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Focus on Drug-Resistant Organisms

by Allen Lefkovitz

At the heart of antibiotic stewardship is the prevention of infections caused by drug-resistant organisms (DRO). DRO develop when infectious organisms adapt to defeat antimicrobial agents (e.g., antibiotics, antifungals) designed to combat them, making the antimicrobial agent less effective or ineffective. While use of antibiotics in food production, use of metals in agriculture (e.g., copper as a fungicide), increased world travel, inadequate sanitation, and variations in access to quality healthcare increase the development of DRO, the overuse and misuse of antibiotics is considered the most significant driving force. The Infectious Diseases Society of America (IDSA) has called antimicrobial resistance "one of the greatest threats to human health worldwide". The "Core Elements of Antibiotic Stewardship for Nursing Homes" by the Centers for Disease Control and Prevention (CDC) begins by stating, "Improving the use of antibiotics in healthcare to protect patients and reduce the threat of antibiotic resistance is a national priority." Organizations, including IDSA and CDC, continue to warn that DRO "seriously threaten" our ongoing ability to provide both life-changing surgeries (e.g., joint replacement, organ transplant) and effective treatment of common infections, especially in vulnerable, high-risk individuals (e.g., infants, older adults, those with cancer). DRO are associated with increased utilization of healthcare resources, increased lengths of stay, use of more toxic antimicrobials (e.g., colistin), and increased mortality.

In November 2019, CDC released a report entitled *Antibiotic Resistance Threats in the United States, 2019* (available for free at:), which classifies 18 DRO as "Urgent", "Serious", or "Concerning". A CDC-funded study published in April 2020 estimated that over 620,000 hospital infections each year were caused by six of the identified 18 DRO. A summary of these six DRO is in Table 1.

Table 1: Six Common DRO Relevant to Long-Term Care Facilities

Organism by Threat Category	Commonly Caused Infections	% Resistance in Adults	Annual Cases	Annual Deaths
CDC "Urgent" Threat Category				
Carbapenem-resistant *Acinetobacter*	BSI; Pneumonia; UTI	41.2%	8,500	700
Carbapenem-resistant Enterobacteriaceae (e.g., *Enterobacter, Escherichia coli, Klebsiella*)	BSI; Pneumonia; UTI	2.7%	13,100	1,100
CDC "Serious" Threat Category				
Methicillin-resistant *Staphylococcus aureus* (MRSA)	BSI, SSI, UTI	42.9%	323,700	10,600
Vancomycin-resistant *Enterococcus* (VRE)	BSI, SSI, UTI	About 30%	54,500	5,400
ESBL-producing Enterobacteriaceae (e.g., *Escherichia coli, Klebsiella*)	BSI; Pneumonia; UTI	Up to 21.3%	197,400	9,100
Multidrug-resistant *Pseudomonas aeruginosa*	BSI; SSI; Pneumonia; UTI	9.1%	32,600	2,700

BSI = bloodstream infections; ESBL = extended-spectrum beta-lactamase; SSI = surgical site infections; UTI = urinary tract infections

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The 2019 CDC report estimates that annually DRO cause more than 2.8 million infections and 35,000 deaths. To help raise awareness, CDC also maintains an "Antibiotic Resistance & Patient Safety Portal" (available at: https://arpsp.cdc.gov/), which includes additional state and national data on many of these DRO as well as some emerging DRO (e.g., daptomycin-resistant *Enterococcus faecalis*, fluoroquinolone-resistant *Pseudomonas aeruginosa*). Although stewardship efforts have begun to show success in the decreasing prevalence of some DRO infections, CDC has observed that DRO infections are increasingly originating within the community, which includes long-term care facilities (LTCF), instead of in hospitals (83% vs. 17%).

Since at least 2006, CDC has recognized LTCF as "reservoirs and vehicles" for both colonization and infection with DRO that "can cause serious disease and mortality". Nearly 16,000 residents of skilled nursing facilities have an infection caused by a DRO in any given week according to minimum data set (MDS) 3.0 data. However, full awareness of DRO infections may be lacking as demonstrated by a 2019 study involving 21 southern California LTCF in which 65% to 80% of residents tested positive for a DRO, but only 18% to 49% of those residents had documentation that they were infected with a DRO.

In addition to improving awareness, CDC emphasizes three foundational activities for all healthcare providers:

Prevent Infection and Spread	Improve Antibiotic Prescribing	Be Alert and Take Action
• Strictly follow infection prevention and control measures • Be aware of all settings where care has been provided • During transfers between settings, communicate if someone is colonized or infected with a DRO • Ensure immunizations are up to date	• Follow clinical treatment guidelines (e.g., do not prescribe antibiotics for viral infections) • Utilize diagnostic testing to ensure optimal selection of drug, dose, and duration • Monitor closely for resolution of infections and treat sepsis promptly if suspected • Consider fungal infections if respiratory infections do not respond to antibiotics	• Be aware of facility and community resistance patterns (e.g., antibiograms) • Work with your lab to notify your facility immediately if a DRO is identified in any culture • Know when to report cases to your health department

Good antibiotic stewardship principles that help combat DRO infections also include correctly establishing the "Four D's":

Diagnosis – ensure established criteria for prescribing an antibiotic are met and document the diagonsis on the order

Dose – adjust based upon individual characteristics (e.g., kidney function, serum concentrations, drug interactions)

Drug – base upon local resistance patterns and culture and sensitivity results, and de-escalate to narrower spectrum antibiotics whenever possible

Duration – use the shortest effective duration and ensure all orders are written with stop dates

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Other important strategies may include:

- frequent educational efforts to remind all caregivers about both infection prevention and control best practices, as well as criteria for the appropriate use of antibiotics
- avoiding unnecessary or prolonged use of catheters and other invasive medical devices
- providing prescribers with local antibiotic resistance patterns
- implementing formulary restrictions on broad spectrum antibiotics

To help expedite their potential approval, the US Food and Drug Administration (FDA) has assisted in the fight against DRO by giving "priority review" to new antibacterial and antifungal agents. Although significant concerns remain about the development "pipeline" of new antimicrobials, since June 2017, eight new antibiotics that target various DRO have been approved (see Table 2). While empiric use of these agents may be considered before culture and sensitivity results return, to help avoid emergence of drug resistance to these newer agents, the FDA-approved labeling urges that these newer antibiotics **only** be used to treat infections that are proven or strongly suspected to be caused by susceptible bacteria.

Table 2: New Antibiotics That Target DRO

		FDA-approved Indications*				
Brand (generic)	**Route**	**ABSSSI**	**CABP**	**cIAI**	**cUTI**	**HAP or VAP**
Baxdela (delafloxacin)	IV, PO	X	X			
Fetroja (cefiderocol)	IV				X	
Nuzyra (omadacycline)	IV, PO	X	X			
Recarbrio (imipenem/cilastatin/relebactam)	IV			X	X	X
Vabomere (meropenem/vaborbactam)	IV				X	
Xenleta (lefamulin)	IV, PO		X			
Xerava (eravacycline)	IV			X		
Zemdri (plazomicin)	IV				X	

ABSSSI = acute bacterial skin and skin structure infections
CABP = community-acquired bacterial pneumonia
cIAI = complicated intra-abdominal infections
cUTI = complicated urinary tract infection, including pyelonephritis
HAP = hospital-acquired bacterial pneumonia
IV = intravenous
PO = oral
VAP = ventilator-associated bacterial pneumonia

* See FDA-approved labeling available at https://dailymed.nlm.nih.gov/ for additional information, including potentially susceptible organisms

New Generic Medications

by Allen Lefkovitz

Generic Name	Brand Name	Date Generic Available
Teriparatide* 20 mcg/dose (620 mcg/2.48 mL) Pen	Forteo® Pen	6/19/20
Sodium Fluoride* 5000 ppm 1.1% Dental Paste	Prevident® Toothpaste	6/15/20
Sodium Fluoride* 5000 ppm 1.1%/5% Sensitive Dental Paste	Prevident® 5000 Sensitive Toothpaste	6/15/20
Tolvaptan 30 mg Tablet	Samsca™ Tablet	5/22/20
Nitroglycerin* 0.1 mg/hr, 0.2 mg/hr, 0.4 mg/hr, and 0.6 mg/hr Transdermal Patch	Nitro-Dur® Transdermal System	5/22/20

* Not an A-rated generic; substitution policies may vary by state and how orders are written

New Drugs

by Dave Pregizer

Kynmobi™ Sublingual Film

Brand Name (Generic Name)	Kynmobi™ [kin-MOE-bee] (apomorphine hydrochloride) [a-poe-MOR-feen]
How Supplied	10 mg, 15 mg, 20 mg, 25 mg, and 30 mg sublingual (SL) film
Therapeutic Class	Non-ergoline dopamine agonist
Approved Indication	Acute intermittent treatment of OFF episodes in those with Parkinson's disease
Usual Dosing	10 mg to 30 mg per dose sublingually (SL) as needed; doses should be separated by at least 2 hours. Maximum single dose of 30 mg and a maximum of 5 doses per day.
Select Drug Interactions	Use with 5-HT3 antagonists (e.g., ondansetron, granisetron) is contraindicated due to the risk of profound hypotension and loss of consciousness. Use with antihypertensives and vasodilators may increase the risk for hypotension, myocardial infarction, falls, and injuries. Dopamine antagonists (e.g., haloperidol, metoclopramide) may reduce the effectiveness of Kynmobi.
Most Common Side Effects	Nausea, oral/pharyngeal soft tissue pain and paraesthesia, oral/pharyngeal soft tissue swelling, dizziness, and somnolence
Miscellaneous	Dose initiation should be supervised by a healthcare provider. Concomitant treatment with an antiemetic (e.g., trimethobenzamide) is recommended beginning 3 days prior to initial dose of Kynmobi. Avoid abrupt discontinuation.
Website	https://www.kynmobi.com/