UNIVERSITY HOSPITAL
Newark, New Jersey

Pharmacy News

Pharmacy News 2017 SPECIAL EDITION

University Hospital
Antimicrobial Stewardship Program

Introduction Letter

In This Issue:

Antimicrobials have transformed the practice of medicine and have saved countless lives. Previously devastating infections have become treatable and other procedures, once hampered by the risks of infection, have become commonplace. However, these miracle drugs are not without risk. The CDC estimate that 20-50% of antibiotic prescriptions are inappropriate or unnecessary. The overuse of antibiotics has been inked to increased rates of *Clostridium difficile* infection, selection of resistant organisms, and adverse drug reactions. Accordingly, antimicrobial stewardship has been advanced as a national priority in healthcare and is now a metric for many rating organizations including the Joint Commission.

University Hospital has instituted a comprehensive antimicrobial stewardship program designed to assist in the utilization of this incredibly important shared resource. The stewardship team is available to assist in the optimization of drug selection, dosing, and streamlining. We look forward to working with you in the near future.

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What is Antimicrobial Stewardship?

Antimicrobial stewardship is a coordinated effort to promote the appropriate and optimal use of antimicrobials. Three main goals behind antimicrobial stewardship include enhancing patient health outcomes, reducing antimicrobial resistance and decreasing unnecessary adverse effects and costs. Antimicrobial stewardship consists of establishing a program or standard within a health system to optimize antimicrobial prescribing and ordering, using evidence-based medicine. The careful conservation of antimicrobials is emphasized in order to resist the gaining problems that pervade many health systems today.

Antimicrobials are powerful tools used in modern medicine for combatting dangerous infections. Keeping the spread of infection to a minimum and

treating the afflicted, antimicrobials are widely prescribed and very frequently used. However, the overuse and unrestricted prescribing of antimicrobials has presented various problems that could threaten its very usefulness. Antimicrobial drug development has been slowing while antimicrobial resistance has been rising. Misuse of antimicrobials has also resulted in unnecessary exposure to serious adverse effects without clear clinical benefits. In order to address these issues, many organizations and health facilities have recognized the importance of antimicrobial stewardship. Antimicrobial stewardship is essential towards countering the issue of spreading antimicrobial resistance and also reducing adverse events associated with unnecessary antimicrobial use.

What's The Problem?	Increasing Antimicrobial Resistance	Unnecessary Use of Antimicrobials
What is Happening?	Inappropriate and frequent use of antimicrobials give rise to organisms that develop to survive the treatments used to fight them	Antimicrobial usage can be expensive and adverse effects can occur without there being a clear benefit for the patient
What's the Solution?	Establish an infection management program that optimizes antimicrobial use and develops treatment guidelines. Educate everyone on the conservation of antimicrobial prescribing and ordering.	
What are Some Relevant Statistics?	According to the Centers for Disease Control and Prevention (CDC): • Each year, at least 2 million people are infected with antimicrobial-resistant bacteria within the United States[2] • Antimicrobials cause 1 out of 5 emergency department visits in relation to Adverse Drug Events (ADEs)[1] • Antimicrobials are the leading cause of ADE-related emergency department visits for children[5]	

References:

1. Budnitz DS, Pollock DA, Weidenbach KN, Mendelsohn AB, Schroeder TJ, Annest JL. National surveillance of emergency department visits for outpatient adverse drug events. JAMA. 2006;296(15):1858-66.
2. Centers for Disease Control and Prevention. Core Elements of Hospital Antibiotic Stewardship Programs. Accessed September 13, 2017. https://www.cdc.gov/getsmart/healthcare/implementation/core-elements.html#_ENREF_2.
3. Doron, S. and Davidson, L. Antimicrobial Stewardship. Mayo Clinic Proceedings. 2011 Nov; 86(11): 1113-23.
4. Infectious Diseases Society of America (IDSA). Combating Antimicrobial Resistance: Policy Recommendations to Save Lives. Clinical Infectious Diseases. 2011 May; 52(5): 397-428.
5. Shehab, N., et al. (2016). "US emergency department visits for outpatient adverse drug events, 2013-2014." JAMA 316(20): 2115-25.
6. The Joint Commission. New Antimicrobial Stewardship Standard. Joint Commission Perspectives. 2016 July;36(7):1-8.

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Policies and Interventions to Improve Antimicrobial Use at University Hospital

The aim of implementing policies and interventions for antibiotic use at the University Hospital is to preserve the effectiveness of antimicrobial agents, maximize patient care and clinical outcomes, and optimize cost-effectiveness in the treatment and prevention of bacterial infection. The Antimicrobial Stewardship Program will monitor the compliance with evidence-based guidelines or best practices regarding antimicrobial prescribing. The recommendations that will be discussed, are based on the CDC's guidelines on antimicrobial stewardship as recommended by the Joint Commission.

Policies to improve antimicrobial use:

- **Implementing facility specific treatment recommendations.** This is based on national guidelines, local susceptibilities and formulary options to optimize antibiotic selection and duration, particularly for common indications for antibiotic use like community-acquired pneumonia, urinary tract infection, intra-abdominal infections, skin and soft tissue infections and surgical prophylaxis.
- **Documenting dose, duration, and indication.** Prescriber are required to specify the dose, duration and indication for all courses of antibiotics which would help ensure that antibiotics are modified as needed and/or discontinued in a timely manner.

Interventions to improve antimicrobial use

Per the CDC, selecting specific interventions are based on the needs of the health facility and the resources available. Antimicrobial stewardship interventions are grouped in three categories: broad, pharmacy-driven and infection and syndrome specific interventions.

- **Broad interventions**
  - **Antibiotic "Time outs".** An antibiotic "time out" prompts a reassessment of the continuing need and choice of antibiotics when the patient's clinical picture is clearer and more diagnostic information is available. It is recommended that all clinicians perform a review of antibiotics 48 hours after antibiotics are initiated for the appropriateness of therapy.
  - **Prior authorization** – Restricting the use of certain antibiotics are based on the spectrum of activity, cost, or associated toxicity. Their use, requires the authorization of experts in antimicrobial use and infectious diseases to ensure the appropriateness of therapy.
- **Pharmacy-driven Interventions.** Some efforts that have been made in the University Hospital include the below and will be further discussed in detail subsequently:
  - **Automatic substitutions from intravenous to oral antibiotic therapy** in appropriate situations, which is the preferred route of administration.
  - **Dose adjustments** in cases of organ dysfunction (e.g. renal adjustment).
  - **Dose optimization** including but not limited to dose adjustments based on therapeutic drug monitoring.
  - **Automatic alerts in situations where therapy might be unnecessarily duplicative** including simultaneous use of multiple agents with overlapping spectra e.g. anaerobic activity, atypical activity, Gram-negative activity and resistant Gram-positive activity.
  - **Time-sensitive automatic stop orders** for specified antibiotic prescriptions, especially antibiotics administered for surgical prophylaxis.
  - **Detection and prevention of antibiotic-related drug-drug interactions**– e.g. interactions between some orally administered fluoroquinolones and certain vitamins.
- **Infection and syndrome specific interventions.** Some Infection specific guidelines are currently being implemented at the University Hospital and continues to be modified to optimize outcomes in antimicrobial use. Some current efforts include:
  - **Treatment of culture proven invasive infections.** Microbial culturing and susceptibility testing provides information needed to tailor antibiotics.

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Policies and Intervention to improve Antimicrobial use at the University Hospital

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- **Empiric coverage of methicillin-resistant *Staphylococcus aureus* (MRSA) infections.** Interventions can include switching an MRSA therapy to a beta-lactam in methicillin-sensitive Staphylococcus aureus infections
- **Skin and soft tissue infections.** Interventions can focus on ensuring patients do not get antibiotics with overly broad spectra and ensuring the correct duration of treatment.
- **Urinary tract infections (UTIs).** Ensuring appropriate therapy and a focus to avoid unnecessary urine cultures and treatment of patients who are asymptomatic
- **Community-acquired pneumonia.** Improving diagnostic accuracy, tailoring of therapy to culture results and optimizing the duration of treatment to ensure compliance with guidelines.

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References:

1. "Get Smart for Healthcare in Hospitals and Long-Term Care." Centers for Disease Control and Prevention, Centers for Disease Control and Prevention, 23 Feb. 2017, www.cdc.gov/getsmart/healthcare/implementation/core-elements.htmlw

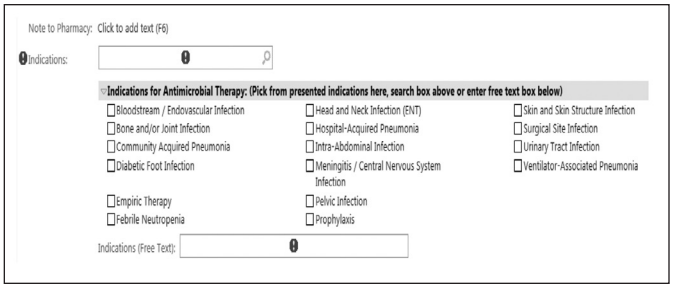
Overview of Antimicrobial Stewardship Interventions at UH

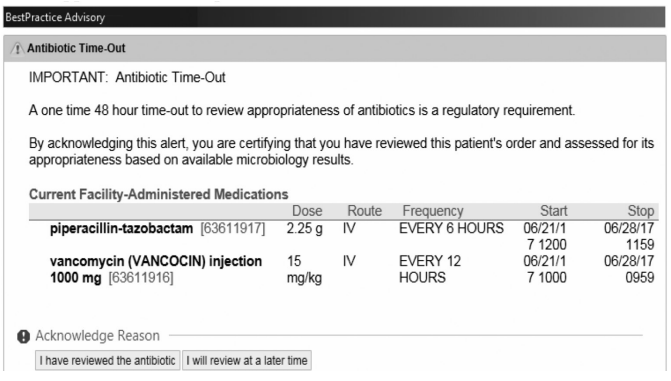
In an effort to improve antibiotic use and reduce its adverse events, University Hospital implemented an Antimicrobial Stewardship program that is compliant with the Joint Commission recommendations. Broad interventions from the medical team as a whole, as well as pharmacy driven interventions, are needed for the stewardship to take effect.

Broad interventions include:

- **Antibiotic "Time Outs"** → Empiric antibiotic therapy is reviewed after 48 hours of initiation. By this time a patient would have a better diagnostic profile and laboratory results to assess whether further antibiotic use is required. The alert that appears in EPIC is pictured here.
- When prescribers enter an order for antibiotics they must include an indication, strength, frequency and route of administration.
- **Prior authorization** → Certain antibiotics have restricted use based on its spectrum of activity, toxicities, and cost. Authorization by an expert in infectious diseases is required to use these drugs.
- Prospective audit and feedback of the therapy given is done by the ID clinical pharmacist, allowing the pharmacist to intervene and optimize patient care.

The various pharmacy driven interventions put into effect include:





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Overview of Antimicrobial Stewardship Interventions at UH

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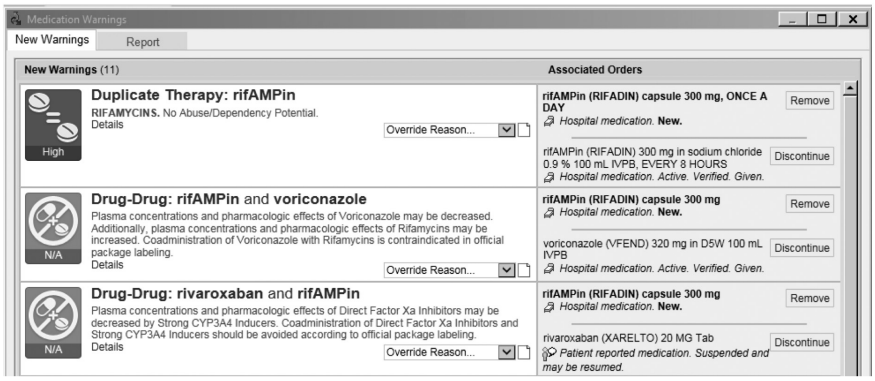
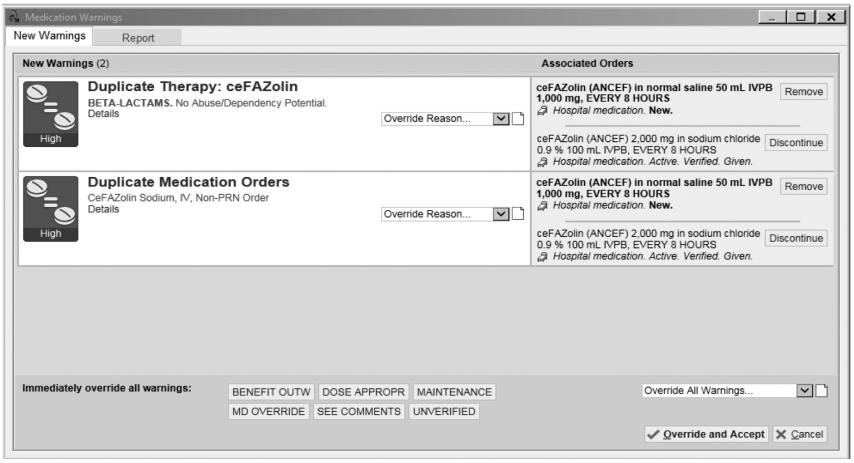


- **Automatic stop orders (ASO)** → Used for time sensitive antibiotics. For instance, piperacillin/ tazobactam has an ASO at three days to reassess if it is still needed.
- **IV to PO policy** → Used when there is therapeutic equivalence and to enhance patient safety by reducing the need for IV access.
    - o Inclusion criteria for the interchange include:
        - IV therapy for at least 24 hours
        - Tolerating concurrent oral medications/ tolerating a solid diet
        - Afebrile with signs of resolving infection, and no antiemetic use within the last 24 hours
    - o Some of the medications that can be interchanged include: Azithromycin, Ciprofloxacin, Clindamycin, Doxycycline, Levofloxacin and Trimethoprim/ Sulfamethoxazole.
- **Dose adjustments** → When verifying orders, pharmacists make adjustments based upon renal/ hepatic function and based upon the results seen in therapeutic drug monitoring.
- **Duplicate therapy** → An automatic alert is created duplicate therapies are ordered. These situations arise when the ordered medications have overlapping coverage, such as Gram negative or Gram positive resistant activity.
- **Drug- drug interactions** → Pharmacist review potential interactions when reviewing orders, allowing for early intervention.

UH is developing guidelines, clinical pathways and order sets for the management of infectious diseases. Currently, there is a guide for ID management in the Emergency Department being created.



References:

1. "Get Smart for Healthcare in Hospitals and Long-Term Care." Centers for Disease Control and Prevention, Centers for Disease Control and Prevention, 23 Feb. 2017, www.cdc.gov/getsmart/healthcare/implementation/core-elements.html.
2. UH IV to Oral Interchange Policy: 707-500-102

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Update to Restricted Anti-Infective Policy at UH

The Restricted Anti-Infective Policy was implemented at University Hospital in June 2015 as part of the antimicrobial stewardship program. This policy was created to address the widespread concern of multi-drug resistant microbes and, ultimately, to improve patient care and clinical outcomes by ensuring the appropriate use of various anti-infectives.

Previously, all of the restricted anti-infectives included in the policy required approval by an authorized provider, or AP, prior to order entry if the anti-infective was intended for systemic administration, such as intravenous or oral routes. However, in July 2017, the anti-infective subcommittee updated this policy to categorize the anti-infectives as either high restricted or restricted. The list of the anti-infectives included in this policy and the rationale for their restriction may be found below.

Who is an authorized provider and may approve the use of restricted anti-infectives?

- Fellows of the Infectious Diseases and Pediatric Infectious Diseases Divisions
- Attending physicians of the Infectious Diseases and Pediatric Infectious Diseases Divisions
- Any attending physician with Infectious Disease certification from the American Board of Internal Medicine and/or the American Board of Pediatrics
- Infectious Diseases Clinical Pharmacy Specialist
- Other providers or in specific patient units

1. High restricted anti-infectives
   - o These anti-infectives require infectious diseases consultation and approval prior to order entry

Category I: High Restricted Infectious Diseases Consultation and Approval must be requested, prior to use		
Generic Name	**Rationale for Restriction****	**Criteria for Exemption**
Ceftaroline	1, 3	No Exemptions
Ceftazidime/avibactam	1, 4	
Ceftolozane/tazobactam*	1, 4	
Cidofovir	1, 4	
Foscarnet	1, 4	
Pentamidine	1, 4	
Posaconazole*	4	
Quinupristin/ dalfopristin*	1, 4	

2. Category II: Restricted anti-infectives

Generic Name	**Rationale for Restriction****	**Criteria for Exemption**
Amphotericin B	1	No Exemptions
Lipid amphotericin B*	1	
Liposomal amphotericin B	1	
Aztreonam	1, 2	Unrestricted in any setting, when ordered by Obstetrics/Gynecology service providers
Colistimethate sodium	1, 4	No Exemptions
Daptomycin	4, 5	
Ertapenem	5, 6	
Fidaxomicin*	4, 7	
Fosfomycin	1	
Imipenem/cilastatin*	6, 8	
Linezolid	4, 5	
Meropenem	5, 6	Unrestricted in any ICU setting **for 5 days only**
Micafungin	4	No Exemptions
Polymyxin B	1, 4	
Tigecycline	1, 4	
Voriconazole	4	

3. Rationale for restriction

***Non-formulary anti-infective**

- Order must be entered in accordance with policies/procedures for non-formulary medications.

****Rationale for Restriction**

1. Rarely indicated as a first line agent; see expert advice from an ID physician
2. Reserve use for patients with severe penicillin hypersensitivity; for other indications seek expert advice
3. Reserve use for methicillin-resistant Staph. aureus (MRSA) or suspected MRSA infections; for other indications seek expert advice
4. Used in the management of complex, resistant or emerging infectious diseases; seek expert advice from an ID physician
5. Potential for overuse in common infections (when other agents may more appropriate)
6. Broad-spectrum agent; linked with emergence of multi-resistant Gram negative organisms
7. New antimicrobial agent; seek expert advice from an ID physician
8. Other agents within the same class preferred as they have less toxicity
9. Other agents within the same class preferred where possible (less expensive)

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Influenza Vaccination Update 2017- 2018 Season

Based on new information or changes in circulating viruses, the CDC is careful to make updated recommendations with each coming year in order to effectively combat influenza. Any licensed, age-appropriate flu vaccination should be administered for anyone 6 months of age and older, every season. For the 2017- 2018 flu season, all vaccines have been updated to match the current circulating viruses.

The viral strains included in this year's vaccines include:

- A/Michigan/45/2015 (H1N1)pdm09
- A/Hong Kong/ 4801/2014 (H3N2)
- B/Brisbane/60/2008 (Victoria lineage)
- B/Phuket/3073/2013 (Yamagata lineage)- covered in quadrivalent vaccines only

There are two new four-component, or quadrivalent, vaccines that have been approved. One is the recombinant influenza vaccine "Flublok Qudrivalent" RIV. The other is the inactive influenza vaccine, "Afluria Quadrivalent" IIV. The CDC now recommends "Flulaval Quadrivalent" age requirements change from 3 years and older to 6 months and older. The trivalent formulation of Afluria is also now recommended for people 5 years and older instead of 9 years. Trivalent formulations do not cover the B/Phuket/3073/2013 strain. The high-dose formulation is a trivalent vaccine recommended for people ages 65 and older due to reports of higher immunogenicity.

The CDC does not recommend use of live attenuated influenza vaccines, which are formulated for intranasal use.The CDC's Advisory Committee on Immunization Practices (ACIP) voted against the use of these vaccines due to its considerably lower efficacy in protecting against the flu virus. Certain high-risk groups and their caregivers should be vaccinated as it is the simplest way to protect against illness. These groups include, children aged 6-59 months, adults aged at least 50 years, immunocompromised persons, pregnant women and persons with a BMI of at least 40.

Patients with egg allergies who have only experienced hives after exposure to eggs may get any licensed flu vaccination that is suitable for their current age and health.

References:

1. Centers for Disease Control and Prevention. Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices (ACIP)—United States, 2017-18. Accessed September 13, 2017. https://www.cdc.gov/flu/professionals/acip/2017-18summary.htm.
2. Centers for Disease Control and Prevention. Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices (ACIP)—United States, 2016-17. Accessed September 20, 2017. https://www.cdc.gov/flu/about/season/flu-season-2016-2017.htm
3. Centers for Disease Control and Prevention. ACIP votes down use of LAIV for 2016-2017 flu season. Accessed September 19, 2017.
4. "Influenza (Flu)." Centers for Disease Control and Prevention, Centers for Disease Control and Prevention, 15 Sept. 2017

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New Drug Approvals: June - August 2017

Drug Name	Generic Name	Therapeutic Class	Approval Date	Indications	Formulary Status	Mechanism of Action	Common Adverse Events	Place in Therapy
Vabomere	Meropenem and Vaborbactam	Antibiotic- Carbapenem; Beta-Lactamase inhibitor	8/29/17	Complicated urinary tract infections including pyelonephritis caused by designated susceptible bacteria	Non-formulary	Meropenem has a bactericidal action resulting from its inhibition of cell wall synthesis. Vaborbactam does not have any antibacterial activity. It is a non-suicidal beta-lactamase inhibitor that protects meropenem from being degraded by certain serine beta-lactamases such as Klebsiella pneumoniae carbapenemase (KPC).	The most commonly reported adverse reactions in >3% are headache, phlebitis/infusion site reactions, diarrhea, hypersensitivity reactions	Vabomere is indicated for the treatment of patients 18 years and older. It should be used only to treat or prevent infections that are proven or strongly suspected to be caused by the following susceptible microorganisms: Escherichia coli, Klebsiella pneumoniae, and Enterobacter cloacae species complex
Mavyret	Glecaprevir and pibrentasvir	Antiviral-Antihepaciviral, NS3/4A Protease Inhibitor; Antihepaciviral, NS5A Inhibitor	8/3/17	Chronic hepatitis C infection	Non-formulary	Glecaprevir is an inhibitor of hepatitis C virus (HCV) NS3/4A protease, necessary for the proteolytic cleavage of the HCV-encoded polyprotein (into mature forms of the NS3, NS4A, NS4B, NS5A, and NS5B proteins) and is essential for viral replication. Pibrentasvir is an inhibitor of HCV NS5A, essential for viral RNA replication and virion assembly.	The most commonly reported adverse reactions (greater than 10%) are headache and fatigue	Mavyret is the first treatment of 8 weeks duration (standard treatment length was previously 12 weeks or more) approved for all HCV genotypes 1-6 in adult patients without cirrhosis or with compensated cirrhosis (Child-Pugh A) who have not been previously treated, It is also indicated for the treatment of adult patients with HCV genotype 1 infection, who previously have been treated with a regimen containing an HCV NS5A inhibitor or an NS3/4A protease
Vosevi	Sofosbuvir, velpatasvir and voxilaprevir	NS5B RNA Polymerase Inhibitor NS5A Inhibitor NS3/4A Protease Inhibitor (Antihepaciviral)	7/18/17	Adult patients with chronic HCV infection without cirrhosis or with compensated cirrhosis (Child-Pugh A) who have: genotype 1, 2, 3, 4, 5, or 6 infection and previously treated with HCV regimen containing NS5A inhibitor, genotype 1a or 3 infection and previously treated with HCV regimen containing sofosbuvir without NS5A inhibitor	Non-formulary	Inhibition of HCV NS5B RNA-dependent RNA polymerase, which is required for viral replication. Sofosbuvir is a prodrug that forms active uridine analog triphosphate, which can be incorporated into HCV RNA by the NS5B polymerase and acts as a chain terminator. Inhibition of HCV NS5A protein, which is required for viral replication.	The most commonly reported adverse reactions (>10%): Headache, fatigue, nausea, diarrhea, increased serum bilirubin	Vosevi is indicated for the treatment of adult patients with chronic HCV infection without cirrhosis or with compensated cirrhosis (Child-Pugh A) who have genotype 1, 2, 3, 4, 5, or 6 infection and have previously been treated with an HCV regimen containing an NS5A inhibitor, or for genotype 1a or 3 infection and have previously been treated with an HCV regimen containing sofosbuvir without an NS5A inhibitor. Current HCV AASLD guidelines have not yet been updated to provide a recommendation for Vosevi's place in therapy; however it will likely provide valuable in patients with HCV who failed DAA therapy.
Baxdela	Delafloxacin	Antibiotic; fluoroquinolone	6/19/17	Adult patients for the treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by designated susceptible bacteria (S. aureus, including MRSA and MSSA, S. haemolyticus, S. lugdunensis, S. agalactiae, S. anginosus group, S. pyogenes, E. faecalis, E. coli, Enterobacter cloacae, Klebsiella pneumoniae, and Pseudomonas aeruginosa.	Non-formulary	Reversible inhibition of NS3/4A protease, which is necessary for proteolytic cleavage of HCV encoded polyprotein (mature forms of NS3, NS4A, NS4B, NS5A, and NS5B proteins) Inhibition of bacterial topoisomerase IV and DNA gyrase (topoisomerase II) enzymes which are required for bacterial DNA replication, transcription, repair, and recombination. Exhibits concentration-dependent bactericidal activity against gram-positive and gram-negative bacteria in vitro.	The most commonly reported adverse reactions (>2%): Diarrhea, nausea, vomiting, headache, and transaminase elevations	Baxdela is a fluoroquinolone antibacterial indicated in adults for the treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by designated susceptible bacteria. In two clinical trials, delafloxacin was found to be noninferior to vancomycin, thus, providing another therapeutic option. Because of the limited clinical experience and availability of numerous options, the role for delafloxacin remains to be determined. To reduce the development of drug-resistant bacteria and maintain the effectiveness of Baxdela and other antibacterial drugs, Baxdela should be used only to treat infections that are proven or strongly suspected to be caused by bacteria.

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1. Vabomere (meropenem and vaborbactam) [prescribing information]. Parsippany, NJ: The Medicines Company; August 2017
2. Mavyret (glecaprevir/pibrentasvir) [prescribing information]. North Chicago, IL: AbbVie Inc; August 2017
3. Vosevi (sofosbuvir, velpatasvir, voxilaprevir) [prescribing information]. Foster City, CA: Gilead Sciences Inc; July 2017
4. Baxdela (delafloxacin) [prescribing information]. Lincolnshire, IL: Melinta Therapeutics Inc; June 2017