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NEWER ANTIMICROBIAL AGENTS: A SYSTEMATIC REVIEW

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ABSTRACT

Antibiotics are one of the most commonly prescribed groups of medications, especially in developing nations, owing to the vast number of infectious diseases prevalent in the community. Since the time of discovery of the phenomenal antimicrobial, penicillin, there has been a great rise in the number of antimicrobials in the market. Antibiotic resistance is increasing to dangerously high levels at national level as well at Global front. Novel resistance mechanisms are emerging and spreading globally, threatening our capability to treat common infectious diseases. Emergence and growth of superbugs is endangering our lives by making existing antibiotics worthless. Antimicrobial resistance is a prevalent danger. Immediate and coordinated measures must be taken worldwide to safeguard remaining antimicrobials and facilitate the development of novel antimicrobials. This review article brings to limelight, the recent drugs in the field of antimicrobial drug development, from the last 10 years till date.

KEY WORDS

Texiobactin, Tigecycline, Ceftaroline, Fidaxomicin.

Newer Antimicrobial Drugs

Texiobactin

Teixobactin is the first member of a novel class of peptidoglycan synthesis inhibitors [1]. Teixobactin had excellent activity against Gram-positive pathogens, including drug-resistant strains. Potency against most species, including difficult-to-treat enterococci and M. tuberculosis was below 1nanogram ml. Teixobactin was exceptionally active against Clostridium difficile and Bacillus anthracis (minimal inhibitory concentration (MIC) of 5 and 20 ng ml, respectively [2, 3].

Teixobactin is a promising therapeutic candidate; it is effective against drug-resistant pathogens in a number of animal models of infection. Binding of teixobactin to WTA precursor contributes to efficient lysis and killing, due to digestion of the cell wall by liberated autolysins. This is akin to the action of another natural product with excellent killing ability, acyldepsipeptide, which converts the ClpP protease into a non-specific hydrolase that digests the cell[4]. These examples show that natural products evolved to exploit the inherent weaknesses of bacteria, and additional com-pounds that subvert important enzymes into killing devices are likely to be discovered. Teixobactin binds to multiple targets, none of which is a protein. Polyprenyl-coupled cell envelope precursors, such as lipid II, are readily accessible on the outside of Gram-positive bacteria and represent an 'Achilles heel' for antibiotic attack[5]. The target of teixobactin, the pyrophosphate-sugar moiety of these molecules, is highly conserved among eubacteria. The producer is a Gram-negative bacterium, and its outer membrane will protect it from re-entry of the compound. This suggests that the producer does not employ an alternative path-way for cell wall synthesis that would protect it from teixobactin, and which other bacteria could borrow. Resistance could eventually emerge from horizontal transmission of a resistance

mechanism from some soil bacterium, and given the highly conserved teixobactin binding motie, this would likely take the form of an antibiotic modifying enzyme. How-ever, although determinants coding for enzymes attacking frequently found antibiotics such as b-lactams or aminoglycosides are common, they are unknown for the rare vancomycin. The recently discovered teixobactin is even less common than vancomycin. After its introduction into the clinic, it took 30 years for vancomycin resistance to appear. The lipid II modification pathway resulting in vancomycin resistance probably originated in the producer of vancomycin, Amycolatopsis orientalis[6]. It will probably take even longer for resistance to the better-protected teixobactin to emerge. Teixobactin is the first member of a new class of lipid II binding antibiotics, structurally distinct from glycopeptides, lantibiotics[7,8], and defensins[9].

Tigecycline:

Tigecycline belongs to a class of drugs, closely related to tetracycline, called glycylcyclines. It inhibits protein synthesis by binding to the 30S ribosomal subunit and preventing the addition of transfer RNA molecules required for the elongation phase [10]. It is a bacteriostatic drug derived from minocycline and approved by the US Food and Drug Administration (FDA) for complicated intra-abdominal infections (cIAIs) and skin-soft tissue infections and community-acquired (CA) pneumonia [11-13]. Tigecycline has a broader spectrum of activity against aerobic and anaerobic gram-negative and positive pathogens. *In vitro* data shows that tigecycline has very good antibacterial activity against ESBL as well. It is not active against *P. aeruginosa*, which is an important gap in its antimicrobial spectrum [14]. Tigecycline efficiently tackles ESBL-producing Enterobacteriaceae, CPKP, and A. baumannii (both MDR and XDR), while tribe Proteae and Pseudomonas are intrinsically resistant pathogens [15, 16, 17].

The clinical studies evaluating the efficacy of tigecycline usually depict the results of its combination with other drugs, thereby masking the real effect of the drug[18-21]. Combination with colistin, meropenem, or aminoglycoside has shown low failure rates in infections caused by XDR-CPKP. However, its excessive use has led to increasing resistance, especially in CPKP[22]. The common side effects include nausea, vomiting, and diarrhea. Its use has also showed controversy as the death rate is shown to be higher with this drug as compared with other antibiotics, although the results were not statistically significant[23, 24]

Fidaxomicin:

Fidaxomicin is a narrow spectrum macrolide. It is mainly active against *Clostridium difficile*, and exerts limited activity against normal intestinal flora. It inhibits RNA polymerase sigma subunit that results in disruption of protein synthesis and cell death in susceptible organisms. It is purely bactericidal. It has minimal systemic absorption, has half-life of 9 hours and excreted mainly through faeces. It is given at a dose of 200 mg orally twice daily for 10 days. The most common adverse reactions reported in clinical trials are nausea, vomiting, gastrointestinal hemorrhage, abdominal pain, neutropenia and anaemia [25, 26]. It is an alternative to the currently used treatment regimens of vancomycin and metronidazole against CDI. In a phase III trial (n = 1000), fidaxomicin 200 mg (twice a day) was found to be non-inferior to vancomycin 125 mg (four times a day) for the treatment of initial or first recurrences of CDI.Recurrence rates of CDI with fidaxomicin were significantly lower (13%) as compared to vancomycin (25%) [27].

Ceftaroline:

Ceftaroline is a novel fifth generation cephalosporin. It is available as Ceftaroline fosamil (a prodrug). It is converted to the bioactive form, ceftaroline in plasma by phosphatases. It is a broad-spectrum antibiotic that is highly effective against Methicillin Resistant *Staphylococcus aureus* (MRSA), penicillin and cephalosporin resistant *S. pneumoniae*, Vancomycin-intermediate *S. aureus* (VISA), and Vancomycin-resistant *S. aureus* (VRSA). Ceftaroline acts by binding to penicillin binding proteins. It shows high affinity for PBP2a present in *Staphylococcus aureus* that is responsible for methicillin resistance. In *S. pneumonia*, ceftaroline binds to all 6 PBPs identified [28-30]. Inside the blood circulation, ceftaroline fosamil (prodrug) is rapidly converted to ceftaroline (active form) by phosphatase enzymes. It exhibits linear pharmacokinetics and has a serum half-life (t½) of 1.6 hr (for a single dose) to 2.7 hr (following multiple doses). Volume of distribution (20 l) of ceftaroline is similar to that of other parenteral cephalosporins with plasma protein binding of 20%. Ceftaroline is metabolized by hydrolysis of its β-lactam ring which results into the formation of an inactive, open-ring metabolite called as ceftaroline M-1. It has a

low potential for drug interactions because of insignificant metabolism by CYP_{450} enzymes [31].

Ceftobiprole:

It is another newer cephalosporin which has completed its trial in 2007 and is awaiting FDA approval due to additional safety data being demanded by FDA. It is the broad-spectrum antibiotic which shows good spectrum of activity against MRSA, penicillin-resistant *S. pneumoniae, P. aeruginosa* and *Enterococci*. Ceftobiprole shows strong affinity for PBP2a of MRSA and PBP2x of *S. pneumoniae*. It is given as 1 hr IV infusion of 500 mg every 12 hrs for gram-positive infection and a 2 hr infusion of 500mg every 8 hrs for gram-negative. Dose adjustment is needed in patients with renal impairment [32,33,34]

Dalbavancin:

it is a semisynthetic glycopeptide with a similar mode of action to vancomycin. It has potent activity against Gram-positive organisms including MRSA [35] Dalbavancin is highly potent against *S.pneumoniae*, *S.aureus*, coagulase-negative *Staphylococci* and vancomycin susceptible *Enterococci*. It is approved for the treatment of acute bacterial skin and skin structure infections caused mainly by Gram positive bacteria. The drug is to be infused IV over 30 minutes, only with 5% Dextrose as it gets precipitated with normal saline. Rapid infusion rates can lead to infusion reactions in form of upper body flushing, urticaria, pruritus, rash and ALT elevations > 3 times the Upper Normal Limit. Diarrhoea should be evaluated for *Clostridium difficile*-associated diarrhea (CDAD). Dalbavancin is 93% bound to albumin. It has an elimination half-life of around 346 hours. It is currently in trials for catheter related bloodstream infections [36,37.]

Oritavancin:

Oritavancin is a phenyl glycopeptide derivative. It shares its structure with vancomycin, and inhibits peptidoglycan biosynthesis by inhibiting both transglycosylation and transpeptidation. It has a selective action due to its strong intramolecular interaction with D-amino acid-containing peptidoglycan residues, not found in mammalian cells. Its pharmacokinetic properties allow less frequent dosing and also improved distribution. The drug has good potency against *S.pneumoniae* and *Staphylococci*. It exerts concentration-dependent cell killing activity against vancomycin-intermediate isolates of *S. aureus* (VISA) including heterogeneous VISA (hVISA) and against vancomycin resistant *Staphylococci* and *Enterococcus faecium* (VRE). It may also have additional activity against *B.anthracis*. It has a long elimination half-life of around 393 hours. A single 1200-mg dose administered IV over 3 hr is given for skin and skin structure infections [38-40]. Because of a long half-life, it is likely that it will be dosed on a daily or alternate day schedule [35]

Telavancin:

Telavancin is highly potent against MRSA, *Streptococci* and Vancomycin resistant Enterococcus (VRE). The drug has been approved for complicated skin and skin structure infections, and for ventilator-associated bacterial pneumonia caused by *S. aureus*. It is 90% plasma protein bound and has an elimination half-life of around 8 hours. It is 76% excreted in urine. Hence, dosage adjustment is required in patients with severe renal impairment. For complicated skin and skin structure infections, an IV dose of 10 mg/kg is administered once a day for a period of 7 to 14 days. Adverse effects include taste disturbance, vomiting and foamy urine. Rapid IV infusion can cause “red man syndrome” like reactions. Diarrhea should be investigated for *Clostridium difficile*-associated diarrhea (CDAD). Possible additive effects with other drugs that prolong the QT interval have been seen [41-43].

Telavancin is rapidly bactericidal and exists as an intravenous preparation to be given once daily. Its current indication is in cSSTI [44].

Doripenem:

It is the newer parenteral carbapenem approved for the treatment of complicated urinary tract infections and intra-abdominal infections. The drug acts by binding to PBPs and thus inhibiting cross-linking of the peptidoglycan structure. The high binding affinity of doripenem to PBP-2 and -3 may enhance its activity against drug-resistant *P.* aeruginosa. Thus, it is a suitable alternative to currently available anti-pseudomonal carbapenems (i.e, imipenem, meropenem) [45]. Doripenem has a unique spectrum of activity. It shows activity against gram-positive cocci like imipenem and activity against gram-negative bacilli like meropenem [46]. Doripenem, like other carbapenems, is stable to ESBLs produced by *E. coli* and Klebsiella species and to AmpC β-lactamases enzymes; but it is vulnerable to certain acquired β-lactamases like class B metallo-β-lactamases produced by some P. aeruginosa isolates and carbapenemases produced by some Enterobacteriaceae

and Acinetobacter species [47] .The elimination half‑life is around 0.95 hr, and 75% of the drug is excreted unchanged in the urine, thus necessitating dosage adjustment in patients with renal impairment. It is administered as a 500 mg IV infusion, thrice daily for 5-14 days. Adverse events include anaemia, anaphylactic reactions, seizures, neutropenia, toxic epidermal necrolysis (TEN) and Stevens Johnson syndrome [48-50].

Razupenem (PZ-601):

It is another novel carbapenem active against multi drug-resistant gram positive and gram-negative (ESBL producers) bacteria and is currently in trials for cSSSI [51].

Retapamulin:

It is a novel topical antibiotic and the first approved member in this new class. It is approved for the treatment of skin and soft tissue infections caused by *S. pyogenes* and *S. aureus* which are resistant to the most commonly used topical antibiotics. It is ineffective against gram-negative organisms [52]. Retapamulin a pleuromutilin which is a protein synthesis inhibitor that acts by binding to 50‑S subunit of bacterial ribosomes. It is bateriostatic at MIC while it becomes bactericidal at 1000x MIC. It is 94% bound to plasma proteins and is metabolized mainly by CYP3A4. Pruritus at application site, bacterial or fungal superinfection on prolonged use including *Clostridium difficile* associated diarrhea (CDAD) and pseudomembranous colitis have been reported [53,54].

Telithromycin:

It is a protein synthesis inhibitor that blocks the progression of the growing polypeptide chain by binding to 50-S subunit of the bacterial ribosome. Telithromycin exhibits 10 times higher affinity to the subunit 50-S than erythromycin. Telithromycin is more active *in vitro* against *S. pneumoniae* compared with clarithromycin and azithromycin and maintains activity against macrolide resistant strains (*S. pneumoniae, S. pyogenes*) [55]. Telithromycin is formulated as 400 mg tablet for oral administration. It is well absorbed orally with 60% bioavailability. Peak plasma concentration of 2.27 mg/l and a terminal half-life of 9.81 hr is achieved with a single 800 mg daily oral dose [56]. Telithromycin is 66-89% bound to serum protein, principally albumin. Drug is cleared primarily by hepatic metabolism, 50% by CYP_{3A4} and 50% by CYP independent metabolism. No dose adjustment is required for patients of hepatic failure or mild to moderate renal disease [57].

Daptomycin:

It is a cyclic lipopeptide antibiotic derived from *Streptomyces roseosporus* and is the first member of this new class of antimicrobials. It was approved by FDA in 2003 for the treatment of SSTIs and approved in 2006 for the treatment of blood stream infections. It shows the unique mechanism of action by inserting its lipophilic tail into the cell membrane of gram-positive organisms without entering the bacterial cytoplasm. This calcium dependent process leads to the formation of channels from which intracellular potassium is lost disrupting the bacterial cell membrane potential and causing cell death [58]. The dose giving maximum efficacy and safety is 4mg/kg daily as a once daily intravenous infusion, possibly due to the prolonged post-antibiotic effect of more than 6 hours. In healthy volunteers it has a half-life of 8 hours. It is excreted renally and consequently the dosage interval should be increased to every 48 hours in renal impairment where the creatinine clearance is <30ml/min or in patients on hemodialysis or continuous ambulatory peritoneal dialysis, where the half-life increases to 28 hours [59]. Since it is not hepatically metabolized, it does not cause any interactions related to the cytochrome P-450 enzyme system [60, 61]. It does not cross the blood brain barrier or enter the cerebrospinal fluid in normal individuals. Bone penetration is poor and daptomycin should therefore not be used in central nervous system or bone infections [62]. It has also not been effective in pneumonia, primarily due to daptomycin inactivation by lung surfactant [63].

Iclaprim:

It is a new dihydrofolate reductase inhibitor belonging to the same class of antibiotics as trimethoprim. Its Gram-positive cover is very promising with potent activity against MRSA, VISA and VRSA [64].it is a synthetic diaminopyrimidine, a selective inhibitor of the enzyme dihydrofolate reductase. Iclaprim is particularly potent against *S. pneumoniae* and *S. aureus*, including trimethoprim-resistant isolates. In contrast to trimethoprim which is most frequently used in combination with sulfamethoxazole, iclaprim is being developed for administration as a single agent, though highly synergistic activity was demonstrated with the sulfonamides like sulfamethoxazole, and sulfadiazine [65]. Iclaprim displays linear pharmacokinetics. The protein binding of iclaprim is 92%-94% and half-life is 2-4 hr [66].

Torezolid:

It is the active moiety of the prodrug, torezolid phosphate, which has 4-16-fold greater potency than linezolid against gram-positive species including MRSA [67] .it is an orally administered novel oxazolidinone. It is 4–8 times more active than linezolid in linezolid-susceptible and resistant strains of *Staphylococci* and *Enterococci* and up to 4 times higher activity against anaerobic bacteria. It has an oral bioavailability of 91% and hence no dosage adjustment is needed between IV and PO doses. It has an elimination half-life of around 12 hrs. It inhibits bacterial protein synthesis at the initiation/elongation step. It binds to the peptidyl transferase center (PTC) of 50S ribosome. It also binds to LepA, a universal bacterial elongation factor. Oxazolidinones bind only to the mitochondrial 70S ribosomes and not the cytoplasmic 80S ribosomes, explaining the myelosuppression and toxic optic neuropathy observed in linezolid-treated patients for as little as 14 days. Tedizolid is indicated in skin and skin structure infections. It is administered as 200 mg oral/IV for 6 days. Adverse events associated may include nausea, headache, anaemia, flushing, hypertension and *C.difficile* colitis [68-70].

Raxibacumab:

It is a recombinant human monoclonal antibody that has been recently developed against Anthrax infections. It can be used both as a prophylactic agent as well as a therapeutic agent. It is highly effective when given in combination with drugs used against *B.anthracis*. The drug targets the protective antigen component of the lethal toxin of the Anthrax bacillus. Common adverse events reported are headache, nausea, respiratory infections, pruritis and pain in the extremities [71-73].

Bedaquiline:

The U.S. Food and Drug Administration (FDA) has approved Bedaquiline for use as part of a combination therapy in adults with pulmonary multidrug-resistant tuberculosis (MDR TB). It inhibits proton pump of mycobacterial ATP synthase by binding to the oligomeric and proteolipic subunit-C of mycobacterial ATP synthase. This leads to inhibition in ATP synthesis and hence bacterial death. Bedaquiline has a half-life of 4-5 months. Increased mortality, QT prolongation, raised liver enzymes, hemoptysis and chest pain are reported adverse events with bedaquiline. It is dosed as follows: Weeks 1 - 2: 400 mg (oral) once daily; Weeks 3 - 24: 200 mg (oral) three times in a week [74,75].

Finafloxacin:

it is a flouroquinolone antibiotic that has been approved recently by the US FDA for swimmer's ear, scientifically termed as acute otitis externa. It is highly active against *Pseudomonas aeruginosa* and *Staphylococcus aureus*. It is available as a topical formulation in the form of eardrops / otic suspension. Commonly reported adverse events include local pruritis and nausea. Also, hypersensitivity reactions may be seen with the drug. It is also being used for the treatment of urinary tract infections [76, 77].

CONCLUSION:

As more resistant organisms are being seen in clinical practice, there is an urgent need for more potent antibiotics. There are only a few drugs which belong to a completely novel class; the rest are only a development of old and existing classes. If we do not take good care of the existent antibiotics by responsible prescribing, we will be at risk of losing even these more efficacious antibiotics. Antibiotics tend to lose their efficacy over time due to the emergence and dissemination of resistance among bacterial pathogens. Strains with resistance to multiple antibiotic classes have emerged among major Gram-positive and Gram-negative species including Staphylococcus aureus, Enterococcus spp., Pseudomonas aeruginosa, Acinetobacter spp. Enterobacteriaceae, and Neisseria gonorrhoeae. With some Gram-negatives, resistance may involve most or even all the available antimicrobial options, resulting in extremely drug-resistant or totally drug-resistant phenotypes. This so-called 'antibiotic resistance crisis' has been compounded by the lagging in antibiotic discovery and development programs occurred in recent years, and is jeopardizing the essential role played by antibiotics in current medical practices.

The emergence of pathogens with a variety of resistance mechanisms has intensified the challenges associated with infection control and treatment strategies. Therefore, prudent use of currently available antimicrobial agents, as well as implementing measures to limit spread of resistance is paramount. Although several new antimicrobials have been recently approved or are in the pipeline showing promise in the battle against resistance, the appropriate use of these agents is required as the true benefits of these

treatments are to be recognized in the clinical care setting.

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