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Infectious Disease [ALERT]

Incisive Commentary and Clinical Abstracts on Current Issues in Infectious Diseases

# Pharmacotherapy Considerations for COVID-19

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**Dr. Ha and Dr. Alegria report no financial relationships relevant to this field of study.**

The 2019 novel coronavirus (2019-nCoV) is the causative pathogen of 2019 coronavirus disease (SARS-CoV-2), an acute respiratory illness, which can range from asymptomatic carriage to life-threatening, severe disease.[1] At the time of this writing, there have been more than 1,000 reported cases in the United States.[2] The global outbreak of 2019-nCoV has spawned interest in potential treatment options, particularly for those with more severe illness. This article provides a brief summary of selected pharmacotherapy options proposed for COVID-19.

## REMDESIVIR

Remdesivir is a prodrug of an adenosine nucleoside, which inhibits viral RNA-dependent RNA polymerase.[3,4] At the time of this writing, remdesivir is not approved by the Food and Drug Administration (FDA) and is available only as an investigational drug through Gilead Sciences.[5] It was studied originally for Ebola virus disease and found to have no benefit vs. comparators. Despite this, remdesivir has been found to have a broad spectrum of activity against various coronaviruses, including SARS-CoV, MERS-CoV, and 2019-nCoV in pre-clinical studies.[6,7]

Although reports on clinical outcomes of remdesivir therapy are limited, it was used in the first confirmed case of COVID-19 in the United States. Initially the patient presented with mild symptoms, but after the first week of largely supportive care, had progression

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of the disease to pneumonia requiring supplemental oxygenation, which prompted the initiation of remdesivir through compassionate use. The patient's clinical condition subsequently improved.[8]

At the time of writing, multiple randomized clinical trials (NCT04252664, NCT04257656, and NCT04280705) are being conducted on remdesivir for treatment of COVID-19 in the United States. In these trials, remdesivir is given as either a five-day or 10-day course, dosed at 200 mg intravenously on day 1, and 100 mg intravenously daily thereafter. Exclusions vary between trials, but, notably, they generally exclude patients 17 years of age or younger, those with severe hepatic or renal impairment, and pregnant or breastfeeding women.[9-11]

## CHLOROQUINE OR HYDROXYCHLOROQUINE

Chloroquine has been proposed as another pharmacotherapy consideration for COVID-19 and has been found to have in vitro activity against SARS-CoV-2.[7] Its antiviral activity may be afforded by an increase in endosomal pH and interference with glycosylation of cellular receptors of SARS-CoV.[12]

Initial reports from more than 100 patients asserted that there was superiority of chloroquine to control treatment in inhibiting exacerbation of pneumonia, promoting negative conversion, and shortening the disease. However, this information is per a news briefing in China and, at the time of this writing, no patient data has been released yet.[12] The purported treatment dosage of chloroquine is 500 mg orally twice daily for 10 days.[13] There is an ongoing Phase III, placebo-controlled clinical trial (NCT04261517) of hydroxychloroquine for pneumonia caused by 2019-nCoV. In this trial, the treatment regimen is hydroxychloroquine 400 mg orally daily for five days.[14]

## LOPINAVIR

Lopinavir is an HIV protease inhibitor that has been reported to have activity against SARS-CoV-2. It is unclear whether inhibitors of HIV protease (in the aspartic protease family) can effectively inhibit that of 2019-nCoV (in the cysteine protease family).[15] Use for COVID-19 is based largely on trials in severe acute respiratory syndrome (SARS) suggesting that lopinavir was associated with improved clinical outcomes and mortality.[16,17]

**Table 1: Selected Potential Antiviral or Adjunctive Therapies for COVID-19[15,20,22]**

- Remdesivir
- Chloroquine
- Hydroxychloroquine
- Lopinavir/ritonavir
- Darunavir/cobicistat
- Ribavirin
- Nitazoxanide
- Nelfinavir
- Penciclovir
- Mefloquine
- Oseltamivir
- Tocilizumab
- Interferon alfa (nebulized)
- Intravenous immunoglobulin
- Baricitinib

As opposed to remdesivir and chloroquine, however, several detailed reports on clinical experience with lopinavir have been published. That said, the data are not encouraging. In a study of five patients with COVID-19 in Singapore who received lopinavir/ritonavir, the clinical benefit was equivocal, and progressive disease occurred in two patients. Of note, this study used a lower dose (200/100 mg orally twice daily) of lopinavir/ritonavir.[18] In a study, four patients in Shanghai with COVID-19, two with mild disease and two with severe disease, received lopinavir/ritonavir (400/100 mg orally twice daily for six to 15 days), along with other treatments including arbidol and traditional Chinese medicine. Three patients improved, two of whom had negative viral testing at the end of data collection. The fourth patient, with severe COVID-19, showed signs of improvement at the end of data collection.[19]

Guidelines for 2019-nCoV pneumonia from the Zhongnan Hospital of Wuhan University Novel Coronavirus

Management and Research Team provided a weak recommendation for the use of lopinavir/ritonavir based on benefits found in patients with SARS or Middle East respiratory syndrome (MERS), especially with earlier administration.[20]

## ADJUNCTIVE THERAPIES

Adjunctive corticosteroids have not shown clinical benefit, have delayed viral RNA clearance in other coronavirus disease (SARS and MERS), and may increase the risk of side effects (e.g., psychosis, diabetes, and avascular necrosis) and increased mortality in influenza.[21] Chinese guidance has suggested the use of tocilizumab for cytokine storm in patients with severe disease (e.g., acute respiratory distress syndrome) and elevated interleukin-6 levels.[22] ■

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## ABSTRACT & COMMENTARY

# Quantifying the Risk of SARS-CoV-2 Transmission in the United States


***By Stan Deresinski, MD, FACP, FIDSA***

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



SYNOPSIS: In the United States, the rate of symptomatic transmission of SARS-CoV-2 to contacts was only 0.45%, but was 10.5% in household contacts; there were tertiary symptomatic transmissions. However, since only symptomatic individuals underwent testing, the actual overall rate of transmission with or without resultant symptomatic illness is likely to be higher.

SOURCE: Burke RM, Midgley CM, Dratch A, et al. Active monitoring of persons exposed to patients with confirmed COVID-19 — United States, January-February 2020. *MMWR Morb Mortal Wkly Rep* 2020;69:245-246.

On Jan. 20, 2020, state and local health departments in the United States, together with Centers for Disease Control and Prevention (CDC) teams began identifying and monitoring all close contacts of patients with confirmed COVID-19. By Feb. 26, 12 travel-related cases and three with no travel history (two of whom were close household contacts of cases) had been diagnosed. These were in addition to 46 cases in repatriated U.S. citizens.

Examination of the first 10 travel-related cases led to the identification of 445 close contacts, with a range of one to 201 per case. Nineteen of the 445 lived in the same household as the case, and five of these continued to have exposure to a case who had been isolated at home. In addition, 104 (23%) were community members who had spent ≥ 10 minutes within 6 feet of a case patient, while 100 (22%) were community members exposed to a patient in a healthcare setting, and 222 (50%) were healthcare personnel.

Contacts were actively monitored for new or worsening symptoms for 14 days. During that time, 54 (12%) met criteria and became persons under investigation (PUI) and were tested for evidence of COVID-19. These people were tested, and two (both household contacts) of the 54 proved to be infected, for a calculated symptomatic attack rate of only 0.45%. However, among household members, this rate was 10.5%. Of interest is that both household secondary cases were not among those with continued contact with a case patient after the latter's diagnosis. To determine the risk of transmission from the two secondary cases (tertiary transmission), 146 of their contacts were monitored for 14 days. While 18 (12%) developed symptoms, none were infected.

## ■ COMMENTARY

In this epidemiological study, the secondary attack rate among symptomatic contacts was only 0.45% overall, but was 10.5% among symptomatic household contacts. At the same time, the tertiary symptomatic attack rate was 0%, indicating an apparent lack of sustained serial transmission of infection. However, it must be emphasized that these results may underestimate the true rate of overall transmission, since only symptomatic contacts underwent testing and we know that COVID-19 infections may be asymptomatic. Nonetheless, the fact that the rate of transmission causing symptomatic infection is approximately 20 times higher in household contacts than in general contacts is an indication that the risk is determined in large part by the intimacy and duration of contact. More work is to be done. ■

ABSTRACT & COMMENTARY

# Combination Therapy of MRSA Bacteremia Was Not Beneficial in a Randomized Clinical Trial

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

SYNOPSIS: In a randomized clinical trial conducted at 27 hospitals in four countries, researchers found that the addition of an antistaphylococcal beta-lactam to vancomycin or daptomycin (99% received vancomycin) did not lead to improved outcomes in MRSA bacteremia. The trial was stopped early because of safety concerns, including a higher risk of acute kidney injury in the combination group.

SOURCE: Tong SYC, Lye DC, Yahav D, et al. Effect of vancomycin or daptomycin with vs without an antistaphylococcal β-lactam on mortality, bacteremia, relapse, or treatment failure in patients with MRSA bacteremia: A randomized clinical trial. *JAMA* 2020;323:527-537.

The treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia with vancomycin or daptomycin (currently the standard of care) leads to death in approximately 20% of cases. Thus, better treatment regimens are needed urgently. Tong and colleagues sought to determine whether adding a beta-lactam agent with antistaphylococcal activity to vancomycin or daptomycin would lead to improved outcomes.

The study was a multicenter, open label, randomized, clinical trial powered to detect superiority. Patients were included if they had a positive blood culture for MRSA, were randomized within 72 hours of the first positive blood culture, were 18 years of age or older, and were likely to remain hospitalized for at least seven days following randomization. They were randomized in a 1:1 ratio to standard therapy, which was intravenous vancomycin dosed to maintain trough levels of 15 to 20 mcg/mL, or daptomycin dosed at 6 to 10 mg/kg per day, or to combination therapy that included vancomycin or daptomycin plus a seven-day course of an intravenous beta-lactam drug (i.e., flucloxacillin, cloxacillin, or cefazolin).

The primary outcome, assessed 90 days after randomization, was a composite measure with four components, including all-cause mortality, persistent bacteremia at day 5, microbiological relapse defined as a positive blood culture for MRSA at least 72 hours following a negative blood culture, and microbiological treatment failure defined as a positive sterile site culture for MRSA at least 14 days after randomization. Participants were recruited between August 2015 and July 2018 from 27 hospitals in Australia, New Zealand, Singapore, and Israel.

Of the 352 patients included in the analysis, 174 were randomized to combination therapy and 178 to standard therapy. The median age was 64 years and most (349/352) received vancomycin. The primary composite outcome at day 90 was met by 59 of 170 patients in the combination group (35%) vs. 68 of 175 in the standard therapy group (39%; difference, -4.2%; 95% confidence interval [CI], -14.3% to 6.0%; $P = 0.42$). For the secondary outcomes, mortality did not differ significantly at any point between the groups. However, persistent bacteremia at day 5 was less common in the combination group (19/166 [11%]) vs. the standard therapy group (35/172 [20%]; difference, -8.9%; 95% CI, -16.6 to -1.2; $P = 0.02$). Acute kidney injury (AKI) occurred significantly more often in the combination group (34/145 [23%]) than in the standard therapy group (9/145 [6%]; difference, 17.2%; 95% CI, 9.3%-25.2%; $P < 0.001$). The trial was stopped early because of the higher AKI incidence in the combination group.

The investigators conducted a post hoc analysis for the AKI cases. Of the 34 patients in the combination therapy group who developed AKI, six required hemodialysis (HD). By day 90, two still required HD and seven had died. In contrast, of the nine patients with AKI in the standard therapy group, two required HD. By day 90, neither was still receiving HD, and three of the nine had died. Furthermore, the severity of the AKI was higher in the combination group. Finally, AKI was associated more with flucloxacillin (28%) and cloxacillin (24%) than with cefazolin (4%).

## [Clinicians need better therapies for MRSA bacteremia.]

### ■ COMMENTARY

Clinicians need better therapies for MRSA bacteremia. As the study by Tong and colleagues demonstrates, combination therapy that includes seven days of an antistaphylococcal beta-lactam does not seem to be the answer. The only advantage for combination therapy was a reduction in persistent bacteremia at day 5. However, the benefit was far outweighed by the higher incidence of AKI, which notably led to the trial being stopped early. This is similar to previous studies that examined aminoglycosides or rifampin in combination with standard therapy for MRSA bacteremia, both of which led to increased toxicity without a discernible benefit. Moreover, a reduction in the duration of MRSA bacteremia has not been shown to lead to better outcomes in prospective studies.

The incidence of AKI with cefazolin was much less than with the antistaphylococcal penicillins. Indeed, the trial left open the possibility that the combination of vancomycin with cefazolin might be effective and not harmful. Further studies to investigate this hypothesis are warranted.

The study was well-designed overall. However, there are a few limitations worth noting. First, other antistaphylococcal penicillins (e.g., nafcillin or oxacillin) might not be as nephrotoxic in combination compared to the ones used in the trial. Second, few patients were prescribed daptomycin, which is less nephrotoxic than vancomycin. Third, vancomycin dosing was based on maintaining trough levels between 15 and 20 mcg/mL, which has been

associated with a higher risk for nephrotoxicity compared to using area-under-the-curve (AUC)-guided dosing.

Fourth, the median age of the patients was 64 years, which raises the issue of whether combination therapy might be safer in younger patients and perhaps beneficial in certain populations, such as patients who use intravenous drugs. Finally, 98% of the patients received antibiotics in the preceding 72 hours before randomization, which might have been a confounding variable.

Using combination therapy for MRSA bacteremia is a tempting concept because of its theoretical benefits and positive results from animal models. We have a good understanding of what does not work, based on previous studies and now the one by Tong and colleagues. Yet, while the study by Tong and colleagues has provided new answers, it also has generated further questions that deserve to be studied using a similar rigorous scientific approach. ■

ABSTRACT & COMMENTARY

# Empiric Anti-MRSA Therapy in Pneumonia May Not Always Be a Good Idea

***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, 88,605 patients in the Veterans Administration system who were hospitalized with pneumonia were examined. Thirty-eight percent received empiric anti-methicillin-resistant *Staphylococcus aureus* (MRSA) treatment. Empiric anti-MRSA treatment was not associated with a reduction in mortality in any subgroup of patients studied and appeared to cause harm in many patients.

SOURCE: Jones BE, Ying J, Stevens V, et al. Empirical anti-MRSA vs standard antibiotic therapy and risk of 30-day mortality in patients hospitalized for pneumonia. *JAMA Int Med* 2020 Feb. 17. Doi: 10.1001/jamainternmed.2019.7495. [Epub ahead of print].

Researchers conducted a retrospective multicenter cohort study of all hospitalizations in which patients received either anti-methicillin-resistant *Staphylococcus aureus* (MRSA) or standard therapy for community-acquired pneumonia (CAP) in the Veterans Health Administration healthcare system from Jan. 1, 2008, to Dec. 31, 2013. Subgroups of patients analyzed included those with intensive care unit admission, MRSA risk factors, positive results of a MRSA surveillance test, and positive results of a MRSA admission culture. Among 88,605 hospitalized patients (86,851 men; median age, 70 years), empirical anti-MRSA therapy was administered to 33,632 (38%); 8,929 patients (10%) died within 30 days.

Compared with standard therapy alone, in weighted propensity score analysis, empirical anti-MRSA therapy plus standard therapy was significantly associated with an increased adjusted risk of death (adjusted risk ratio [aRR]), 1.4), kidney injury (aRR, 1.4), secondary *Clostridioides difficile* infections (aRR 1.6), vancomycin-resistant *Enterococcus* spp. infections (aRR, 1.6), and secondary gram-negative rod infections (aRR, 1.5). Similar associations were found between anti-MRSA therapy use and 30-day mortality (aRR, 1.6), and among patients admitted to the intensive care unit (aRR, 1.3), those with a high risk for MRSA (aRR, 1.2), and those with MRSA detected on surveillance testing (aRR, 1.6). No significant favorable association was found between empirical anti-MRSA therapy and death among patients with MRSA detected on culture (aRR, 1.1).

## ■ COMMENTARY

This is an interesting study that certainly casts doubt on the current widely accepted practice of administering empiric anti-MRSA therapy to a large percentage of patients admitted to the hospital with CAP, especially elderly patients, those recently (or remotely) hospitalized, and patients coming from skilled nursing facilities. Although this study certainly has a robust sample size, I cannot help but think that one of the reasons this retrospective study appeared to show "harm" from empiric anti-

MRSA therapy is that some subtle factors influenced clinicians to preferentially prescribe empiric anti-MRSA therapy to sicker patients.

The fact that even those who had positive cultures for MRSA and those who had a positive MRSA surveillance screening test did not benefit from empiric anti-MRSA therapy is particularly counter-intuitive. This may be related to the relatively poor positive predictive value of isolation of *S. aureus* from expectorated sputum and can reflect oropharyngeal colonization rather than the etiologic agent of the pneumonia.

Although this study has limitations (which the authors acknowledge), the results should seriously call into question the common practice of administering empiric anti-MRSA therapy to most patients with CAP, since not only did most patients fail to benefit, but many actually were harmed by this practice. Clearly, we need better diagnostic tests for rapidly determining the etiology of CAP, and, of course, both new and old anti-MRSA antibiotics should be studied in well-designed, prospective, randomized trials. ■

PHARMACOLOGY UPDATE

# Imipenem, Cilastatin, Relebactam (Recarbrio)

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

Imipenem-cilastatin-relebactam (IMI/REL) is a broad-spectrum antibiotic that combines three active ingredients: Imipenem (IMI) is a carbapenem antibiotic that inhibits bacterial cell wall synthesis through binding penicillin binding proteins, cilastatin sodium is a renal dehydropeptidase inhibitor that prevents inactivation if imipenem by renal enzymes, and relebactam is a class A/C beta-lactamase inhibitor preventing degradation of imipenem.

In July 2019, the Food and Drug Administration (FDA) approved IMI/REL for the treatment of complicated urinary tract infections (cUTI), including pyelonephritis and complicated intra-abdominal infections (cIAI). In a Phase III, randomized, double-blind, controlled trial, investigators examined the efficacy and safety of IMI/REL compared to imipenem/cilastatin (IMI) plus colistin for the treatment of imipenem-nonsusceptible bacterial infections in 31 patients. The primary endpoint of overall favorable response was demonstrated in 71% of the IMI/REL group vs. 70% of the IMI plus colistin group (difference -7.3%; 90% confidence interval [CI], -27.5%, 21.4). Treatment emergent nephrotoxicity occurred in 10% of the IMI/REL group vs. 56% of the IMI plus colistin group ($P$ = 0.002). An overview of Phase II and Phase III clinical trials evaluating the use of IMI/REL is summarized in Table 1.[2-5]

## MICROBIOLOGY[1]

The FDA susceptibility breakpoint for IMI/REL against *Enterobacteriaceae* is ≤ 1/4 mcg/mL, with isolates with a minimum inhibitory concentration (MIC) of 2/4 mcg/mL considered intermediate, and ≥ /4 mcg/mL considered resistant. Clinical efficacy was shown for the following *Enterobacteriaceae*: *Klebsiella aerogenes*, *Enterobacter cloacae*, *Escherichia coli*, *Klebsiella pneumoniae*, *Citrobacter freundii*, and *Klebsiella oxytoca*. The *Pseudomonas aeruginosa* breakpoint for IMI/REL is ≤ 2/4 mcg/mL, with isolates with a MIC of 4/4 mcg/mL considered intermediate and ≥ 8/4 mcg/mL considered resistant. Additionally, the breakpoint for IMI/REL against anaerobic microorganisms is ≤ 4/4 mcg/mL, with isolates with a MIC of 8/4 mcg/mL considered

**Table 1: Overview of Phase II and Phase III Trials Evaluating IMI/REL[2-5]**

| Clinical Trial | Design | Study Intervention | Infection | Primary Outcomes |
|---|---|---|---|---|
| Sims et al[2] | Phase II, randomized double-blind, dose-ranging | IMI-REL vs. IMI 500 mg every 6 hours | cUTI | Favorable microbiological response at EOT: 95.5%/98.6% IMI/REL vs. 98.7% IMI |
| Lucasti et al[3] | Phase II, randomized double-blind, dose-ranging | IMI-REL vs. IMI 500 mg every 6 hours | cIAI | Favorable microbiological response at EOT: 96.3%/98.8% IMI/REL vs. 95.2% IMI |
| RESTORE-IMI-1[4] | Phase III, randomized double-blind, non-inferiority | IMI-REL 500 mg every 6 hours vs. IMI 500 mg every 6 hours + colistin (300 mg load, 150 mg every 12 hours) | HAP, VAP, cIAI, cUTI | Favorable overall response: 71.4% IMI/REL vs. 70% IMI + colistin |
| RESTORE IMI-2[5] | Phase III, randomized double-blind, comparator-controlled | IMI-REL 500 mg every 6 hours vs. piperacillin/tazobactam 4.5 g every 6 hours | HAP/VAP | Results to be published 28-day survival |

IMI-REL = imipenem, cilastatin, relebactam; IMI = imipenem, cilastatin; cUTI = complicated urinary tract infection; cIAI = complicated intra-abdominal infection; HAP = hospital-acquired pneumonia; VAP = ventilator-associated pneumonia; EOT = end of therapy

intermediate and ≥ 16/4 mcg/mL considered resistant. Clinical efficacy was shown for the following anaerobes: *Bacteroides caccae*, *Bacteroides fragilis*, *Bacteroides ovatus*, *Bacteroides stercoris*, *Bacteroides thetaiotaomicron*, *Fusobacterium nucleatum*, and *Parabacteroides distasonis*. IMI/REL is not active against most isolates that contain metallo-beta-lactamases (MBLs) and some oxacillinases with carbapenemase activity.

## PHARMACOKINETICS/PHARMACODYNAMICS[1]

IMI/REL is available as an intravenous formulation for administration. The steady-state volume of distribution of imipenem, cilastatin, and relebactam is 24.3 L, 13.8 L, and 19 L, respectively. Plasma binding protein is 20%, 40%, and 22% for each of the components.

Imipenem is primarily metabolized by dehyropeptidases in the kidneys, while cilastatin and relebactam are minimally metabolized. All components are mainly excreted by the kidneys, and approximately 63% of imipenem, 77% of cilastatin, and 90% of relebactam were detected as unchanged drug in the urine.

The average half-life is one hour for imipenem and 1.2 hours for relebactam. The pharmacokinetic/pharmacodynamic parameter that best correlates with efficacy based on animal and in vitro models for imipenem is percent time of dosing interval that unbound plasma concentration of imipenem exceeds imipenem/relebactam MIC (% fT > MIC) against infecting organism. Relebactam's pharmacokinetic/pharmacodynamic parameter is best demonstrated by the ratio of 24-hour unbound plasma relebactam AUC to IMI/REL MIC (fAUC 0 – 24 hr/MIC). (*See Table 2.*)

## ADVERSE EFFECTS/WARNINGS[1]

For patients with known hypersensitivity to imipenem, cilastatin, or relebactam, this antimicrobial is contraindicated. Seizures and other central nervous system (CNS) adverse reactions have been reported most commonly in patients with CNS disorders (brain lesions, history of seizures) and/or compromised renal function.

Common side effects (> 2%) include nausea, vomiting, diarrhea, phlebitis, pyrexia, headache, AST/ALT elevation, and hypertension. Rare adverse effects include agranulocytosis, increased eosinophils, hemolytic anemia, seizure, hepatic failure, and jaundice.

Clinically relevant drug-drug interactions include combination of IMI/REL with ganciclovir or valganciclovir and valproate. Increased risk of seizures has been observed with imipenem/cilastatin and ganciclovir or valganciclovir;

**Table 2: IMI/REL Dosage and Adjustments for Renal Impairment[1]**

| Estimated CrCl (mL/min)* | Recommended Dose + | Dosing Interval |
|---|---|---|
| > 90 | 1.25 g (imipenem 500 mg, cilastatin 500 mg, relebactam 250 mg) | Every 6 hours |
| 60-89 | 1 g (imipenem 400 mg, cilastatin 400 mg, relebactam 200 mg) | Every 6 hours |
| 30-59 | 0.75 g (imipenem 300 mg, cilastatin 300 mg, relebactam 150 mg) | Every 6 hours |
| 15-29 | 0.5 g (imipenem 200 mg, cilastatin 200 mg, relebactam 100 mg) | Every 6 hours |
| < 15 | Avoid unless IHD instituted within 48 hours | - |
| ESRD on hemodialysis[c] | 0.5 g (imipenem 200 mg, cilastatin 200 mg, relebactam 100 mg) | Every 6 hours |
| Peritoneal dialysis | Not recommended (inadequate data) | - |

CrCl = creatinine clearance; ESRD = end-stage renal disease; IHD = intermittent hemodialysis
* Cockroft-Gault formula
+ Administer intravenously over 30 minutes
[c] Administration should be timed after hemodialysis and at intervals following IHD

thus, both antimicrobials should not be used unless the potential benefits outweigh the risks. Carbapenems have been shown to decrease valproic acid concentrations, which may increase the risk of breakthrough seizures; therefore, alternative antibiotics should be considered for patients whose seizures are well-controlled on valproic acid.

## CONCLUSION

Imipenem-cilastatin-relebactam is a broad-spectrum antibiotic approved for the treatment of cUTI and cIAI in patients who have limited or no alternative treatment options. This antimicrobial combines imipenem/cilastatin with a new beta-lactamase inhibitor, relebactam. It provides enhanced activity against most strains of KPC-producing ESBLs and carbapenem-resistant *Enterobacteriaceae* (CRE), and restores susceptibility of imipenem against *Pseudomonas* spp. It appears to have a more favorable safety profile compared to colistin for the treatment of multidrug-resistant organisms. ■

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# Updates

By Carol A. Kemper, MD, FACP

## Urinary Fermentation Syndrome?

SOURCE: Kruckenberg KM, DiMartini AF, Rymer JA, et al. Urinary auto-brewery syndrome: A case report. *Ann Intern Med* 2020 Feb. 25. doi: 10.7326/L19-0661.

A case of intestinal fermentation syndrome, often referred to as "auto-brewery syndrome," was reviewed recently in this column in December 2019.[1] In brief, a previously healthy 46-year-old man had several traumatic falls when inebriated, complicated by intracerebral hemorrhage, and he had been arrested for driving under the influence. Despite protestations that he was not a drinker, his blood alcohol levels were repeatedly elevated (50 to 400 mg/dL). After investigation, it was observed that his blood alcohol level increased following a carbohydrate challenge. Both *Saccharomyces cerevisiae* and *Saccharomyces boulardii* were isolated in stool cultures; cultures obtained from the upper small gut and cecum grew *Candida albicans* and *Candida 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. Finally, treatment with micafungin 150 mg daily for six weeks was successful at eradicating his yeast colonization, and he resumed a fairly normal, inebriate-free life.
In a fascinating twist to this tale, a 61-year-old woman with diabetes was turned down for a renal transplant because her urine ethanol levels were elevated repeatedly, raising suspicions of occult alcohol abuse. She had repeatedly denied alcohol use, and did not appear to be inebriated during any of her clinical evaluations. But the transplant center insisted on referring her for alcohol addiction treatment.

[Clinicians should be aware of the possibility of deceptively elevated ethanol levels in blood and urine specimens from yeast fermentation in either the gut or the bladder.]

However, a second transplant center astutely observed that although urine tests for alcohol were positive repeatedly, plasma tests for ethanol were negative, and urine studies for ethyl glucuronide and ethyl sulfate, metabolites of ethanol, both were negative. Frequent glycosuria (> 1,000 mg/dL) was observed. Urine culture yielded *Candida glabrata*. Yeast-rich fractions of urine were incubated over a 24-hour period and measured ethanol levels increased from a baseline of 44 mg/dL to 476 mg/dL and 816 mg/dL at 25°C and 37°C, respectively. At 37°C, her freshly voided urine produced 32 mg/dL of ethanol per hour! Attempts to clear the bladder of yeast with antifungal therapy were unsuccessful, but she was able to be placed on a transplant list.

Clinicians should be aware of the possibility of deceptively elevated ethanol levels in blood and urine specimens from yeast fermentation in either the gut or the bladder.

### REFERENCE

1. 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.

## Residential Legionellosis From Potable Water

SOURCE: Schumacher A, Kocharian A, Koch A, Marx J. Fatal case of Legionnaires' disease after home exposure to *Legionella pneumophila* serogroup 3 — Wisconsin, 2018. *MMWR Morb Mortal Wkly Rep* 2020;69: 207-211.

*Legionella* in residential, potable water is well-described but seldom causes significant infection. In 2018, the Wisconsin Department of Public Health received a report of a positive culture for *Legionella pneumophila* serogroup 3 that proved fatal in a 70-year-old man with known immunosuppression. He had been diagnosed with combined immunodeficiency syndrome two years earlier, and had just completed a 30-day course of levofloxacin treatment for lower extremity cellulitis and abscess. Toward the end of his treatment course, he developed fever and rash, with progressive mental status changes and shortness of breath. He presented to a local emergency room, where he tested positive for rhinovirus and parainfluenza 1 and had a normal chest radiograph. Because of the fever and immunosuppression, he was admitted.
On his fifth day of hospitalization, the fever persisted, the cough worsened, and the chest

radiograph showed a left upper lobe infiltrate. Urinary antigen tests for *Legionella pneumophila* 1 were negative. He was started on broad-spectrum antibiotics with meropenem, and two days later, he received inhaled tobramycin. He died on the 10th day of hospitalization. Bronchoalveolar lavage fluid cultured for *Legionella* grew *Legionella pneumophila* serogroup 3 six days later.

Because of the possibility of nosocomial exposure in the hospital, epidemiologic investigation of the hospital water system was performed the day following this culture result. Nine potential water sources in the hospital were cultured, including inpatient and outpatient sink faucets, a shower, an ice machine, and a warm water pool. None were positive. Additional samples collected about three weeks later and cultured at both the hospital and the state laboratory again were negative.

Specimens collected from two showers in the home, which is served by a municipal water system, both were positive for *L. pneumophila* serogroup 3. Later studies confirmed that these isolates matched the patient isolate by both PFGE and whole-genome multilocus sequencing. The investigation concluded that the home was the source of the *Legionella* infection.

[This case report highlights the importance of *Legionella* culture of lower respiratory tract specimens — rather than depending on the urinary antigen test, which tests only for serogroup 1.]

A plumber was called in, and following the advice of a home guidance manual, drained the system, shocked it with chlorine, and then ran the system at 148°F for three days, flushing all the pipes. The shower heads were cleaned and soaked in vinegar. Despite this, two cultures obtained from eight different fixtures about one week later were persistently positive, including the sink sprayer and a bathroom sink faucet. The family was counseled to monitor their systems and consult a physician in the event of illness.

This case report highlights the importance of *Legionella* culture of lower respiratory tract specimens — rather than depending on the urinary antigen test, which tests only for serogroup 1. The Centers for Disease Control and Prevention recommends both cultures and urinary antigen for *Legionella*, although polymerase chain reaction (PCR) testing on lower respiratory specimens also may be useful — and faster than culture.

Further, this case demonstrates the difficulty in eradicating home sources for *Legionella* infection. In my personal experience dealing with mycobacterial illness, I have recommended removing or replacing all sprayers, aerators, and shower heads, before shocking the system with chlorine, rather than attempting to clean them.

## Which Treatment for SARS-CoV-2 Is Best?

SOURCE: Gao J, Tian Z, Yang X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies (letter). *BioSci Trends* 2020 Feb. 19. doi:10.5582/bst/2020.01047. [Epub ahead of print].

A hot topic of conversation this week is how best to treat our three critically ill SARS-CoV-2 patients in the intensive care unit (ICU). Facilities nearby are using remdesivir, and another is using hydroxychloroquine.

Chloroquine has been found to block SARS-CoV-2 infection, with cytotoxic activity demonstrated in vitro by increasing the endosomal pH, interfering with viral fusion, and interfering with glycosylation of cellular receptors. The National Health Commission of the People's Republic of China has been quickly conducting several clinical trials of various agents, including hydroxychloroquine and chloroquine. In a comparison of chloroquine to a "control" treatment of more than 100 patients, researchers found active treatment was superior to the control in "inhibiting the exacerbation of pneumonia, improved lung findings, and shortening the disease course," and in promoting clearance of the virus in respiratory specimens. It was fairly well tolerated, with no severe adverse reactions. Chloroquine will be included in the upcoming version of China's treatment guidelines. ■

ABIM CME MOC ACCREDITED

## CME INSTRUCTIONS

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## CME QUESTIONS

**1. Which of the following is correct regarding the Centers for Disease Control and Prevention study of the rate of symptomatic transmission of SARS-CoV-2 in the United States?**

a. The symptomatic attack rate among household contacts was 10.5%.

b. The symptomatic attack rate among all contacts was 5.4%.

c. The symptomatic attack rate among household contacts was approximately the same as that of all contacts.

d. The symptomatic tertiary attack rate (affecting "contacts of contacts") was the same as that among primary contacts.

**2. Which of the following is correct regarding the randomized clinical trial of combination therapy for patients with methicillin-resistant *Staphylococcus aureus* bacteremia?**

a. Combination therapy was associated with reduced mortality.

b. Combination therapy was associated with statistically significant improvement in the composite study endpoint.

c. Combination therapy was associated with a significantly increased risk of acute kidney injury.

d. The use of cefazolin was associated with a greater risk of acute kidney injury than was the use of an antistaphylococcal penicillin.

**3. Which of the following is correct regarding imipenem/cilastatin/relebactam?**

a. It is not active against anaerobes.

b. Both cilastatin and relebactam are beta-lactamase inhibitors.

c. It is active against organisms expressing metallo-beta-lactamases.

d. It is active against many isolates of *Pseudomonas aeruginosa* and many *Enterobacteriaceae*.

## CME OBJECTIVES

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

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