Newer Antibiotics: Need for More Studies in Neonates and Children

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Abstract

This article reviews few trials assessing the use of newer antibiotics in the neonates and children. Published data show that more studies are conducted in the adult population (50 times) when compared to children with respect to the testing of newer antibiotics. The figures are approximately 177 and 580 times more as compared to neonatal and preterm babies, respectively. Although there is paucity of data in the pediatric domain, carbavance (meropenem + vaborbactam) and solithromycin deserve special mention, as they are currently being used in pediatric clinical trials.

Keywords: New antibiotics, Pediatric population, Resistance.

Pediatric Infectious Disease (2019): 10.5005/jp-journals-10081-1212

Introduction

Ninety-one years after the invention of penicillin, a silent epidemic of antibiotic resistance is emerging. There is a dearth of new antibiotics to fall back upon. Newly approved antibiotics tend to be reserved as a last line of defense against multidrug-resistant (MDR) infections, thus minimizing its sales value. Drugs on which millions are spent on research and development (R&D) sometimes, therefore, do not see the light of day. This is a major deterrent for investment in R&D by pharmaceuticals, which has resulted in a bleak future for development of new antibiotic molecules.

Since 1962, there is a void in the antibacterial armamentarium termed as "innovation gap" which is due to the lack of discovery and addition of novel structural classes of antibiotics.

Since 2000, only three new classes of antibiotics have been introduced to the market for human use,[1] limited to topical use. The Infectious Diseases Society of America (IDSA) launched a novel initiative "the '10 × '20'"[2] with the hope of developing 10 new systemic antimicrobials before the year 2020 through a breakthrough innovation of classes of antimicrobials, in addition to finding newer molecules from the preexisting classes of antimicrobials.

In the present era, gram-positive bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA), MDR, and pan drug-resistant; gram-negative bacteria that include strains of *Acinetobacter baumannii*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and a third class comprising MDR and extensively drug-resistant (XDR) strains of *Mycobacterium tuberculosis* (MDR-TB and XDR-TB) are the major groups of bacteria that contribute to the current antimicrobial resistance.[3] *Enterococcus faecium*, *S. aureus*, *K. pneumoniae*, *A. baumannii*, *P. aeruginosa*, and Enterobacteriaceae are the XDR superbugs[4] that have earned the famous acronym of "ESKAPE."

There is paucity of pediatric data especially in clinical trials of newer antibiotics.

At present, 76 clinical trials are underway evaluating antibiotics in the pediatric population as against 4,078 adult trials. Of these 76 trials, only 23 have recruited neonates and among that only 8 clinical trials globally recruited preterm neonates.

The infective syndromes that were evaluated in these trials were the following:

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How to cite this article: Unni JC. Newer Antibiotics: Need for More Studies in Neonates and Children. Pediatr Inf Dis 2019;1(4):164–168.

Source of support: Nil

Conflict of interest: None

Gastrointestinal (GI), urinary tract, and skin and soft tissue infection (SSTI).[5]

According to the Pew Charitable Trusts' antibiotic pipeline imipenem/cilastatin + relebactam, cadazolid, carbavance (meropenem + vaborbactam), eravacycline, and solithromycin are the 5 antibiotics that have been agreed upon among the 37 antibiotics listed as of May 2016.[6]

So far only carbavance (meropenem + vaborbactam) (2015) are currently undergoing pediatric trials targeting MDR gram-negative organisms, and solithromycin (2016) being evaluated for gonococcal infections, anthrax, tularemia, and bacterial pneumonia.

Similarly, in 2015 to 2016, trials were agreed upon for a novel tetracycline group drug eravacycline for the treatment of urinary tract infection (UTI) and complicated intra-abdominal infections (cIAIs) followed by cadazolid for *Clostridium difficile* and imipenem/cilastatin + relebactam for gram-negative bacterial infections.[7]

However, published data are still lacking for the above studies.

Oxazolidinones

The first one to get licensed under this category was linezolid, which has laid the foundation for the discovery of newer molecules in the similar class.

Tedizolid a new oxazolidinone family is undergoing trials for skin and soft tissue infections (SStTIs), similarly a novel molecule cadazolid is also undergoing clinical trials for *C. difficile*-associated diarrhea (CDAD) and radezolid is in phase II studies for skin and skin soft tissue infections (uncomplicated) and community-acquired pneumonia. Another drug called MRX1 is being evaluated for

gram-positives like MRSA, penicillin resistant/intermediate *S. pneumoniae* and Vancomycin-Resistant Enterococci (VRE). Sutezolid, another new member of this class is now in phase I studies for XDR TB following the bedaquiline and delamanid way. AZD5847, another upcoming drug in this class is in phase I studies as an antitubercular drug. In comparison to the conventional antitubercular therapy (ATT), the efficacy of AZD5847 was found to be additive.[8]

In phase I and II trials, cadazolid the newer molecule that has undergone trials in comparison to vancomycin was shown to be safe, well tolerated, and efficacious. The phase II study concluded that the effect of all doses of cadazolid was numerically similar to, or better than, vancomycin positioning itself as a potential future viable therapeutic option for the treatment of CDAD in children.

However, the phase III trial have raised issues about the drug's efficacy. As the International Multi-centre Program Assessing Cadazolid treatment (IMPACT) 1 study met its primary end point in comparison to the second phase III study, IMPACT 2 failed to do so.[9]

In various systematic reviews, tedizolid had a better therapeutic response in comparison to vancomycin at end of therapy and posttherapy evaluation suggesting that that tedizolid provides an alternative option for the management of serious SStIs caused by suspected or documented MRSA and showed minimal drug reactions in phase II and III trials.[10]

Newer Glycolipopeptides

Daptomycin is a lipopeptide antibiotic with unique action on cell membrane. It is effective against gram-positive cocci like enterococcus (including glycopeptide-resistant enterococcus), MRSA, Streptococcus, Corynebacterium and *Borrelia* spp. It is used for treating skin and skin structure infections caused by gram-negatives, *S. aureus* bacteremia, and right-sided *S. aureus* endocarditis. It binds avidly to pulmonary surfactant, so cannot be used in the treatment of pneumonia. Daptomycin resistance uncommon even today but is being increasingly reported in GRE. When used for prolonged period for MRSA-like infections, there is a risk of reversible and often asymptomatic myopathy.[11]

Few other agents also in this group also deserve attention. Telavancin is useful against MRSA and gram-positives. The US Food and Drug Administration (FDA) has approved the drug in September 2009 for the treatment of complicated SStTI and in June 2013 for Hospital Acquired (HA) HA-MRSA and Ventilator Associated Pneumonia (VAPs) caused by *S. aureus*. Prolonged use of this agent, especially in patients with renal compromise has shown higher toxicity as compared to vancomycin.[12]

In August 2014, the FDA approved oritavancin for the treatment of acute bacterial skin and skin structure infections (ABSSSIs)—also MRSA (once a day (OD) dosing). Dalbavancin is also approved by the FDA in August 2014 for ABSSSIs and also MRSA and methicillin-resistant Strep (once a week dosing). Dalbavancin and oritavancin offer extended dosing intervals and are cheaper. They have lower rates of adverse effects when compared to telavancin.[13] Surotomycin is under phase II trial for CDAD in children.[14] However, further studies are needed to establish its appropriate pediatric dosage before they can be licensed for use in newborns and children (Tables 1 and 2).

New Streptogramins

Dalfopristin–quinupristin is already in use for infections with MRSA, Coagulase Negative *Staph. aureus* (CONS), penicillin-susceptible and penicillin-resistant *S. pneumoniae*, and vancomycin-resistant *E. faecium* but not *E. faecalis* and Vancomycin Intermediate *Staph. aureus* (VISA). NXL-103, a combination of flopristin and linopristin, is under evaluation for community acquired pneumonia (CAP) and SSTI spectrum—*S. aureus* (including MRSA), *S. pneumoniae*, *S. pyogenes*, *E. faecium*, *E. faecalis*, *H. influenzae*, and *H. parainfluenzae*. No systematic review of their use in children is available at present.[15]

Table 1: Newer antibiotics already in use in children

Cefepime	*Febrile neutropenia—resistant gram-positive and gram-negative bacteria*
Meropenem/imipenam	Gram-positive and gram-negative bacteria—*Pseudomonas aeruginosa* and anaerobes. No activity against *Stenotrophomonas maltophilia*
Linezolid	MRSA, VRE, and *Streptococcus pneumoniae*, *Mycobacterium tuberculosis*, and *Nocardia*
Tigecycline	Gram-positive, gram-negative, and anaerobes
Teicoplanin	Gram-positive—MRSA; *Enterococcus faecalis*
Aztreonam	Gram-negative and aerobic bacteria, Enterobacteriaceae, and *P. aeruginosa* (no gram-positive cover)
Polymyxin E (colistin)	Last-resort antibiotics for MDR *Pseudomonas*, *K. pneumoniae*, *Acinetobacter*. NDM-1 metallo-β-lactamase MDR Enterobacteriaceae have also shown susceptibility
Levofloxacin/moxifloxacin	Gram-positive, gram-negative and atypical bacteria; penicillin resistant *S. pneumoniae*
Piperacillin–tazobactam	Gram-positive, gram-negative and *P. aeruginosa*

Table 2: Newer antibiotics in pipeline

Oxazolidinones	*Radezolid, tedizolid, cadazolid, and MRX-I*
Glycolipopeptides	Oritavancin, dalbavancin, surotomycin
Streptogramins	NXL 103
Quinolones	Nemonoxacin, delafloxacin, and avarofloxacin
β-lactam antibiotics	Ceftaroline and ceftobiprole
β-lactam/β-lactamase inhibitors	Ceftolozane/tazobactam, ceftazidime/avibactam, imipenem/relebactam, meropenem/vaborbactam
Carbapenems	Ertapenem, doripenem
Tetracycline	Omadacycline and eravacycline
Macrolides	Modithromycin and solithromycin
Aminoglycosides	Plazomicin

Newer Quinolones

As of now, no significant clinical trials are done in children for any of these newer quinolones. Many of the new fluoroquinolones have antipseudomonal activity and additional anti-MRSA activity. Nemonoxacin is active against gram-positives, gram-negatives,

MRSA, vanco-resistant pathogens, and *C. difficile* isolates that are resistant to other quinolones. It is also more potent than levofloxacin or moxifloxacin. It is less active against gram-negatives like *E. coli*, *Proteus mirabilis*, and *P. aeruginosa* causing CAP and skin infections.[16]

Delafloxacin is approved by FDA in June 2017 for cSSSI covering both gram-positives and gram-negative spectrum.[17] Gemifloxacin is useful against gram-positive (*Streptococcus*, *Staphylococcus*) and atypical pathogens (*Chlamydia pneumoniae*, *Mycoplasma*, *Legionella*) but less against *Pseudomonas* when compared to ciprofloxacin. It has anaerobic activity and poor action against methicillin-resistant strains. The drug has high affinity for DNA gyrase and topoisomerase IV. It is also noted to have good activity against fluoroquinolone-resistant strains including fluoroquinolone-resistant *H. influenzae*.[18] Other newer agents still under trial include avarofloxacin, finafloxacin, and zabofloxacin.[19] Besifloxacin is another novel topical quinolone which is found to be useful in bacterial conjunctivitis.[20] Gatifloxacin has been banned due to the risk of severe hyperglycemia, and trovafloxacin has been withdrawn from the market due to the risk of hepatotoxicity.

Newer β-lactam Antibiotics

Cefditoren pivoxil is a third-generation oral cephalosporin which is effective against *S. pneumoniae*, *H. influenzae*, *Moraxella catarrhalis*, *S. aureus* (not MRSA strains), and *Streptococcus pyogenes* (penicillin-susceptible strains only). The main indication is in rhinosinusitis.[21] Ceftaroline and ceftobiprole are the "fifth-generation" cephalosporins useful against MRSA, *S. pyogenes*, *S. agalactiae*, and *S. pneumoniae*, hVISA, and Vancomycin Resistant *Staph. aureus* (VRSA)—gram-negative-ceftazidime-susceptible *E. coli* and *K. pneumoniae*, β-lactamase positive and negative *H. influenzae*. It has got synergistic action when combined with amikacin, tazobactam, meropenem, and aztreonam. Ceftaroline can be used in children aged >2 months having ABSSSIs and community-acquired bacterial pneumonia. The spectrum of organisms covered is staphylococcal and streptococcal infections, including MRSA and penicillin-resistant *Streptococcus pneumonia*.[22]

Newer β-lactam/β-lactamase inhibitors

Ceftolozane/tazobactam combination has superior *in vitro* activity against ceftazidime-resistant *E. coli*, *K. pneumoniae*, and *Enterobacter* and *Citrobacter* species when compared with ceftriaxone, cefepime, and piperacillin/tazobactam and also has significant action against extended-spectrum β-lactamases (ESBL)-producing *P. mirabilis*. Ceftazidime/avibactam is another combination effective against MDR gram-negative; all Enterobacteriaceae, including ceftazidime-resistant strains and *Burkholderia cepacia* complex. It can be used in cIAIs along with metronidazole and complicated UTIs (cUTIs). Data in children are extremely limited for both these antibiotics.[23]

Imipenem/relebactam combination is used against *E. coli*, *K. pneumoniae*, *Enterobacter* spp. including KPC producing Enterobacteriaceae and MDR *P. aeruginosa*. The main indication is in cUTI.[24] Meropenem/vaborbactam is another newly developed combination useful against *E. coli*, *K. pneumoniae*, and *Enterobacter* spp., including MDR KPC-producing strains. Relebactam and vaborbactam serve to broaden the spectrum of imipenem and meropenem, respectively, against β-lactamase-producing gram-negative bacilli.[25] The exact roles for imipenem-relebactam and meropenem-vaborbactam combinations will be defined by efficacy and safety data from further clinical trials. Potential roles in therapy for these agents include suspected or documented infections caused by resistant gram-negative bacilli-producing ESBL, KPC, and/or AmpC β-lactamases. It is also useful in carbapenem-resistant Enterobacteriaceae (CRE) infections and *P. aeruginosa* infections.[26]

Newer Carbapenems

Ertapenem was approved by the FDA in 2001. Its spectrum includes gram-positive and -negative aerobic as well as anaerobic bacteria excluding the nonfermenters, MRSA, and drug-resistant enterococci. It is effective against most resistant Enterobacteriaceae producing ESBLs and/or AmpC-type β-lactamases and is noted to have limited *in vitro* activity against *P. aeruginosa* and *Acinetobacter* species. It is not suitable for the empiric treatment of serious acquired nosocomial infections. It is recommended for prophylaxis of surgical-site infection following elective colorectal surgery. Unlike imipenem, ertapenem does not require coadministration with cilastatin.

Doripenem was approved by FDA in 2007. Its spectrum is more similar to that of meropenem and imipenem compared to ertapenem. Thus, it is effective against gram-positive and -negative aerobes and anaerobes including *P. aeruginosa*, *Acinetobacter* species, but not MRSA, VRE, and other strains resistant to imipenem and meropenem. It is effective against β-lactamase producing strains of Enterobacteriaceae. Doripenem is approved for the treatment of IAIs and complicated UTIs including pyelonephritis. Dosage adjustment is required in renal failure patients.[27]

Newer Tetracyclines

Tigecycline is the most common newer tetracycline currently used. Apart from this, a few are under development. Omadacycline is a newer one that circumvents common tetracycline resistance mechanisms. It is useful in gram-positive infections including MRSA, penicillin, and MDR *S. pneumoniae*, VRE, and also in gram-negative infections, anaerobes, atypical bacteria including *Legionella* spp. and *Chlamydia* spp. It is currently in phase III for its use in CSSSI and CAP. Eravacycline is another agent in phase III studies for its use in cIAIs with good gram-positive and gram-negative (MDR) spectrum. Data in children are extremely limited for both these new drugs.[28]

Newer Macrolides

Published data show a diminishing use of telithromycin in CAP due to reports of severe hepatotoxicity and strengthened safety warnings. Fidaxomicin a newer bactericidal drug, that is minimally absorbed, which causes minimal disruption of healthy GI flora is useful in selective eradication of pathogenic *C. difficile*, thereby reducing recurrence.[29] Modithromycin is another agent useful in gram-positive and gram-negative (MDR) infections with notable effect in MDR *Neisseria gonorrhoeae* infections.[30]

Solithromycin is a "fourth-generation" macrolide that is useful against MDR *S. pneumoniae* and nontypeable *H. influenzae*.[31]

However, due to unresolved issues on hepatotoxicity, their clinical utility as therapeutic agents for CAP and other gram-positive infections is limited.

Newer Trimethoprim-related Drug Iclaprim

Iclaprim has undergone phase III trials in adults and yet to undergo trials in children[32] and is currently being developed as intravenous

and oral formulation. This drug has a wider therapeutic coverage of several resistant strains that tackle *S. aureus* and *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, and *Legionella* spp., making it an ideal drug for respiratory tract infections.[32]

New Aminoglycoside Plazomicin

Plazomicin acts against gram-positive and gram-negative infections. It acts in synergy with daptomycin and ceftobiprole against MRSA, hVISA, and VISA. It also has synergistic activity with doripenem, imipenem, piperacillin/tazobactam, and cefepime against *P. aeruginosa*. It has undergone phase II study in patients with cUTIs and acute pyelonephritis, including cases with concurrent bacteremia. Safety and efficacy are not established in children below 18 years.[33]

Take-home Message

There are about 41 new antibiotics in development. Of these, 15 are in phase I, 13 in phase II, and 11 in phase III. Two antibiotics have completed phase III and have new drug applications. Only about 60% of drugs that enter phase III end up in getting approval. Based on the pipeline analysis, it is very clear that enough drugs are not available to patients. Although the bacterial resistance is developing rapidly, newer antibiotics in pipeline provide us some hope; and in this regard, we need more research in neonates, children, and adolescents. MRSA, VRSA, VRE, ESBL, Pseudomonas are major resistant organisms against which most new antibiotics are targeted. Judicious use of the antibiotics is the need of the hour to put breaks on the rapid development of extensive drug resistance.

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