AHC Media

Vol. 34, Issue 3, December 2014
www.ahcmedia.com

Infectious Disease [ALERT]

Incisive Commentary and Clinical Abstracts on Current Issues in Infectious Diseases

ABSTRACT & COMMENTARY

Subglottic Secretion Suctioning Reduces Vent-Associated Pneumonia, Antibiotic Use

Should subglottic suctioning be added to VAP prevention bundles?

By Richard R. Watkins, MD, MS, FACP

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

SOURCE: Damas P, et al. Prevention of Ventilator-Associated Pneumonia and Ventilator-Associated Conditions: A Randomized Controlled Trial With Subglottic Secretion Suctioning. *Crit Care Med*. 2014 Oct 23. [Epub ahead of print]

Ventilator-associated pneumonia (VAP) is a serious complication for intubated patients. It causes significant morbidity and mortality, increases healthcare costs and is the main reason for antibiotic use in the intensive care unit (ICU). Thus, strategies that reduce the incidence of VAP would greatly benefit both patients and the healthcare system. Previous studies have shown that suctioning subglottic secretions in ventilated patients can reduce VAP. Damas and colleagues sought to determine whether subglottic secretion suctioning would be effective in reducing VAP at a tertiary center where a prevention bundle was in place, as well as reducing overall antibiotic usage.

The study enrolled patients hospitalized in one of the ICUs at the University Hospital of Liege between January 23, 2012 and March 31, 2013 who were intubated with a particular endotracheal tube (Teleflex Isis™) that permitted subglottic secretion

Financial Disclosure: *Infectious Disease Alert*'s editor, Stan Deresinski, MD, FACP, FIDSA, does research for the National Institutes of Health, and is an advisory board member and consultant for Merck; Updates author, Carol A. Kemper, MD, FACP, does research for Abbott Laboratories and Merck. Peer reviewer Timothy Jenkins, MD, and executive editor Gary Evans report no financial relationships to this field of study.

Infectious Disease [ALERT]

Infectious Disease Alert,
ISSN 0739-7348, is published monthly by
AHC Media, LLC
One Atlanta Plaza
950 East Paces Ferry NE, Suite 2850
Atlanta, GA 30326.
www.ahcmedia.com

Periodicals Postage Paid at Atlanta, GA 30304 and at additional mailing offices.

GST Registration Number: R128870672.
POSTMASTER: Send address changes to
***Infectious Disease Alert*,**
P.O. Box 550669,
Atlanta, GA 30355.

SUBSCRIBER INFORMATION
1-800-688-2421
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www.ahcmedia.com

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Subscription Prices
United States:
Print: 1 year with free *AMA PRA Category 1 Credits™*: $349
Add $19.99 for shipping & handling.
Online only: 1 year (Single user) with ***free*** *AMA PRA Category 1 Credits™*: $299

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suctioning. Patients were randomized to two groups, group 1 received subglottic secretion suctioning (experimental) and group 2 did not (control). The institution had a VAP bundle in place since 2009 that included semirecumbent positioning of at least 30°, oral care that included teeth brushing with 0.2% chlorhexidine and application of 1% chlorhexidine gel, control of cuff pressure of the endotracheal tube between 20 and 30 cm H2O, and daily assessment of sedation. All randomized patients were screened daily for the occurrence of VAP.

The diagnosis was suspected by clinical criteria including a new infiltrate on chest radiograph, fever or hypothermia, leukocytosis or leukopenia, purulent tracheal secretions and worsening of oxygenation. VAP was confirmed by quantitative bacterial culture of >106 CFU/mL from an endotracheal specimen of >104 CFU/mL from bronchoalveolar lavage fluid. The primary endpoint was the occurrence of VAP in the experimental and control groups. The secondary endpoints were the occurrence of ventilator-associated conditions (VAC) and infection-related ventilator-associated complications (IVAC), as well as the proportion of antibiotic days during ICU stay.

A total of 352 patients were randomized, 170 to group 1 and 182 to group 2. After 48 hours of ventilation, VAP was suspected in 27 and confirmed in 15 patients (8.8%) in group 1 while it was suspected in 41 and confirmed in 32 patients (17.6%) in group 2 (P = 0.018). Subglottic secretion suctioning resulted in an event reduction of 8.8%, indicating that 9 episodes of VAP could be avoided for every 100 intubated patients. Furthermore, logistic regression analysis showed the protective role of subglottic suctioning (OR = 0.45; 95% CI, 0.24-0.87) and that none of the potential confounding variables identified impacted the significance of suctioning. Regarding the secondary endpoints, VAC and IVAC prevalence were comparable between the two groups (P = 0.56 and 0.47, respectively). During the entire ICU stay, antibiotics were given a median of 7 days in group 1 and 8 days in group 2 (P = 0.45). The total number of antibiotic days was significantly lower in group 1 (1,064) compared to group 2 (1,222) (P = 0.001) and more patients in group 1 had no days on antibiotics (16.4%) compared to group 2 (7.4%) (P = 0.02). Finally, the length of ICU stay, duration of mechanical ventilation, tracheostomy rate, ICU mortality and hospital mortality did not differ significantly between the two groups.

■ COMMENTARY

The results from this randomized trial show that suctioning of subglottic secretions significantly reduces VAP and antibiotic consumption. While these findings are noteworthy, the study did have a few limitations. First, it was conducted at a single center so the results might not apply to other settings. Second, it was not possible to blind the control and experimental groups. Third, only patients with a particular type of endotracheal tube were enrolled in the study. Finally, the overall number of VAP cases was relatively small. Nevertheless, there were no reported complications of subglottic suctioning and the observed reduction in antibiotic consumption is important from an antibiotic stewardship perspective.

The widespread adoption of prevention bundles in the U.S. over the past few years has led to a substantial decrease in the rate of VAP (1 to 3 episodes/1,000 ventilator days). Although VAP has not declined as much in Europe (12-18 episodes/1,000 ventilator days) as the U.S., this may be due to differences in how VAP is defined. Indeed, a frequent criticism of studies on VAP is that the definition of VAP remains controversial. It would therefore be useful to researchers and clinicians alike if a universal definition of VAP could be agreed upon and widely adopted.

The findings from the study by Damas and colleagues support previous data that also showed the benefit of subglottic secretion suctioning. Although it seems reasonable to add subglottic secretion suctioning to VAP prevention bundles, it will likely take another randomized clinical trial from North America to also show a significant benefit before this intervention becomes widely implemented in American ICUs.

ABSTRACT & COMMENTARY

Statins May Preserve Renal Function in Patients Receiving HAART

By Dean L. Winslow, MD, FACP, FIDSA

Clinical Professor of Medicine and Pediatrics Division of Infectious Diseases and Geographic Medicine, Stanford University School of Medicine, Associate Editor of Infectious Disease Alert

Dr. Winslow is a consultant for Siemens Diagnostic

SYNOPSIS: 147 patients on stable antiretroviral therapy (ART) were randomized to receiving rosuvustatin 10 mg daily or placebo. After 24 weeks rosovustatin both reduced cystatin C and slowed kidney function decline as assessed by a serum creatinine-based equation.

SOURCE: Longenecker CT, et al. Rosovustatin preserves renal function and lowers cystatin C in HIV-infected subjects on antiretroviral therapy: the SATURN-HIV trial. CID 2014;59:1148-56.

The Stopping Atherosclerosis and Treating Unhealthy Bone with Rosovustatin in HIV (SATURN-HIV) trial randomized 147 patients on stable ART with LDL cholesterol <=130 mg/dL to blinded rosovustatin 10 mg daily or placebo. Baseline and 0- to 24-week changes in plasma cystatin C, measures of vascular disease, inflammation and immune activation were measured.

The median age of patients was 46 with 78% male and 68% African-American. Tenofovir (TDF) was used in 88% and protease inhibitors (PI's) in 49% of subjects. Baseline cystatin C was associated with carotid intima-media thickening by ultrasound and epicardial adipose tissue independently of age, sex, and race. Using the CKD-EPI creatinine-based equation to estimate glomerular filtration rate (eGFR), after 24 weeks statin use slowed mean eGFR decline (+1.68 mL/min in the statin group vs. -3.08 mL/min in the placebo group) and decreased mean cystatin C (-0.034 mg/L vs. +0.010 mg/L). Within the statin group changes in cystatin C correlated with changes in endothelial function (flow-mediated dilation and hyperemic velocity-time integral), endothelial activation (sVCAM and sICAM), inflammation (IL-6, sTNF-RI and sTNF-RII) and T-cell activation (T-cell CD38 and HLA-DR expression).

■ COMMENTARY

One of the unfortunate problems of HIV disease pathogenesis is that despite effective control of HIV replication by HAART, elevated levels of systemic immune activation, inflammation and coagulation persist (compared to age-matched HIV-negative controls). This is felt to contribute to diverse conditions including HIV-associated nephropathy, more rapid progression to cirrhosis in HIV patients co-infected with HBV and HCV, and even atherosclerosis.

Another concern is that while TDF-containing ART (and perhaps other antiretroviral agents), while very effective, clearly result in fairly significant (and often irreversible) reductions in eGFR.

Cystatin C is an interesting molecule since it is elevated both in the presence of inflammation and in patients with reduced GFR. The significant effect of rosovustatin on reducing cystatin C, while reducing more direct measures of inflammation, endothelial function and reducing the decline in renal function is good news. If additional studies confirm this to be a class effect of statins, adjunctive use of statins in HV may become standard of care, as it has been for several years in patients with diabetes. ■

ABSTRACT & COMMENTARY

ID Ground Rounds — Stanford University: Male, 46, HIV Patient with Fever and Dyspnea

By Carlos A. Gomez, MD

Infectious Diseases Fellow, Stanford University Hospital

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

CASE HISTORY

A 46-year-old man was admitted to our hospital due to progressive dyspnea, non-productive cough and fever. Two months prior to admission, he started to develop sustained weight loss and dyspnea associated with exertion. Ten-days prior to his presentation, dyspnea progressed to minimal exertion significantly limiting his functional status. He also developed fever (38.3°C), non-productive cough and dysphagia. He sought care at a local Emergency Department and was discharged the same day with steroid inhalers, oral fluconazole for thrush and a 3-day course of prednisone. He was admitted to our institution 5 days later due to worsening of respiratory symptoms. At admission, he denied pleurisy, dysuria, diarrhea, focal neurological deficits, headaches or vision disturbances.

HIV HISTORY

The patient was diagnosed with HIV infection in 1986 but first developed AIDS in 1994 when he was found to have pulmonary *Mycobacterium Avium* complex (MAC) infection and chronic diarrhea. He was started on antiretroviral therapy (ARV) and appropriate antimicrobial prophylaxis with adequate immunological recovery. Unfortunately, the patient abandoned ARV therapy in mid-2008 at a time when his CD4+ T cell count was 450 cells/mm3. Besides HIV infection, his past medical history was unremarkable. There was no history of other sexually transmitted disease. He had developed disseminated skin rash after trimethoprim-sulfamethoxazole exposure. He quit smoking 5-year prior presentation and denied IV drug use. He had often traveled throughout the Central Valley of California but there was no history of other recent domestic or international travel nor of contacts with ill individuals. He had no history of opportunistic infections other than those previously mentioned.

PHYSICAL EXAMINATION

On physical examination, he looked cachectic and chronically ill but not in respiratory distress. His temperature was 38.7°C, blood pressure was 106/66 mmHg, heart rate was 97 beats per minute, respiratory rate was 30 breaths per minute. His oxygen saturation was 95% at 0.5 L/min of oxygen by nasal cannula. Oral mucosa inspection revealed thrush. Left greater than right basilar inspiratory crackles were noted. Otherwise, his examination was unremarkable.

LAB TEST AND IMAGING

Laboratory investigation revealed a normal WBC (8100, 72% neutrophils); hemoglobin and platelets counts were also within normal levels. His creatinine was 1.1 mg/dL. Liver tests were normal. His urinalysis showed no pyuria. Arterial blood gases showed a pH of 7.46 and PaO_2 146, with a normal calculated A-a gradient; LDH 287 U/L, CD4+ cell count: 12 cells/mm,^{3} HIV viral load 133.000 copies. Blood cultures, pneumococcal urine antigen and legionella urine antigen were each negative. Initial chest X-ray showed diffuse bilateral ground-glass opacities in the left lower lobe. A non-contrast CT of the chest showed multilobar ground-glass opacities which were more coalescent in the left lower lobe.

CLINICAL COURSE

The patient was admitted to a medical ward and treatment was started with IV ceftriaxone and azithromycin for presumed community acquired pneumonia. After 48 hours, his oxygen requirements increased to 3 L/min in order to keep his oxygen saturation above 90%. He remained febrile with no significant clinical improvement. Microscopy of a sputum specimen obtained by induction showed > 10 epithelial cells, and a negative Gram stain. Direct Fluorescent Antibody (DFA) staining for Pneumocystis was negative. Blood cultures and a respiratory viral panel from nasopharyngeal swab were negative. A serum ß-D-Glucan (Fungitell test) was positive at 129 pg/mL (cutoff ≥ 80 pg/mL). On Day 3 of hospital stay, before the ß-D-Glucan test was reported, he underwent bronchoscopy with bronchoalveolar lavage (BAL). DFA for PCP performed on a BAL specimen was positive and treatment with atovaquone 750mg BID was instituted. The patient failed TMP-SMX desensitization due to development of skin rash and lip edema. Unfortunately, despite multidisciplinary efforts the patient declined ARV therapy and was discharged on atovaquone which was to be continued for prophylaxis against recurrence of PCP.

DISCUSSION

Pneumocystis jiroveci, the etiologic agent of human

pneumocystis pneumonia (still referred as PCP) remains an important opportunistic agent in HIV-patients who remain unaware of their diagnosis and those with CD4+ count ≤ 200 cells/mm^3 in the absence of adequate PCP prophylaxis.[1] Since the introduction of TMP-SMX as an effective PCP prophylaxis strategy in 1989 and the subsequent advent of highly active antiretroviral therapy (HAART) in 1996, the incidence of PCP in HIV population has markedly and sustainably declined. PCP should be suspected in the appropriate host presenting with the triad of resting or exertional dyspnea, fever and non-productive cough. Hypoxemia is the cardinal manifestation of PCP; oxygen desaturation following mild exertion is often abnormal and might be used to identify patients at early disease stages, including the 10% with no abnormalities observed on chest X-ray. Extrapulmonary manifestations of PCP are very rare but instances of involvement of lymphoid-tissues, bone marrow, spleen, GI tract, ocular, and thyroid gland have been reported. The most common radiographic pattern in chest radiographs is diffuse, bilateral, symmetrical reticulo-nodular infiltrates, which correlates with ground-glass opacities found in CT.[2] Pleural effusion, consolidation, mediastinal adenopathy and cavitation are uncommon in the absence of other pulmonary pathogens. The presence of spontaneous pneumothorax in an HIV-patient should raise the suspicion for PCP2. Of note, the presence of oro-pharyngeal candidiasis has historically been associated with high risk of PCP and its presence alone, is an indication for PCP prophylaxis.

The suspicion of PCP raises a diagnostic dilemma for the clinician. Due to the inability to culture the organism, a microbiological diagnosis relies on the visualization of the organism in respiratory secretions. Induced sputum with the use of various stains techniques (e.g. Direct Fluorescent Antibody, Grocott-Gomori's methenamine silver, and Giemsa stain) has reported a wide range of sensitivity (60-95%).[1,3] In experienced centers, DFA staining in induced sputum has demonstrated a sensitivity as high as 90% when compared with DFA in BAL samples. The above implies the availability of fluorescent microscopy, laboratory expertise, and a standardized protocol that includes motivated and highly trained respiratory therapy personnel to guarantee lower respiratory tract sampling. As these conditions are not available everywhere, the availability of a PCP-specific serum marker has been highly desirable. (1-3)-ß-D-glucan (ß-glucan), is a component of many fungi wall, including *P. Jirovecii*, and has emerged as a potential diagnostic tool in HIV-patients with possible PCP. When a cutoff value of ≥ 80 pg/mL was used in HIV-patients with suggestive respiratory symptoms, the sensitivity of the ß-glucan test was 92.8% and its specificity 75%.[4] False positive results may occur in patients treated receiving piperacillin/tazobactam or in the presence of systemic infections due to other fungi, such as invasive aspergillosis and histoplasmosis. Remarkably, mucosal candidiasis was not statistically significant associated with elevated ß-glucan serum levels.[4] Polymerase chain reaction (PCR) is an emerging method for PCP diagnosis with a high sensitivity, but its inability to distinguish true infection versus mere colonization is problematic. The potential role of quantitative PCR and its integration in PCP-diagnostic algorithms is under study.

A strong suspicion of PCP should trigger the timely initiation of therapy for this infection. TMP-SMX remains the treatment of choice for PCP and should be preferred over other alternative options (e.g. primaquine/clindamycin, dapsone/trimethoprim (in the absence of G6PD deficiency), atovaquone or IV pentamidine). Cases of severe PCP, defined as the presence of PaO_2 <70 mmHg while breathing ambient air or an alveolar-arterial O_2 gradient ≥35 mmHg, require the use of adjunctive corticosteroid therapy. In contrast to the findings in this patient, the gas exchange abnormalities are usually greatly out of proportion to the radiographic findings. In this case, the use of prednisone prior to the current admission may have blunted the pulmonary inflammatory response leading to the normal oxygenation observed at the initial presentation. ■

Diagnosis: *Pneumocystis jiroveci* pneumonia.

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Tedizolid — Formulary Considerations

By Tiffany Wong, PharmD

Clinical Pharmacist in Internal Medicine, Stanford University

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

GENERIC NAME: Tedizolid phosphate

TRADE NAME: Sivextro™

FDA APPROVAL DATE: June 20th, 2014

SIMILAR DRUGS ON FORMULARY:

Linezolid (Zyvox) — oxazolidinone antibiotic

INDICATIONS[1]

FDA approved for the treatment of acute bacterial skin and skin structure infections (ABSSSIs) caused by susceptible gram-positive organisms including *Staphylococcus aureus* (MRSA and MSSA), *Streptococcus agalactiae*, *Streptococcus anginosus* group, *Streptococcus pyogenes*, and *Enterococcus faecalis*.

PHARMACOLOGY[1]

Tedizolid phosphate is a prodrug that is converted to tedizolid. Tedizolid is an oxazolidinone antibiotic that binds the 50S subunit of the bacterial ribosome leading to inhibition of protein synthesis.

PHARMACOKINETICS[1]
PHARMACODYNAMICS[1]

AUC/minimum inhibitory concentration (MIC) correlates with tedizolid activity in animal infection models.

MICROBIOLOGY[1]

In-vitro and clinical studies have shown tedizolid to be active against the following aerobic, gram-positive bacteria:

- *Staphylococcus aureus* (including MRSA and MSSA isolates)
- *Streptococcus agalactiae*
- *Streptococcus anginosus* group (including *S. anginosus*, *S. intermedius*, and *S. constellatus*)
- *Streptococcus pyogenes*
- *Enterococcus faecalis*.

In vitro time-kill studies show tedizolid is bacteriostatic against enterococci, staphylococci, and streptococci.

Only in-vitro data have shown at least 90% of the following bacteria to exhibit a minimum inhibitory concentration (MIC) ≤ 0.5 mcg/mL for tedizolid. The safety and efficacy of tedizolid in treating infections due to these microorganisms have not been established in clinical trials.

- *Staphylococcus epidermidis* (including methicillin-susceptible and methicillin-resistant isolates)
- *Staphylococcus haemolyticus*
- *Staphylococcus lugdunensis*
- *Enterococcus faecium*

Oxazolidinone resistance occurs via mutations in the chromosomal genes encoding 23S rRNA of ribosomal proteins (L3 and L4) which confers cross-resistance to tedizolid. In-vitro studies showed that reduced tedizolid susceptibilities from spontaneous mutations occur at an infrequent rate (10-10) and the presence

<table>
<tr><td>Absorption</td><td><table><tr><td></td><td>Oral</td><td>Intravenous (IV)</td></tr><tr><td>Peak Concentration</td><td>3 hours (fasting)</td><td>End of 1 hour infusion</td></tr></table>
Absolute bioavailability 91%
AUC unchanged by food
No dose adjustment between IV and oral formulations</td></tr>
<tr><td>Distribution</td><td>Protein binding ~ 70 to 90%
Volume of distribution ~ 67 to 80 L
Penetrates adipose and skeletal muscle tissue</td></tr>
<tr><td>Metabolism</td><td>No metabolites
Not metabolized by CYP450 enzymes</td></tr>
<tr><td>Elimination</td><td>Half-life ~ 12 hours
Majority eliminated by liver as inactive sulfate conjugate
82% feces, 18% urine
<3% excreted in feces or urine unchanged</td></tr>
</table>

Pharmacokinetic Parameters of Tedizolid*	Oral		Intravenous	
	Single Dose	Steady State	Single Dose	Steady State
C_{max} (mcg/mL)	2.0 (0.7)	2.2 (0.6)	2.3 (0.6)	3.0 (0.7)
T_{max} (hr)†	2.5 (1.0 - 8.0)	3.5 (1.0 - 6.0)	1.1 (0.9 - 1.5)	1.2 (0.9 - 1.5)
AUC (mcg·hr/mL)‡	23.8 (6.8)	25.6 (8.4)	26.6 (5.2)	29.2 (6.2)
CL or CL/F (L/hr)	6.9 (1.7)	8.4 (2.1)	6.4 (1.2)	5.9 (1.4)

* C_{max}, maximum concentration; T_{max}, time to reach C_{max}; AUC, area under the concentration-time curve; CL, systemic clearance; CL/F, apparent oral clearance
† Median (range)
‡ AUC is $AUC_{0-\infty}$ (AUC from time 0 to infinity) for single-dose administration and AUC_{0-24} (AUC from time 0 to 24 hours) for multiple-dose administration

of the chloramphenicol-florfenicol resistance (cfr) gene did not result in tedizolid resistance.

No in-vitro studies showed synergy nor antagonism with the following antibiotics when combined with tedizolid:
- Aztreonam
- Ceftriaxone
- Ceftazidime
- Imipenem
- Rifampin
- Trimethoprim/sulfamethoxazole
- Minocycline
- Clindamycin
- Ciprofloxacin
- Daptomycin
- Vancomycin
- Gentamicin
- Amphotericin B
- Ketoconazole
- Terbinafine

CLINICAL TRIALS/EVIDENCE SUMMARY[2-5]

PHASE 2 TRIALS
In a double-blind Phase 2 clinical trial, 188 patients were randomized to 200, 300, or 400 mg once daily tedizolid phosphate treatment for 5 to 7 days. Eligible infection types included abscess, surgical or post traumatic wound, and deep extensive cellulitis with clinical signs and symptoms of serious infections. The primary outcome was clinical response rate at the test-of-cure visit (7 to 14 days after completing treatment). Clinical cure rate was 87.8% in the modified intention to treat population, 95.7% in the clinically evaluable population, and 96.2% in the microbiological evaluable population.

Of 196 isolates, the most common pathogen was S. aureus (76% MRSA and 24% MSSA). The MICs for *S. aureus* were 0.12-0.5 µg/mL. Overall microbiological eradication rates at the test-of-cure visit were 97.7%, 97.9%, and 95.7% for all pathogens, MRSA, and MSSA, respectively.

PHASE 3 TRIALS
In accordance with the FDA guidance on the development of systemic drugs to treat ABSSSIs, the ESTABLISH-1 and ESTABLISH-2 trials were conducted demonstrating non-inferiority to currently approved antibiotics, linezolid, as well as the efficacy of intravenous to oral tedizolid.

ADVERSE REACTIONS[1]

Adverse reactions were evaluated in Phase 2 and Phase 3 clinical trials comparing tedizolid to a comparator antibiotic (linezolid). The most common adverse reactions are nausea (8%), headache (6%), diarrhea (4%), vomiting (3%), and dizziness (2%).
Selected adverse reactions occurring in <2% of patients receiving tedizolid
Blood/Lymphatics: anemia
Cardiovascular: palpitations, tachycardia
Eye Disorders: asthenopia, vision blurred, visual impairment, vitreous floaters
General: infusion-related reactions
Immune System Disorders: drug hypersensitivity
Infections: *Clostridium difficile*-associated diarrhea (CDAD), oral candidiasis, vulvovaginal mycotic infection
Investigations: hepatic transaminases increased, white blood cell count decreased
Nervous System Disorders: hypoesthesia, paresthesia, seventh nerve paralysis
Psychiatric Disorders: insomnia
Skin and Subcutaneous Tissue Disorders: pruritus, urticarial, dermatitis
Vascular Disorders: flushing, hypertension

CONTRAINDICATIONS[1]

None

WARNINGS/PRECAUTIONS[1]

• Neutropenia — The safety and efficacy of tedizolid has not been established in patients with neutropenia (neutrophil counts < 1000 cells/mm^3). Animal studies

Tedizolid Phosphate vs Linezolid for Treatment of Acute Bacterial Skin and Skin Structure Infections – The ESTABLISH-1 Randomized Trial				
Objective	To establish the efficacy and safety of tedizolid phosphate vs linezolid in treating ABSSSIs			
Trial Type	Randomized, double-blind, multicenter, non-inferiority			
Treatment Regimen	Tedizolid phosphate 200 mg oral daily for 6 days vs linezolid 600 mg oral twice daily for 10 days			
Patient Population	Adults (≥ 18yo) with cellulitis/erysipelas, major cutaneous abscess, or wound infection surrounded by erythema accompanied by lymphadenopathy or systemic sign of infection and a suspected or documented gram-positive pathogen			
Outcomes	Clinical Response (ITT analysis), No. (%)	Tedizolid phosphate (n = 332)	Linezolid (n = 335)	Absolute Treatment Difference† (95% CI), %
	Treatment responder at 48 – 72h	264 (79.5)	266 (79.4)	0.1 (-6.1 to 6.2)
	• ≥ 20% decrease in lesion area, no fever	259 (78)	255 (76.1)	1.9 (-4.5 to 8.3)
	Clinical success at the EOT	230 (69.3)	241 (71.9)	-2.6 (-9.6 to 4.2)
Conclusion	Treatment of ABSSSIs with oral tedizolid was statistically non-inferior in efficacy to oral linezolid at both early and late time points.			

Tedizolid for 6 days versus linezolid for 10 days for acute bacterial skin and skin-structure infections (ESTABLISH-2): a randomized, double-blind, phase 3, non-inferiority trial				
Objective	To assess the efficacy and safety of intravenous to oral tedizolid for treatment of patients with ABSSSIs			
Trial Type	Randomized, double-blind, multicenter, parallel-group, non-inferiority			
Treatment Regimen	Tedizolid phosphate 200 mg IV once daily for 6 days vs linezolid 600 mg IV twice daily for 10 days (optional oral step-down)			
Patient Population	Adults (≥ 12yo) with cellulitis/erysipelas, major cutaneous abscess, or wound infection with at least one regional or systemic sign of infection			
Outcomes	Clinical Response (ITT analysis), No. (%)	Tedizolid phosphate (n = 332)	Linezolid (n = 334)	Difference (95% CI), %
	Treatment responder at 48 – 72h	283 (85)	276 (83)	2.6 (-3.0 to 8.2)
	Post-therapy assessment‡	292 (88)	293 (88)	0.3 (-4.8 to 5.3)
Conclusions	Clinical success rates for ABSSSIs treated with IV tedizolid with an option to switch to oral drug were non-inferior to linezolid therapy.			

showed the antibacterial activity of tedizolid was reduced in the absence of granulocytes.
• *Clostridium difficile*-associated diarrhea (CDAD) – Cases of CDAD have been reported with tedizolid ranging from mild diarrhea to fatal colitis.
• Drug-resistant bacteria — Prescribing tedizolid in absence of proven or suspected bacterial infection or prophylactic indication increases the risk of drug-resistant bacteria.

PREGNANCY CATEGORY C

Tedizolid has not been studied in pregnant women. Tedizolid phosphate has been shown to produce fetal developmental toxicities in mice, rats, and rabbits.

LACTATION[1]

Excretion in to human breast milk is unknown. Tedizolid is excreted in to breast milk of rats.

POTENTIAL FOR MEDICATION ERRORS

• This drug is not a high-alert drug and is not a high-alert drug category according to ISMP.
• This drug has low risk for error based on potential for look-alike/sound/alike drug names.

SAFETY STRATEGIES AND COMPETENCY[1]

• No safety strategies are needed for this drug.
• No technology-based user alerts are needed for this drug.
• No competencies are needed for this drug.

DRUG INTERACTIONS[1]

No drug interactions involving CYP enzymes or membrane transporters were found.

In-vitro, tedizolid is a reversible inhibitor of monoamine oxidase (MAO). MAO inhibitor interactions could not be evaluated because patients taking MAO inhibitors were excluded from the Phase 2 and 3 clinical trials. Tedizolid was not found to enhance pressor responses in pseudoephedrine and tyramine challenge studies. Patients taking

Adverse Reactions	Pooled Phase 3 ABSSSI Clinical Trials	
	SIVEXTRO (200 mg oral/intravenous once daily for 6 days) (N=662)	Linezolid (600 mg oral/intravenous twice daily for 10 days) (N=662)
Gastrointestinal Disorders		
Nausea	8%	12%
Diarrhea	4%	5%
Vomiting	3%	6%
Nervous System Disorder		
Headache	6%	6%
Dizziness	2%	2%

Laboratory Assay	Potentially Clinically Significant Values*†	
	SIVEXTRO (200 mg oral/intravenous once daily for 6 days) (N=618)‡	Linezolid (600 mg oral/intravenous twice daily for 10 days) (N=617)
Hemoglobin (<10.1 g/dL [M]) (<9 g/dL [F])	3.1%	3.7%
Platelet count (<112 × 10^3/mm^3)	2.3%	4.9%
Absolute neutrophil count (<0.8 × 10^3/mm^3)	0.5%	0.6%

M = male; F = female
* <75% (<50% for absolute neutrophil count) of lower limit of normal (LLN) for values normal at baseline
† Represents lowest abnormal post-baseline value through the last dose of active drug
‡ Number of patients with non-missing laboratory values

serotonergic agents (i.e. serotonin reuptake inhibitors, tricyclic antidepressants, etc.) were excluded from Phase 3 clinical trials. No difference in serotonergic effects of tedizolid versus placebo was found in animal studies.

DOSAGE AND ADMINISTRATION[1]

No dose adjustment necessary when changing from intravenous to oral administration. No dose adjustments necessary in patients with renal impairment, hemodialysis, or hepatic impairment.

PYXIS OVERRIDE STATUS

This drug does not need override privileges in Pyxis.

COST CONCLUSIONS

Tedizolid is a new oxazolidinone antibiotic that has activity against *Staphylococcus aureus* (MRSA and MSSA), *Streptococcus agalactiae*, *Streptococcus anginosus* group, *Streptococcus pyogenes*, and *Enterococcus faecalis*. Phase 3 clinical trials have shown tedizolid to be non-inferior to linezolid for treatment of acute bacterial skin and skin structure infections. Tedizolid is well tolerated with possibly less hematological adverse reactions than linezolid, although its safety in patients with decreased white blood cells has not been established. Dosing is once daily with no dose adjustments for IV to oral administration as well as renal or hepatic impairment.

REFERENCES

1. Prescribing Information: Sivextro. Lexington, MA: Cubist Pharmaceuticals U.S.; 2014.
2. O'Riordan W, et al. Tedizolid phosphate for the management of acute bacterial skin and skin structure infections: Efficacy summary. *Clin Infect Dis* 2014;58(S1):S43-50.
3. Das Debaditya, et al. Tedizolid phosphate for the management of acute bacterial skin and skin structure infections: Safety summary. *Clin Infect Dis* 2014;58(S1):S51-7.

Infection	Route	Dosage	Frequency	Infusion Time	Duration of Treatment
Acute Bacterial Skin and Skin Structure Infection (ABSSSI)	Intravenous	200 mg	Once daily	1 hour	6 days
	Oral	200 mg	Once daily	Not Applicable	

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

4. Prokocimer P, et al. Tedizolid phosphate vs linezolid for treatment of acute bacterial skin and skin structure infections: The ESTABLISH-1 randomized trial. *JAMA* 2013;309(6):559-569.

5. Moran G, et al. Tedizolid for 6 days versus linezolid for 10 days for acute bacterial skin and skin-structure infections (ESTABLISH-2): A randomized, double-blind, phase 3, non-inferiority trial. *Lancet Infect Dis* 2014. DOI:10.1016/S1473-3099(14)70737-6.

Infectious Disease [ALERT]

Updates

By Carol A. Kemper, MD, FACP

Screening for *C. diff* asymptomatic carriage

Hung Y-P, et al. Clinical impact of *Clostridium difficile* colonization. *J Microbiol Immunol Infect* 2014; http://dx.doi.org/10.1016/j.jmii/2014.04.11; and Alasmari F, et al. Prevalence and risk factors for asymptomatic Clostridium difficile carriage. *CID* 2014;59(2):216-222.

Asymptomatic carriage of *C. difficile* in adult hospitalized patients varies regionally, but estimates suggest that 4% to 23% of patients being admitted to hospital in the U.S. may be colonized with toxogenic strains of *C. difficile* (TCD). Not only are these patients at risk for active *C. difficile* infection (CDI), they are a significant source for skin and environmental contamination, similar to patients with active CDI. Some experts have advocated for greater attention to individuals admitted to hospital with asymptomatic *C. difficile* colonization, although no formal guidelines advocate for such. In addition, while treatment of these asymptomatic patients with metronidazole or vancomycin is not supported by current evidence, some physicians presumptively "prophylax" these individuals with metronidazole or vancomycin, especially when administering other antimicrobials, presuming the risk of active CDI is not trivial.

Because surveillance is not inexpensive, screening efforts should focus only on persons at high risk for *C. difficile* carriage. In an attempt to define those risk factors, Alasmari et al. screened 259 patients being hospitalized at Barnes-Jewish Hospital from 2010-2011. Forty (15%) were colonized with toxogenic strains of C. difficile (TCD) and 15 (6%) had non-toxogenic strains. Comparing these two groups, rates of recent hospitalization (50% vs 50%) and recent antibacterial exposure within 90 days (55% vs 56%) were similar; although admission from a SNF or other health-care facility was slightly greater for those with TCD strains than those with non-TCD (33% vs 24%). One or more outpatient clinic visits were documented within 30 days of hospitalization

for 85% of those with TCD, and 20% were on hemodialysis (compared with only 3.9% of non-colonized patients). There was considerable strain heterogeneity, and only 1 (3%) of those with TCD strains was found to have ribotype 027.

As the result of this and other similar data, our hospital facility has been performing surveillance rectal swabs for CD PCR for more than one year, placing any positives in contact isolation. The results are available twice daily. Surveillance was initially limited to those being directly admitted from a SNF or outside health care facility, but has been expanded to include: (1) any residence at a SNF, rehab, outside health care facility, or our own hospital within 30 days; (2) hemodialysis; and (3) a prior history of CDI at any time. It is estimated that up to 14% of persons with active CDI may remain colonized and continue to shed organisms for up to one year.

Rates of asymptomatic carriage at our facility are tracking at about 11% (informal data for the previous 6 months, 59/557 positive PCRs for TCD). Most of the positives are admitted from SNFs or other health care facilities. Approximately 250 persons are screened per quarter, for an estimated cost to the hospital of $20,000 quarterly — less than the estimated cost to the hospital of a single episode of CDI. Tacquired." In a twist of modern health care semantics, 2-3 of the active CDI cases identified per month were previously identified as being carriers, and thus no longer "count" as hospital-onset (HO)-CDI for reporting purposes. Over the past 3 years, rates of HO-CDI have steadily dropped at our facility — finally reaching our goal this year, well worth the cost. Now, if we only knew what to do medically with the positives.

Cefriaxone – is work horse finally fading?

ASM and CLSI White Paper on MSSA and Ceftriaxone Etests. July 11, 2104: http://bit.ly/1A0eJyB

Cefriaxone is one of those rare work horse antibiotics — one of the few antibiotics I reached for 30 years ago as an intern, and continue to use daily. It covers all manner of ills, is well tolerated, even at higher dosages, requires no specific monitoring or renal dose adjustment, and is generally administered once a day. From an ID perspective, it doesn't get any better.

Recent data has, however, raised concerns that Ceftriaxone may be losing it's grip on MSSA, as some studies have suggested an upward trend in MICs for MSSA. This has led some experts to recommend against the routine use of Ceftriaxone for the treatment of more severe MSSA infections, such as endocarditis or joint infection, at least not before confirming susceptibility. But most clinical laboratories do not routinely perform CFTX MICs to staphylococci; and oxacillin is ordinarily used to indirectly predict cephalosporin susceptibility. Furthermore, even if an Etest for CFTX MIC for an MSSA isolate is obtained – there are no current CLSI criteria for CFTX breakpoints for staphylococci. The 2012 CLSI M100 breakpoint previously used for defining susceptibility was < 8 mcg/ml, 16-32 mcg/mL (intermediate), and > 64 mcg/ml (resistant). In contrast, the Food and Drug Administration (FDA) susceptible breakpoints are < 4 mcg/mL (susceptible), 8 mcg/mL (intermediate), and > 16 mcg/mL (resistant).

Adding to the confusion, a recent article (Pickering et al.) first published in *CID* (online March 14, 2014) stating that MSSA isolates at their community teaching facility were 60% resistant to ceftriaxone has been retracted due to an honest error in interpretation of a key laboratory test. The data presented were obtained using Etest ceftriaxone strips (which are not FDA-cleared for testing of staphylococci). The CDC since obtained 16 of the MSSA isolates from the Pickering study, which were tested using broth microdilution and disk diffusion, and also with two different strip Etests. All of the isolates tested CFTX-susceptible by both broth microdilution (BMD) (MIC range, 2-4 mcg/mL) and disk diffusion (zone range 22-27 mm). In contrast, CFTX MICs obtained with the two E tests were generally higher than those obtained by BMD; 42% of the isolates tested by Etest demonstrated MICs of 16-32 mcg/mL — which would be presumed to be at least intermediate, if not resistant by Etest alone. Based on this and other data, the ASM has stated the Etest will overcall resistance of MSSA isolates, and is inadequate for testing staphylococci to CFTX.
So what's an ID practitioner to do? Limited data suggest that CFTX may, in fact, be less bactericidal than either cefazolin or vancomycin in in vitro models. And there appears to be a strong inverse correlation between CFTX MICs and antibacterial activity. In a small in vitro model, bacterial killing at 24 hrs was reduced significantly for escalating CFTX MICs of 2, 4 and 8 mcg/mL. Available in vitro evidence suggests that CFTX may not be adequate in the treatment of serious MSSA infection when the MIC is > 2 mcg/ml -- but may be a very reasonable option at lower MICs, although there remains limited published clinical data demonstrating its efficacy in serious MSSA infection. But if the MIC can not readily be determined – you may be stuck.

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 to the right or log on to **www.cmecity.com** to take a post-test; tests can be taken after each issue or collectively at the end of the semester. First-time users will have to register on the site using the 8-digit subscriber number printed on their mailing label, invoice or renewal notice.
3. Pass the online tests with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.
4. After successfully completing the last test of the semester, 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. A study of subglottic secretion suctioning found that how many episodes of ventilator-associated pneumonia (VAP) could be prevented for every 100 intubated patients?

A. 4
B. 7
C. 9
D. 12

2. Which of the following is correct regarding the study by Longnecker and colleagues of statin therapy in HIV infected patients receiving antiretroviral therapy?

A. Pravastatin administration improved renal function.

B. Simvastatin administration was associated with impaired renal function.

C. Rosuvustatin administration was associated with slowing of decline in renal function.

D. Rosuvustatin administration is contraindicated in patients receiving tenofovir because it worsens renal function.

3. Which of the following is correct with regard to PCP?

A. Intravenously administered pentamidine is the treatment of choice when the PaO2 is <70 mm Hg while breathing ambient air.

B. Serum testing for ß-D-Glucan has been reported to have a sensitivity >90% in the diagnosis of this infection.

C. Adjunctive corticosteroid therapy is indicated when the arterial PO2 is <80 mm Hg or the alveolar-arterial O2 gradient is <35 mm Hg.

D. Polymerase chain reaction testing for PCP has low sensitivity and high positive predictive value.

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

TIPPING POINT

Why Saudi camels unlikely to be culled though they are a MERS-CoV reservoir. "Camels in the Kingdom are like dairy cows, beef cows, racehorses, pulling horses, beloved Labradors, and living daily reminders of holy scripture, all in one." National Geographic: http://bit.ly/1oOJmOS

Infectious Disease [ALERT]

2014 Index

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