed *C. difficile* infection.

d. Colonization with *C. difficile* was not a significant risk factor for the development of disease due to this organism.

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.