WHAT'S HAPPENING AT UCSD?

NOVEMBER 13–19, 2017

U.S. Antibiotic Awareness Week

U.S. Antibiotic Awareness Week is an annual, one-week observance to raise awareness of antibiotic resistance and the importance of appropriate antibiotic prescribing and use. For more information, visit the CDC website here.

INSIDE THIS ISSUE

What’s happening at UCSD
Antibiotic Awareness Week
National Drug Shortage
Influenza Season Reminders
Hepatitis A Outbreak Updates
New FDA-approved Antimicrobials
Nitrofurantoin in Renal Impairment
Antimicrobial Stewardship tools and resources
Link to Antiibiogram 2017-Q2
UCSD Anti-infective Utilization Graphs
Resistance Series Part I: AmpC

HAVE AN IDEA?

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NATIONAL DRUG SHORTAGE

NS & D5W 50 mL & 100 mL IV BAGS

In late September 2017, the Baxter pharmaceutical manufacturing plant in Puerto Rico temporarily shut down due to damage caused by Hurricane Maria. This has resulted in a nation-wide shortage of sodium chloride 0.9% (normal saline) and dextrose 5% (D5W) 50 mL and 100 mL IV bags. This is a long-term shortage with no estimated end date.

WHAT CHANGES HAVE BEEN MADE?

In an effort to conserve our hospital supply at UCSD Health, selected antibiotics were switched from IVPB to slow IV Push on October 26, 2017.

- Automatic switch from IVPB to slow IV push (in sterile water) for:
  - Aztreonam 1 g, 2 g
  - Ceftazidime 1 g, 2 g
  - Cefoxitin 1 g, 2 g
  - Cefuroxime 750 mg, 1500 mg
  - Cefazolin 1 g, 2 g

- Recently, UCSD Health also switched to pre-made IVPB for:
  - Piperacillin-tazobactam 2.25 g, 3.375 g, 4.5 g
  - Penicillin G 3 million units

WHAT ELSE CAN YOU DO TO HELP?

- Encourage switching to non-IV routes (i.e. oral, via NG tube, IM, etc.) when clinically appropriate.
- Continue to assess and re-evaluate antimicrobial appropriateness and deescalate or discontinue therapy when possible.
Hepatitis A
What You Need to Know

As of October 24th, 2017, in San Diego County there have been...

516 confirmed cases
19 deaths
83,963 vaccinations administered
7,872 hygiene kits distributed

As of Sept 1, the outbreak has been classified as a public health emergency. For weekly updates, please visit the San Diego County HHSA website.

For Healthcare Personnel

Beginning in May 2017, more than 1,700 clinical health care workers have been vaccinated against hepatitis A. Due to the potential of a limited vaccine supply, we have been asked by County Public Health Services as well as the Centers for Disease Control (CDC) to modify our vaccination strategies and further prioritize vaccination to the highest-risk population. This includes individuals active in the clinical environment such as physician, nursing, pharmacy, and respiratory therapy students, personnel, and volunteers; workers in contact with sanitation and plumbing (facilities, engineering and environmental services employees); and food services personnel.

We strongly encourage hepatitis A vaccination for all of our at-risk health care force and are offering free vaccination during our influenza vaccination clinics. Check out the full schedule of vaccination clinic dates.

Team members who do not provide patient care or work in the clinical environment are encouraged to speak to their primary care providers regarding vaccination. Individuals who believe they may have been vaccinated or had hepatitis A disease may also contact their primary care providers for antibody testing. If the antibody test is positive, there is no need to administer an additional shot, as immunity if reliably life-long.

For Patients

EPIC queries have been developed in the ED, ambulatory, and inpatient areas to identify patient at risk of acquiring acute hepatitis A and needing vaccination.

In the ED and inpatient areas, there is no need to check for immunity if the patient is expected to stay for less than 48 hr (turnaround time for antibody testing) AND meets criteria for vaccination AND is not listed in the San Diego Immunization Registry; in this setting, just vaccinate. If time permits, consider antibody testing prior to vaccination.

In the ambulatory setting, UCSD Health is planning a vaccination campaign at 30 SROs (single-room occupancies) for marginally-housed patients who are at high risk. This effort is being coordinated by UCSD with volunteer nurses and should be underway by the end of October. If any nursing staff are interested in participating, please contact Darcy Wooten, MD at dawooten@ucsd.edu.

For more information on UCSD Health’s response to the Hepatitis A epidemic, please visit the Pulse website.
Winter is coming, and along with holidays and cooler weather come its seasonal viruses, and with the viruses come patients presenting with upper respiratory tract symptoms seeking evaluation and advice. The majority of these patients will have a viral illness (such as influenza, respiratory syncytial virus (RSV), or other virus) and will need guidance on managing their symptoms. Some will also need reassurance and education that these viral symptoms are not treated with antibiotics.

Influenza, first isolated in 1933, is a major source of morbidity and mortality. According to the CDC, there have been from 9.2 to 35.6 million illnesses, 140,000 to 710,000 hospitalizations, and 12,000 to 56,000 deaths annually from influenza since 2010 in the United States alone. The annual flu vaccine is the main preventative measure we have to combat this huge burden of disease. The WHO has been anticipating the dominant circulating flu viruses and making recommendations for the strains to include in the annual flu vaccine since 1978.

**GET VACCINATED!**

For the 2017-2018 flu season, the Advisory Committee on Immunization Practices (ACIP) recommends annual influenza vaccination for everyone 6 months or older. Of note, the nasal spray flu vaccine (Flumist®) should not be used this season due to lack of efficacy against this season's viral strains.

There are two types of intramuscular flu vaccines:

1. Trivalent flu vaccine protects against two strains of influenza A (H1N1 and H3N2) and one strain of influenza B virus
2. Quadrivalent flu vaccine aims to give broader protection against two influenza A viruses and two influenza B viruses; UCSD is providing the quadrivalent vaccine to all employees

**INFLUENZA TREATMENT**

Persons at risk for severe disease should be treated with antiviral therapy; oseltamivir is the preferred antiviral agent. Oseltamivir can shorten the duration of flu symptoms by 1-2 days and prevent potential complications if initiated within 48 hours of the onset of symptoms.

For patient education materials, check out the following links:

CDC [GET SMART website](http://www.cdc.gov/flu/)

CDC patient education [influenza brochure](http://www.cdc.gov/flu/resources/pdf/getsmart.consumer.pdf)

For additional influenza resources:

UC San Diego Health Pulse: [The Flu and You](http://www.ucsd.edu/news/)

CDC: [Influenza website](http://www.cdc.gov/flu/about/index.htm)

**INFLUENZA TESTING**

The influenza PCR (or if RSV is also of concern, the influenza/RSV PCR) is the appropriate test to perform when evaluating the majority of patients this season for influenza.

Note: The respiratory panel nucleic acid (RPNA) test is available UCSD and can diagnose several other viruses and a few bacteria. Due to the high cost of the RPNA, it should only be ordered for highly immunocompromised patients who are predisposed to a wide differential of respiratory pathogens.

**ANTIBIOTIC STEWARDSHIP**

Patients with viral syndromes should NOT be given antibiotics. It is important to provide patients with reassurance that antibiotics will not treat viral disease and have a risk of unnecessary side effects including diarrhea/nausea or sometimes rash. Symptomatic therapies can be offered for patients with a viral syndrome including pharmacologic and non-pharmacologic treatments:

Pharmacologic

- Acetaminophen or NSAIDs may be recommended for myalgias, headaches, and fevers
- Antihistamine and decongestant combinations can be offered for congestion
- Cough therapies may be considered although evidence of efficacy is variable

Non-pharmacologic

- Hot tea
- Rest
- Throat lozenges
- Smoking cessation
**VABOMERE™ (MEROPENEM–VABORBACTAM)**

On August 29th, 2017, the FDA approved Vabomere™ (meropenem-vaborbactam), an intravenous combination beta-lactam/beta-lactamase inhibitor for the treatment of complicated urinary tract infections (cUTI) including pyelonephritis. The approval of Vabomere™ was based on the results of two Phase III studies which demonstrated that Vabomere™ was non-inferior to piperacillin-tazobactam as well as other standard of care antibiotics, and was active against some meropenem-resistant isolates.

In clinical trials, Vabomere™ was active against *Enterobacter cloacae, E. coli,* and *K. pneumoniae* in the presence of some beta-lactamases and extended-spectrum beta-lactamases (ESBLs) including KPC, but not against all beta-lactamases with carbapenemase activity. Additionally, *in vitro* data suggests that Vabomere™ is active against most other *Enterobacteriaceae* and *Pseudomonas,* although clinical efficacy has not been established in clinical trials. For full prescribing information, click here.

**BAXDELA™ (DELAFLOXACIN)**

On June 19, 2017, the FDA approved a new fluoroquinolone, Baxdela™ (delafloxacin) oral tablets and injection, for the treatment of acute bacterial skin and skin structure infections (ABSSSI). The approval of Baxdela™ was based on the results of two Phase III studies in patients with ABSSSI, demonstrating that IV and oral Baxdela™ monotherapy was statistically non-inferior to the combination of vancomycin plus aztreonam at the FDA primary endpoint of early clinical response at 48-72 hours.

Baxdela™ has been shown to be active against *Staphylococcus aureus* (including MRSA); select coagulase-negative *Staphylococci, Streptococci,* and *Enterobacteriaceae;* and *Pseudomonas.* For full prescribing information, click here.
In 2009, Bains and colleagues\(^4\) evaluated the safety and efficacy of nitrofurantoin in 356 patients with an estimated glomerular filtration rate (eGFR) \(\leq 50\) mL/min (renal impairment group, \(n = 122\)) or eGFR > 50 mL/min (control group, \(n = 234\)). Notably, the studied renal-impaired population was predominantly elderly females with an average CrCl of 40 mL/min. Clinical cure (71% vs. 78%) and the rate of adverse events (7% vs. 8%) were similar between both groups (eGFR \(\leq 50\) mL/min vs. GFR > 50 mL/min, respectively). Based on these results, the authors concluded that nitrofurantoin achieves adequate clinical efficacy and is well tolerated in patients with renal impairment (eGFR \(\leq 50\) mL/min).

A 2013 study by Geerts and colleagues\(^7\) assessed the safety and efficacy of nitrofurantoin in a cohort of 21,317 females with varying degrees of renal function. Notably, only a small fraction of women subjects had known moderate (eGFR 30 - 49 mL/min/1.73 m\(^2\), \(n = 166\)) or severe (eGFR 10 - 29 mL/min/1.73 m\(^2\), \(n = 20\)) renal impairment. Overall, nitrofurantoin effectiveness, defined as not requiring a second antibiotic within 1 month of the study drug, was similar between patients with normal renal function (eGFR 80 mL/min/1.73 m\(^2\)) and moderate renal impairment (84.3% vs. 79.9%, respectively), but was reduced to 70.0% for women with severe renal impairment. Additionally, the risk of adverse events was significantly higher in patients with renal impairment (adjusted hazard ratio 4.13, 95% CI 1.31-13.09, eGFR \(\leq 50\) mL/min/1.73 m\(^2\)) , with the most common being pulmonary reactions (\(n = 28\)). Although this study included a limited number of patients with eGFR < 50 mL/min, the authors concluded that nitrofurantoin treatment may be effective in women with UTI and renal impairment, but that there was a significant association between renal impairment and pulmonary adverse events.

Finally, the AGS cited data from a retrospective cohort\(^6\) of Canadian women aged \(\geq 65\) years or older prescribed nitrofurantoin in the setting of relatively low vs. high eGFR (mean eGFR 38 mL/min/1.73 m\(^2\) (\(n = 3,739\)) vs. 69 mL/min/1.73 m\(^2\) (\(n = 70,758\)), respectively). This sub-analysis demonstrated similar rates of treatment failure requiring either a second antibiotic (11.0% vs. 13.8%) or hospitalization for UTI (5.9% vs. 1.1%) for patients with relatively low vs. high eGFR, respectively.

To date, no prospective trials evaluating the safety and efficacy in patients with varying degrees of renal impairment have been conducted. Further, the FDA has not updated nitrofurantoin labeling information based on the paucity of post-marketing evidence supporting its use in patients with impaired renal function.

In conclusion, nitrofurantoin is FDA-approved\(^1\) and a recommended first-line treatment\(^2\) for acute, uncomplicated cystitis of susceptible pathogens in patients with CrCl > 60 mL/min\(^1\), and is included in the revised Beers Criteria for patients with CrCl > 30 mL/min.\(^3\) Based on available evidence\(^1-8\), it may be reasonable to consider short-term use of nitrofurantoin in patients with CrCl as low as 40 mL/min if the benefits outweigh the risks, with close monitoring of adverse events including hemolytic anemia, peripheral neuropathy, and pulmonary reactions.

References (full citation available upon request)

ANTI-INFECTIVE UTILIZATION

The graphs below illustrate the most recent data (April-June 2017) for antibacterial and antifungal utilization at UC San Diego Health.

**Antibacterial DOT/1000 Patient Days**

- Jan to Mar 2016
- April to June 2016
- July to Sept 2016
- Oct to Dec 2016
- Jan to Mar 2017
- April to June 2017

*Methodology for calculating days of treatment changed Jan to Mar 2017

Source: EPIC

**Antifungal DOT/1000 Patient Days**

- Jan to Mar 2016
- April to June 2016
- July to Sept 2016
- Oct to Dec 2016
- Jan to Mar 2017
- April to June 2017

*Methodology for calculating days of treatment changed Jan to Mar 2017

Source: EPIC

DOT: Days of Therapy
The risk of emerging resistance varies depending on the organisms and geographic distribution; *E. cloacae* has the highest rate of resistance to broad-spectrum cephalosporins, up to 20%. Plasmid-mediated AmpC is also of substantial concern leading to potential resistance in *Klebsiella pneumoniae*, *Escherichia coli*, *Proteus mirabilis* and *Salmonella*. The presence of AmpC is difficult to detect in the laboratory setting. Chromosomal-mediated AmpC beta-lactamase producers will often exhibit a "susceptible" result to extended-spectrum cephalosporins on initial *in vitro* evaluation, which can lead to treatment failure if left undetected. Furthermore, the Verigene® Gram-negative blood-culture nucleic acid (BC-GN) diagnostic test does not detect inducible chromosomal AmpC beta-lactamase genes. Therefore, AmpC resistance is primarily identified by clinical and microbiologic failure.

Given the inability to detect AmpC in the laboratory, the selection of antimicrobial therapy should be based on the pathogen susceptibility report and modified in the event of treatment failure. Furthermore, it may be prudent to avoid third-generation cephalosporins, especially for severe infections or prolonged treatment courses. Historically, carbapenems have been the mainstay of treatment for AmpC-producing organisms, but new literature suggests that alternative treatment options may include piperacillin-tazobactam, fluoroquinolones, nitrofurantoin (for uncomplicated cystitis only), sulfamethoxazole-trimethoprim, and cefepime. Cefepime has a low risk for inducing AmpC and has stability against AmpC beta-lactamases, although its efficacy may be questionable in isolates with higher MIC values. Aminoglycosides may also be considered, but are generally not warranted if other effective treatment options are available. Overall, treatment approaches should include optimization of drug exposure and pharmacodynamics via augmented dosing and/or administration by extended-infusion.

Antibiotic resistance is a growing public health concern, and today clinicians encounter this issue more frequently in the healthcare setting. All healthcare providers can prevent the spread of resistant infections by practicing antimicrobial stewardship, recognizing resistant organisms, and judiciously utilizing broad-spectrum antimicrobial agents.

References: (Full citation available upon request)