



Recent Developments in Infectious Disease Chemotherapy: Review for Emergency Department Practitioners 2020

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Abstract

Purpose of Review We discuss and review new antimicrobials for treatment of bacterial, viral, fungal, and parasitic infections with indications, contraindications, and side effects for each. We will also review new information and indications on older agents that are relevant to clinical practice. Many of them may be unfamiliar to Emergency Physicians given their newness and at times hospital restrictions on their use. We also review some new promising agents that are not yet in the clinical pipeline.

Recent Findings As new antibiotics become available for clinicians to use, new information becomes available with respect to the drugs' indications, efficacy, pathogen resistance, drug-drug interactions, and side effects.

Summary This article provides Emergency Department clinicians with a useful summary with new information on antibiotic use and recent research into agents which may become available.

Keywords Antibiotic · Resistance · Emergency · Development

Introduction

Antibiotics play a critical role in pharmacological management of Emergency Department patients presenting with apparent infectious disease [1]. Antibiotic resistance development is a constant threat whether bacterial, viral, or fungal infections are concerned [2•, 3••, 4]. As the new agents emerge and become available for clinical use, some antimicrobials lose effectiveness in some areas, while others become repurposed for a new indication. As multidrug resistant organisms increase in prevalence so is the need for antimicrobial polypharmacy early on in the management of the critically ill infected patients as well as prolonged courses of antibiotics, increasingly done on an outpatient basis [2•, 5]. Whether the Emergency Physician initiates treatment with an antimicrobial or is faced with a patient already taking one, a good understanding of shifting indications and contraindications for their use as well as drug-drug interactions and side effects continues

to be important. Thus, staying abreast of new developments in infectious disease pharmaceutical armamentarium is a must for Emergency Medicine providers.

Antibiotic Resistance

Antibiotic-resistant bacteria continue to spread worldwide and are a persistent and severe health threat [2•] with morbidity and mortality increasing annually [6]. There are multiple implications to physicians caring for patients with presentations concerning for infectious etiology, including the frequent need for early administration of multiple broad-spectrum antibiotics [7]. Emergency Departments (EDs) are a common entry point for care for patients with a range of infectious diseases [3••], and ED physicians are on the front line for early and sometimes the only antibacterial therapy choice for these patients. Patients affected by extended spectrum β -lactamase-producing and colistin-resistant *Pseudomonas aeruginosa*, carbapenem-resistant Enterobacteriaceae, methicillin-resistant *Staphylococcus aureus*, and drug-resistant *Neisseria gonorrhoeae* are encountered routinely in US Emergency Departments [3••]. Multidrug-resistant bacteria are affecting all populations and have been implicated even in neonatal sepsis requiring broader coverage in that patient group [8, 9]. It is important for ED providers to stay abreast of new

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therapies and concepts for these common and serious infections [3••].

Antibiotic resistance development is not limited to bacteria; it involves all human pathogens. Pathogenic viruses have been known to become resistant to antivirals, with influenza A and B now commonly resistant to adamantane compounds and occasionally resistant to newer neuraminidase inhibitors [4, 10]. Several antiviral compounds are being currently studied, including favipiravir and fludase with potential broad activity against many pathogenic RNA viruses such as Ebola, West Nile, rabies, and Zika in addition to influenza viruses [10]. Another drug in clinical trials for influenza treatment is the neuraminidase inhibitor laninamivir which would be available as a nasal inhalation if approved [11]. Nitazoxanide, an anti-parasitic agent, used to treat cryptosporidium infection in AIDS patients is currently in trials for influenza treatment due to its apparent antiviral activity [11]. Development of a more effective flu vaccine would do much to control influenza epidemics [4]. As far as other viral diseases are concerned, Presatovir (GS-5806) is in trials for Respiratory Syncytial Virus infection [11] and sofosbuvir, a drug previously approved for hepatitis C treatment, is in trials for treatment of Zika virus infection [12]. While several new compounds are being studied, nothing new has become available for herpes virus illnesses since our last update [13].

Recently, several fungal disease outbreaks have been noted worldwide, ranging from keratitis in contact lens wearers to health care–associated fungal infections with high mortality [14]. Even as both invasive fungal infections and fungal resistance to currently limited antifungal drugs are becoming more common, and there are several molecules being studied for a number of fungal diseases [15], there have not been any new antifungals approved for use in the USA since our last review in 2017. Some strains of *Candida glabrata* and *auris* implicated in disseminated disease are now multidrug resistant [16].

The risk factors for infection with antibiotic-resistant bacteria include prior history of such an infection, chronic vascular access or chronic wound, and immunocompromised status stemming from chronic severe illness, malignancy, or primary immunologic defects [3••]. The need to use broad-spectrum antibiotics liberally and early unfortunately contributes to constantly emerging and evolving patterns of pathogen resistance [9, 17]. Meanwhile, it has become a routine to use antibiotics liberally in situations where previously they were used infrequently, such as in patients with simple skin abscesses [18].

Several pathogens were recently identified by the World Health Organization (WHO) as a critical priority, based on mortality, health care burden, and prevalence of resistance [1, 7] (Table 1). The only two new antibacterial classes to be approved in the past 20 years—lipopeptides and oxazolidinones—are active against gram-positive pathogens [1]. Quinolones, which first appeared in 1960, was the last novel class of antibiotics discovered to be active against

Table 1 Critical priority bacteria according to WHO [1, 2•]

Multidrug-resistant tuberculosis, Carbapenem-resistant <i>Acinetobacter baumannii</i> and <i>Pseudomonas aeruginosa</i> , carbapenem and third-generation cephalosporin-resistant Enterobacteriaceae, vancomycin-resistant <i>Enterococcus faecium</i> , methicillin-resistant <i>Staphylococcus aureus</i> , clarithromycin-resistant <i>Helicobacter pylori</i> , fluoroquinolone-resistant <i>Campylobacter</i> spp., <i>Neisseria gonorrhoeae</i> , and <i>Salmonella typhi</i>
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gram-negative bacteria [1]. Unfortunately many large pharmaceutical companies have limited investment into research in the past decade to discover new antibiotics in part due to negative financial incentives [19]. By definition, antimicrobials are meant in general to cure disease rather than to be taken forever as, for example, medications to treat diabetes or hypertension. Furthermore, antimicrobial husbandry includes attempts to limit pathogen resistance by limiting the time course of treatment. Additionally, the FDA requires that new agents for use in simple infections show superiority, which would require a very large number of subjects enrolled in a study, since most of these infections resolve spontaneously [19].

Infections caused by resistant bacteria cause up to two-fold increase in adverse outcomes, even when the pathogen remains susceptible to the antibiotic but a higher minimal inhibitory concentration (MIC) is present [20•], especially if septic shock develops [21]. This contributes to the need to use antibiotics in higher doses and for longer courses. There is evidence that even β -lactams in high concentrations can produce a range of organ toxicity especially in the critically ill, including neurologic, hepatic, renal, and hematological side effects whose frequency may be currently underestimated [22]. Cephalosporins, including novel ones, appear to be proconvulsive, especially in patients with epilepsy [22]. Not only are resistant bacteria more difficult to control in case of infection, but surgical antibiotic prophylaxis has also become less effective, as evidenced for example by an increase in bacteremia after invasive urological procedures despite fluoroquinolone prophylaxis [20•]. This is an important point to keep in mind for Emergency Department doctors when these patients present.

Other important mechanisms for development and spread of resistant bacteria have been recently emphasized. For example, many bacteria and fungi have the ability to form biofilms by both free living and pathogenic species, thereby limiting local antibiotic penetration [5]. Chronic infection in rhinosinusitis, purulent ulcers, and cystic fibrosis seem to be due to biofilms in large part [2•]. As another example,

Table 2 Select new FDA-approved antibiotics on the market in the USA since year 2017 Google Scholar and Medscape Search [25–27]

Drug class	Names and notes	Indications	Select side effects	Comments
Aminomethylecyclines	Omadacycline	Skin and soft tissue infections, pneumonia caused by Gram-positive pathogens including MRSA, <i>S. pneumoniae</i> and VRE, some Gram negatives, Fragilis, Legionella, and Chlamydia	Similar to newer tetracyclines such as doxycycline	In trials for pneumonia treatment mortality rate was higher in omadacycline group
Tetracyclines	Sarecycline	Approved for treatment of acne vulgaris.	Similar to newer tetracyclines such as doxycycline	
Tetracyclines	Eravacycline	Complicated intraabdominal infections have broad-spectrum activity for treatment of Gram+ and Gram– intraabdominal infections	Infusion site reaction, tetracycline class adverse reactions	Related to tigecycline. Not approved for urinary tract infections
Aminoglycoside	Plazomicin	Complicated UTI and ventilator-associated pneumonia [28] caused by Gram-negative pathogens when no other treatment option exists	Acute kidney injury, especially in patients with renal disease. Aminoglycoside class adverse reaction including at times irreversible ototoxicity, especially in patients with family history of hearing problems and neuromuscular blockade, especially in patients with preexisting neuromuscular disorders	
Nitroimidazole	Pretomanid	Limited patient populations with extensively drug resistant or non-responsive with multidrug-resistant <i>M. tuberculosis</i> infection only in combination with bedaquiline and linezolid	Hepatotoxicity, myelosuppression, neurotoxicity, QT prolongation, lactic acidosis, multiple drug-drug interactions	
Fluoroquinolones	Delafloxacin [29]	Broad spectrum including MRSA, other Gram positives and Gram negatives for skin and soft tissue infections	Carries the same black box warning as other fluoroquinolones, appears to have less QTc prolongation compared to other fluoroquinolones	Not for patient with diarrhea associated with fever or bloody stools Single-dose treatment
Rifamycins	Rifamycin	Traveler's diarrhea caused by noninvasive <i>E. coli</i> in adults	Dyspepsia; generally low risk of side effects	
Nitroimidazole	Secnidazole	Treatment of bacterial vaginosis	Candidal vulvovaginitis	
Carbapenem with β lactam inhibitor	Meropenem/vaborbactam	Complicated UTIs caused by Gram-negative organisms	Risk of seizures with meropenem in patients with CNS disorders, reduced valproic acid serum concentration	
Cephalosporin	Cefiderocol [30]	Complicated UTIs caused by MDR Gram negatives with no other option, has been used for treatment of ventilator-associated pneumonia [28]	Potential for QT prolongation, fetal toxicity, multiple drug-drug interactions	Increased mortality in critically ill patient with pneumonia or sepsis with carbapenem-resistant pathogens observed Oral and injectable formulations are available
Pleuromutilin	Lefamulin	Community-acquired pneumonia, active against <i>S. pneumoniae</i> , <i>H. flu</i> , <i>Legionella</i> , <i>C. pneumoniae</i> , MSSA, mycoplasma	Risk of seizures with carbapenem antibiotics in patients with CNS disorders may decrease valproic acid serum concentrations	
Imipenem/cilastatin/relebactam	Carbapenem/dehydropeptidase inhibitor/B-lactamase inhibitor	Complicated UTIs and intraabdominal infection in patients where no alternative treatment is available		

VRE vancomycin-resistant enterococcus, MDR multidrug resistant, MSSA methicillin-sensitive *Staphylococcus aureus*, MRSA methicillin-resistant *Staphylococcus aureus*

Table 3 Select new FDA-approved anti-tuberculosis drugs and antivirals on the market in the USA since year 2017

Drug class	Names and notes	Indications	Side effects	Comments
Antiviral protein inhibitor	Tecovirimat	Small pox in adults and children	Headache in healthy volunteers; hypoglycemia when combined with repaglinide	Available through Strategic national Stockpile. Unknown efficacy in humans
Endonuclease inhibitor	Baloxavir marboxil	Influenza up to 48 h in duration in patients 12 years of age or older	No significant side effects described	Single-dose completes the course of treatment, avoid co administration with antacids, laxatives, or oral supplements
Non-nucleoside reverse transcriptase inhibitor	Doravirine	Combination therapy for HIV infection	Uncommon; immune reconstitution inflammatory syndrome	Do not co-administer strong cytochrome P450 enzyme inducers
Monoclonal anti MDR HIV antibody	Ibalizumab-uiyk	MDR HIV infection	Diarrhea, rash; immune reconstitution inflammatory syndrome	
Anti-hepatitis C combination drug	Glecaprevir and pibrentasvir	Hepatitis C infection	Reactivation of hepatitis B that can result in fulminant hepatitis; worsening liver failure;	Contraindicated in patients with severe liver impairment; avoid co-administering strong cytochrome P450 enzyme inducers
Anti-hepatitis C combination drug	Sofosbuvir/velpatasvir/voxilaprevir	Hepatitis C infection	Reactivation of hepatitis B that can result in fulminant hepatitis, case reports of severe bradycardia when amiodarone is co-administered; headache	Not recommended in patients with moderate to severe hepatic impairment; do not co administer rifampin;

Pseudomonas aeruginosa resistance to fluoroquinolones may be induced by diltiazem, a commonly used calcium channel blocker [2•].

Even when an antibiotic is withdrawn, or its use restricted, it does not guarantee that a bacterium will become susceptible to it again. Multidrug-resistant traits do not affect Gonorrhea

biological fitness, so it persists despite the lack of antibiotic exposure selection pressure [23].

Broad-spectrum antibiotic use puts patients at risk for developing *Clostridium difficile* colitis (CDI). A recent Cochrane review emphasized increased symptomatic cure with vancomycin when compared to metronidazole,

Table 4 Select new indications for old antibiotics [23, 31]

Name	Explored new indications	Comments
Gentamicin, kanamycin	<i>N. gonorrhoeae</i> infections	
Ertapenem	<i>N. gonorrhoeae</i> infections	
Fosfomycin	<i>N. gonorrhoeae</i> infections	
Spectinomycin	<i>N. gonorrhoeae</i> infections	First developed in 1960, abandoned after resistance emerged and new agents appeared, used again in some European countries, China, and South Korea [23]
Ramoplanin	<i>Clostridium difficile</i>	Not absorbed from oral administration
Minocycline	MRSA	
Mecillinam [32]	MDR Enterobacteriaceae	Not available in the USA
Tetracyclines, β -lactams, microcyclics	Neuroprotection in Parkinson's disease [33]	Exploring anti-inflammatory properties
Nebulized antibiotics formulations	Amikacin, ciprofloxacin for ventilator-associated pneumonia [28]	Currently only colistin, aztreonam, and tobramycin improved for use exclusively in patients with cystic fibrosis

Table 5 Select novel antibiotics in development [23, 31, 34] Google Scholar search

Drug class	Names and notes	Indications	Comments
Defensins [5]	Brilacidin	Broad-spectrum antibacterial activity	
Medicinal leech and other animal venom as source for antimicrobial peptides [35, 36]	Several peptides are studied		Interest based on ability of leech to store blood for a long time
Extremophile bacteria as sources of antibiotics [36, 37]			Fusaricidin B isolated from hot spring-derived bacteria is assigned a new application for tuberculosis treatment
Fluoroketolides	Solithromycin [23]	Activity against <i>N. gonorrhoeae</i> , <i>C. trachomatis</i> , <i>M. genitalium</i> , and Gram-positive respiratory pathogens	
Spiropyrimidinetrione topoisomerase II inhibitor	Zoliflodacin	Activity against XDR <i>N. gonorrhoeae</i> and <i>C. trachomatis</i>	
Triazaacenaphthylenes	Gepotidacin	Activity against MRSA, ESBL Enterobacteriaceae, and <i>N. gonorrhoeae</i>	
Cephalosporin/vancomycin heterodimer	Cefilavancin	Gram-positive pathogens	
Ethambutol	SQ 109	<i>M. tuberculosis</i>	
Non-absorbable small molecule antibiotic	Ridinilazole	<i>Clostridium difficile</i> all strains	Granted fast track status by FDA
Polymixins [38]	NAB741, CB-182804	Gram negatives	Early stages
Peptidomimetic	Murepavadin [28, 39]	<i>P. aeruginosa</i> infections	Novel mechanism of action pseudomonas specific
Carbapenems	Tebipenem [40]	Broad spectrum	First carbapenem with oral formulation available
Fluoroquinolones	Nemonoxacin; zabofloxacin	Broad spectrum with anti MRSA activity	Approved and used in several countries
Boronic acids	RPX7009 [41]		B-Lactamase inhibitors

fidaxomicin compared to vancomycin, and possibly teicoplanin compared to vancomycin [24] in CDI patients. Importantly, no recent studies looked at optimal treatment of severe *C. difficile* colitis [24].

Conclusion

Even though many clinicians are alarmed at the slow and uneven pace of the new antibiotics development [2•, 20•], a good many antimicrobial agents are now on the market (Table 2) as well as new anti-tuberculosis and antiviral medications (Table 3) since our last paper was published. Opening up new indications for old antibiotics becomes an increasingly important topic (Table 4) with a few stories of success over the years—anti-community MRSA armamentarium includes doxycycline and trimethoprim-sulfamethoxazole, while the new research focuses on testing old antibiotics for *Neisseria gonorrhoeae* treatment and using anti-inflammatory properties of antibiotics in treatment of progressive degenerative neurological disorders. Several promising molecules are undergoing trials to establish their efficacy as therapeutic agents

(Table 5). Unfortunately, if the history is any guide, only select few will become available for use for an Emergency Physician any time soon [2•, 19].

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- Of major importance

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