Review Article

Management of community-acquired bacterial pneumonia in adults: Limitations of current antibiotics and future therapies

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ABSTRACT

Community-acquired bacterial pneumonia (CABP) is one of the leading causes of morbidity and mortality in India and worldwide. Evidence indicates that Gram-positive, Gram-negative, and atypical bacteria are encountered with near-equal frequency. Despite guideline recommendations and antibiotic options for the management of CABP, burden of morbidity and mortality is high, which is attributable to a variety of factors. Failure of empirical therapy, probably because of insufficient microbial coverage, increasing bacterial resistance, and adverse effects of existing treatments, underlies the unsuccessful treatment of CABP, especially in India. Multiple novel therapies that have entered clinical development phases have potential to address some of these issues. This article discusses the current treatment guidelines in CABP, management limitations, and emerging potential treatment options in the management of CABP.

KEY WORDS: Adult, antibiotic, bacteria, community acquired bacterial pneumonia, resistance

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INTRODUCTION

Community-acquired bacterial pneumonia (CABP) is a common, acute, severe infection of the lung parenchyma. It is a major cause of mortality in adults in Asia.[1] It is one of the most frequent respiratory illnesses among various infections triggering sepsis.[2] The Global Burden of Disease Study identified lower respiratory tract infection (LRTI) as the second most common cause of death and years of life lost.[3] The incidence of pneumonia is estimated to be between 1.5 and 14.0 cases per 1000 person-years.[4] The reported age-standardized death rate for LRTI is 41.7/100,000 population.[3] The reported incidence rate of CABP in India is 4 million cases per year.[5] Further, estimates suggest that India accounts for 23% of the global pneumonia burden and 36% of the World Health Organization regional burden.[6] Microbiologically, bacteria are common agents in pneumonia, with *Streptococcus pneumoniae* being the most common cause worldwide.[2,7] However, mortality with *Pseudomonas aeruginosa*, *Klebsiella* spp., *Escherichia coli*, and *Staphylococcus aureus* infections is substantially higher compared to other organisms.[8] Therefore, identification of the causative agent and initiation of appropriate antibiotics are important.

Treatment aims include microbiological eradication, clinical improvement, minimization of hospital stay, and prevention of reinfection.[9] Guideline-directed treatment

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reduces the mortality in CABP.[10] However, treatment failure with empirical antibiotics is common.[11] Early and late (≤72 h and >72 h of hospitalization) treatment failure rates vary from 2.4% to 31% and 3.9% to 11%, respectively. The factors identified for such failures include but are not limited to high-risk pneumonia, liver disease, multilobar infiltrates, *Legionella* pneumonia, Gram-negative pneumonia, pleural effusion, cavitation, leukopenia, and discordant antimicrobial therapy.[12] Amidst these factors, development of multidrug resistance (MDR) and declining susceptibility to available antimicrobials in various pathogens, treatment of CABP demands careful attention.[13] Furthermore, the adverse effects associated with different treatments such as gastrointestinal intolerance with macrolides can lead to treatment discontinuation, necessitating change of therapies.[14] Moreover, a meta-analysis identified that the use of combination treatments such as beta-lactam plus macrolide or fluoroquinolones (FQs) is associated with treatment discontinuations more than monotherapy.[15] Thus, multiple factors concurrently demand attention to improve outcomes in CABP. With increasing identification of Gram-negative and atypical bacteria in CABP, there is a need for novel therapies with broad-coverage. Here, we discussed the present guideline recommendations, treatment options, and limitations of current treatments and novel therapies in clinical development for the management of CABP.

GUIDELINE RECOMMENDATIONS FOR THE MANAGEMENT OF COMMUNITY-ACQUIRED BACTERIAL PNEUMONIA

Currently, the guidelines from the Infectious Diseases Society of America and the American Thoracic Society,[16] the British Thoracic Society,[17] and the Indian Chest Society and the National College of Chest Physicians (India),[18] provide recommendations for the management of CABP in adults. The major recommendations on the treatment of bacterial CABP are summarized in Table 1. Despite guideline recommendations and best of the efforts from the physicians, many a time, isolation of the causative organism is not possible, and empirical treatment is to be administered as per the local resistance patterns.

LIMITATIONS OF CURRENT TREATMENTS

Depending on culture sensitivity, the choice of antibiotic may vary; the limitations discussed below relate to the guideline-directed therapy. These limitations are discussed under different headings as below.

Antibiotic resistance

Resistance in beta-lactams: With the discovery of penicillins, the new era of antibiotics had begun which soon witnessed two important limitations – development of resistance and ineffectiveness in high bacterial inoculum without evidence of apparent resistance. These limitations were also observed with newer beta-lactams.[15] In pneumococcal pneumonia, beta-lactam as monotherapy may not be optimal therapy even if bacteria remain susceptible to them.[19] Penicillin-nonsusceptible *S. pneumoniae* is seen worldwide including developed countries like the US. However, after two decades of conjugate pneumococcal vaccine use, a reduction in penicillin resistance has been reported. However, it remains high in areas with lesser use of vaccine and high antibiotic consumption. Resistance in cephalosporins is suggested to be low.[20] However, cefepime resistance in *P. aeruginosa* has been reported.[21] Penicillin-resistant *S. aureus* has been isolated in CABP. Plasmid-encoded mechanism of resistance in *S. aureus* allowed rapid spread of resistance in community. Development of methicillin resistance in *S. aureus* was a cause of concern as *mecA* gene associated with mutant strains showed resistance to multiple antibiotics, including carbapenems as well as penicillins and cephalosporins.[20] The prevalence of methicillin resistance in *S. aureus* (MRSA) in CABP is reported to be low. Smith *et al*. reported isolation of *S. aureus* in <4% of cases over 1993–2011. However, community-acquired MRSA is associated with significant mortality, necessitating appropriate antibiotics such as linezolid or vancomycin.[22]

The development of resistance among macrolides in *S. pneumoniae* is due to methylation of ribosomal macrolide target sites and drug efflux.[20] Although the resistance to macrolides is on the rise, its use is still prevalent in CABP. The rate of macrolide resistance in *S. pneumoniae* varies between 20% and 40%.[23] In India, macrolide resistance rate of 5%–13% has been reported among respiratory pathogens.[5,24]

The overall resistance in FQs remains low in LRTIs. Major mechanism includes mutations in the quinolone resistance-determining regions of genes encoding subunits of topoisomerase IV or DNA gyrase. In *S. pneumoniae*, resistance rates in the US, Canada, China, and Spain were reported to be 1.0%, 0%–1.4%, 2.6%, and 0.5%–5.6%, respectively.[20] Emergence of resistance has also been reported with levofloxacin in some case reports.[25]

Vancomycin resistance in MRSA isolates involves shift in minimal inhibitory concentration of vancomycin. Alteration in cell wall causing reduced susceptibility to vancomycin is a major mechanism in vancomycin-intermediate *S. aureus* (VISA).[20] Identification of heterogeneous VISA (hVISA) is important as higher inpatient mortality with hVISA has been reported compared to vancomycin-susceptible isolates (44.8% vs. 24.1%, $P = 0.049$).[26]

Piperacillin along with tazobactam is commonly used in more severe forms of pneumonia. A study from Yayan *et al*. reported that, in patients with *Klebsiella pneumonia*, 75.3% showed resistance to piperacillin.[27] Inappropriate

Table 1: Guideline recommendations for the management of CABP in adults

Guideline	Regimen	Drugs
IDSA/ATS[16]		
OPD treatment		
Previously healthy without risk factors for resistant *S. pneumoniae*	Macrolide Doxycycline	Azithromycin, clarithromycin, and erythromycin
Comorbidities/USE of antibiotics in last 3 months/other risk factors for resistant *S. pneumoniae*	Respiratory FQ Beta-lactam + macrolide	Moxifloxacin/levofloxacin 750 mg High-dose amoxicillin/amoxicillin-clavulanate/ceftriaxone/cefpodoxime/cefuroxime
Allergy to penicillins	Respiratory FQ	Moxifloxacin, levofloxacin 750 mg
Inpatient treatment		
Non-ICU setting	Respiratory FQ β-lactam + macrolide	Moxifloxacin, levofloxacin 750 mg β-lactams: Cefotaxime/ceftriaxone/ampicillin
ICU	β-lactam + FQ β-lactam + azithromycin	
ICU with *P. aeruginosa*	β-lactam + ciprofloxacin/levofloxacin 750 mg β-lactam + aminoglycoside + azithromycin β-lactam + aminoglycoside + anti-pneumococcal, anti-pseudomonal FQ	β-lactams: Piperacillin/tazobactam/cefepime/imipenem/meropenem
BTS[17]		
Empirical treatment	β-lactam	Amoxicillin 500 mg t.i.d.
Penicillin allergy	Doxycycline or clarithromycin	
Prehospital treatment for life-threatening illness	β-lactam	Penicillin G 1.2 g IV/amoxicillin 1 g
Inhospital treatment: Moderate severity		
Initial treatment	β-lactam + macrolide	β-lactam: Amoxicillin
Oral therapy contraindicated	β-lactam + clarithromycin	β-lactam: Amoxicillin/benzylpenicillin, IV
Intolerance to penicillins or macrolides	Oral: Doxycycline/levofloxacin/moxifloxacin IV: Levofloxacin/β-lactam + clarithromycin	β-lactam: Cefuroxime/cefotaxime/ceftriaxone
In-hospital treatment: High severity	β-lactam + clarithromycin	β-lactam: Amoxicillin-clavulanate; if penicillin allergic - cefuroxime/cefotaxime/ceftriaxone
ICS/NCCP (I)[18]		
OPD setting		
Empirical antibiotic	Oral macrolide/β-lactam	
Presence of comorbidities	β-lactams + macrolides	
Non-ICU setting	β- lactams + macrolides Respiratory FQ	As above
ICU setting		
No *P. aeruginosa*	β-lactams + macrolides	As above
Presence of *P. aeruginosa*	β- lactams±aminoglycoside/FQ[#]	As above

[#]TB is not a diagnostic consideration at admission. BTS: British Thoracic Society, FQ: Fluoroquinolone, ICU: Intensive care unit, ICS NCCP (I): Indian Chest Society and National College of Chest Physicians (India), IDSA/ATS: Infectious Disease Society of America/American Thoracic Society, IV: Intravenous, OPD: Outpatient department, t.i.d.: Three times a day, *S. pneumoniae*: Streptococcus pneumoniae, *P. aeruginosa*: *Pseudomonas aeruginosa*

therapy is found to be associated with bacteremia due to resistant pathogens such as MDR *S. pneumoniae,* MRSA, MDR *P. aeruginosa*, and an extended-spectrum beta-lactamase-producing *Enterobacteriaceae*.[28] This necessitates the appropriate use of such broad-spectrum antibiotics to prevent emergences of resistance.

Effectiveness of carbapenems against deadly *P. aeruginosa* makes these antibiotics special for the treatment of CABP. Although infrequent, resistant *P. aeruginosa* isolates in CABP are associated with increased mortality.[29] A 10-year evaluation of resistance patterns in CABP patients reported imipenem, meropenem, piperacillin, and piperacillin/tazobactam resistance in 28.6%, 20.2%, 24.2%, and 23.1% *P aeruginosa* isolates and in 55.6%, 42.3%, 44.4%, and 44.4% MDR *P. aeruginosa* isolates, respectively.[21] This highlights the existence of resistance to higher-ceiling antibiotics, demanding careful evaluation of isolates before initiating therapy.

Aminoglycosides, especially amikacin resistance, have also been reported. A study from Egypt reported resistance in 17% of Gram-negative isolates. In major isolates, the levels of resistance were 30.8% in *Enterobacter aerogenes*, 25% in *K. pneumoniae*, 20% in *P. aeruginosa*, and 16% in *E. coli*.[30]

Atypical pathogens and their resistance

Globally, *Mycoplasma pneumoniae*, *Legionella pneumophila*, and *Chlamydophila pneumoniae* are atypical bacteria commonly involved in CABP.[31] Atypical pathogens such as *Mycoplasma* and *Legionella* constitute up to 20% of etiological agents in hospitalized patients with CABP. Thus, it is imperative that empirical antibiotic coverage should include atypical pathogens. However, a 2012 Cochrane systematic review of 28 randomized controlled trials (RCTs) evaluating empirical coverage of atypical pathogens reported no difference in mortality between the atypical arm and the nonatypical arm (relative risk: 1.14; 95% confidence interval [CI]: 0.84–1.55).

Interestingly, a nonsignificant trend toward clinical success and a significant advantage to bacteriological eradication were Reported in atypical arm.[32] Emergence of resistance is an important factor that makes the treatment difficult. Macrolide-resistant *M. pneumoniae* have been reported and are associated with longer duration of antibiotic therapy and longer time for the resolution of fever.[33] Given these results, atypical coverage should be the part of initial empirical therapy to improve the clinical success rate.

Inadequate penetration in lungs

Antibacterial agents are one of the life-saving agents. Their variable penetration to different target sites of infection, drug solubility, and extent of protein binding determines the effectiveness besides their antibacterial activity. Hydrophilic agents such as β-lactams (penicillins, cephalosporins, carbapenems, and monobactams), vancomycin, and aminoglycosides tend to have impaired permeability in lungs, necessitating increase in dose.[34] In the management of pneumonia caused by extracellular pathogens, epithelial lining fluid (ELF) is considered to be the site of action. The ELF-to-plasma concentration ratio varies in beta-lactams from 0.21 for ceftazidime to 1.04 for cefepime. Piperacillin has a ratio of nearly 0.50 (for tazobactam: 0.65–1.21) and for ampicillin, ratio is 0.53 (for sulbactam: 0.61). Meropenem reported to have a lower ratio in severely ill patients than healthy volunteers (0.25 vs. 0.65) whereas doripenem and imipenem have a ratio of 0.34 and 0.44, respectively, in healthy volunteers. These findings indicate a lower probability of penetration in lung epithelium for carbapenems than penicillins. Vancomycin achieves a ratio of 0.18–0.50, indicating a need for higher doses to achieve therapeutic drug concentration in the lungs. In comparison to these molecules, FQs have shown a ratio of >1 and aminoglycosides achieving a ratio of >1 after few hours of dosing. Despite the fact that lung concentration achieved to therapeutic levels with some agents, the redistribution effect might affect the lung concentrations and therefore, their effect on clinical outcome remains to be studied.[34]

Besides ELF concentration, achievement of adequate concentration intracellularly in alveolar macrophages (AMs) is essential for effective clearance of microbes, including intracellular pathogens. Macrolides and levofloxacin have been identified to attain greater ELF concentration in infected lung tissue compared to other respiratory antibiotics.[35] Such favorable characteristics will assist in making a choice of antibiotic depending on the identification of extracellular and intracellular pathogens.

Undesirable adverse effects

Although the antibiotics indicated in the management of CABP are generally considered safe, there are certain undesirable effects that need a special mention. Hypersensitivity reactions to beta-lactams are important as its reported incidence is nearly 10%. However, establishing true causal relationship of allergic reactions to beta-lactams is essential to prevent unnecessary shifting to alternate broad-spectrum antibiotics. Anaphylaxis is an important limitation, and penicillin-induced anaphylaxis is reported in 1.4–4/10,000 treated patients. However, the incidence of anaphylaxis with cephalosporins and other beta-lactams is not known.[36] In penicillin skin test-positive patients, monobactams may be safely used and has a lower tendency for immunogenic reactions.[36,37] Patients treated with imipenem need to be carefully monitored for seizures and blood dyscrasias, whereas patients treated with meropenem need to be monitored carefully for gastrointestinal disturbance and neutropenia.[37] Possibility of bleeding diathesis with ticarcillin and somewhat lesser with azlocillin and piperacillin needs careful monitoring.[38] Among FQs, levofloxacin and moxifloxacin have the lowest potential to induce central nervous system adverse effects, but QTc prolongation is seen more frequently with moxifloxacin than levofloxacin.[39] In aminoglycosides, nephrotoxicity and ototoxicity are important limitations. Nephrotoxicity may occur in nearly 20% of the patients treated with aminoglycosides.[40] Vancomycin-associated nephrotoxicity is also a major limitation for its use and demands careful monitoring of renal function.[41]

Therefore, an ideal antibiotic for the management of CABP in the current scenario should have minimal antibiotic resistance or be active against resistant pathogens; have broader microbiological coverage to include Gram-positive, Gram-negative, and atypical bacteria; have better penetration in the lung with higher concentration achievement in ELF; and have better tolerability and safety profile. A look at future therapies can tell us if any of these can be ideal antibiotics for the management of CABP.

Other factors

Besides the factors limited to medications, various other factors contribute to the limited use of current drugs in the management of CABP.

Patient comorbidities

The presence of comorbidities such as renal failure can affect various drugs. Dose modifications in drugs such as vancomycin and daptomycin are necessary for patients with renal failure.[42]

Polymicrobial infections

The presence of multiple pathogens has been identified in patients admitted to intensive care unit, which leads to inappropriate selection of initial antibiotic. This may affect the mortality outcome in CABP.[43]

Lack of local antibiotic treatment guidelines

Availability of antibiotic treatment guidelines based on local pathogen isolation and susceptibility patterns is essential to guide empirical antibiotic therapy in CABP.[44]

Inappropriate use and/or duration of antibiotic therapy

In patients with CABP, inappropriate antibiotic use leads to higher length of hospital stay and higher rate of 30-day readmission.[45] Further, the use of antibiotic treatment for

longer than recommended duration is prevalent in patients with CABP, contributing to increased antibiotic resistance and cost of illness.[46] In fact, early antibiotic de-escalation is not associated with increased short-term mortality and reduced duration of hospital stay.[47] Thus, there is a need to adopt an individualized approach in the treatment of CABP.

Complications and/or multiorgan involvement

CABP is associated with acute cardiac complications such as myocardial infarction, arrhythmia, and heart failure, but the mechanisms of this association remain unclear. Long-term mortality is also high in CABP, which needs to be considered while treating with antibiotics. However, optimal approaches to reduce such complications need to be explored in future.[48]

Cost

Multiple factors are determinant for cost in CABP management. Complications and previous hospitalization are important contributors to the overall cost. Antibiotic treatments with beta-lactams or FQ monotherapy or beta-lactam/macrolide combination therapy did not affect the cost-effectiveness of strategies employed in CABP.[49,50]

FUTURE THERAPIES

Despite advancements in antibiotic treatments, the mortality burden with CABP remains a significant concern. A 10-year prospective cohort study in Canadian individuals reported that over a median of 9.8 years, 2858 patients with CABP died compared with 9399 control cases (absolute risk difference, 30/1000 patient years; adjusted hazard ratio, 1.65; 95% CI, 1.57–1.73; $P = 0.001$). This confers high risk of long-term adverse events compared to the general population.[51] Therefore, there is a need for newer antibiotics that can provide better outcomes in CABP. Use of higher and newer antibiotics is dented by culture. Hence, a good microbiology laboratory backup is essential to avoid overuse and misuse of antibiotics. Here, we discussed in brief some of the future antibiotics that hold potential to be indicated in CABP [Table 2].

Table 2: Newer antibiotics with potential use in community-acquired bacterial pneumonia

Class	Molecule
Beta-lactams and/or beta-lactamase inhibitor	Ceftolozane-tazobactam
	Ceftazidime-avibactam
	Meropenem-vaborbactam
	Imipenem-relebactam
	Aztreonam-avibactam
	Cefiderocol (S-649266)
	Ceftobiprole
Macrolide	Solithromycin
Aminoglycosides	Plazomicin
Fluoroquinolones	Levonadifloxacin (WCK 771 and WCK 2349)
Tetracycline	Eravacycline
Pleuromutilin	Lefamulin
Oxazolidinone	Tedizolid
Lipoglycopeptide	Telavancin
Outer Membrane Protein Targeting Antibiotics	Murepavadin

Newer beta-lactams and beta-lactamase inhibitors

Use of beta-lactam in combination with inhibitors of beta-lactamases has been a miracle success amidst failure of monotherapies. Successful use of amoxicillin–clavulanic acid, ampicillin–sulbactam, and piperacillin–tazobactam for most of the complicated infections has saved lives of many. This has led to the development of newer beta-lactamase inhibitors such as avibactam, vaborbactam, and relebactam, which are being used in combination with different antibiotics.[52] However, in the current scenario, it may not be advisable to deviate to newer antibiotics without strong laboratory evidence.

Ceftolozane–tazobactam

This combination has been recently approved by the United States Food and Drug Administration (USFDA) for the treatment of complicated intra-abdominal infections (cIAI) and complicated urinary tract infections (cUTI). It has demonstrated *in vitro* activity against *Enterobacteriaceae* in the presence of some extended-spectrum beta-lactamases (ESBLs) and other beta-lactamases of the following groups: TEM, SHV, CTX-M, and OXA. However, it is not active against bacteria that produce serine carbapenemases (*Klebsiella pneumoniae* carbapenemase [KPC]) and metallo-beta-lactamases.[53] It has shown good ELF penetration, but for the treatment of pneumonia, requirement of increased dosage has been suggested in pharmacokinetic/pharmacodynamic evaluation.[54] A retrospective study in MDR *P. aeruginosa* isolated from different infections with majority being respiratory infections ($n = 18/21$) showed clinical success in 71% of cases, and three cases had resistance mediated in part by AmpC-related mechanism.[55] These data indicate possible use of this combination in pneumonia, especially with MDR *P. aeruginosa*, but warrants future investigations to confirm utility in CABP.

Ceftazidime–avibactam

This combination of ceftazidime with novel beta-lactamase inhibitor, avibactam, has excellent *in vitro* activity against major Gram-negative pathogens such as *Enterobacteriaceae* and drug-resistant *P. aeruginosa* including extended-spectrum beta-lactamase-, AmpC-, KPC-, and OXA-48-producing isolates. However, it has no activity against metallo-beta-lactamase-producing strains. Its efficacy has been established in cUTI, cIAI, and hospital-acquired pneumonia (HAP).[56] The ELF exposure of both drugs is nearly 30% of the plasma levels.[57] This combination, therefore, can be a possible candidate for CABP due to Gram-negative isolates as a potential alternative to carbapenems or even as empirical therapy in infection with ESBL-producing or CRE-producing Gram-negative bacteria.

Meropenem–vaborbactam

Vaborbactam is a potent inhibitor of many beta-lactamases that protects from Class A and Class C serine beta lactamases, including KPC producing Gram negative

organisms. Its addition to meropenem reduces the MIC by over 16-fold for different *Enterobacteriaceae*.[58] It has no effect on meropenem-nonsusceptible *A. baumannii* containing OXA-type carbapenemases or for *P. aeruginosa*. Recent studies have demonstrated superiority of meropenem–vaborbactam over piperacillin–tazobactam for the treatment of cUTI, including acute pyelonephritis. Furthermore, higher clinical cure rates compared to best available therapy in the treatment of CRE as well as hospital- and ventilator-associated bacterial pneumonia (HAP/VAP) have been reported.[59] The intrapulmonary penetration identified after this combination was 0.63 for meropenem and 0.53 for vaborbactam.[60] Currently, a multicenter RCT involving adults with (HAP/VAP) is underway, comparing it with piperacillin/tazobactam (ClinicalTirals.gov identifier: NCT03006679). Given these data, this combination holds potential for use in CABP.

Imipenem–relebactam

Relebactam potentially inhibits the activity of beta-lactamases belonging to class A and C, but has no activity against metallo-beta-lactamase and class D carbapenemases. Relebactam in combination with imipenem–cilastatin has shown activity against MDR Gram-negative isolates including *P. aeruginosa* and KPC-producing *K. pneumoniae* and *Enterobacter* spp.[61] The ELF levels achieved relative to that of plasma concentration are 54% and 55% with relebactam and imipenem, respectively.[62] Studies in HAP/VAP are underway (ClinicalTrials.gov Identifier: NCT02493764, NCT02452047). Considering these data, it can be a potential candidate for evaluation in future studies for CABP.

Aztreonam–avibactam

This combination is under evaluation for the treatment of IAI along with metallo-beta-lactamase-producing Gram-negative infections. Currently, a Phase II trial is evaluating the PK, safety, and tolerability in treating hospitalized patients with cIAI (ClinicalTrials.gov Identifier: NCT02655419).[63] ELF concentration of aztreonam is reported to range from 36% to 80%. Thus, to treat a lung infection, it is necessary to adjust the dosing regimen to maintain a serum concentration that allows for an ELF concentration 4–6 times the MIC for at least 40% of the dosing interval.[64]

Cefiderocol (S-649266)

A novel, siderophore cephalosporin, which is not used in combination with beta-lactamase inhibitors but has activity against beta-lactamase and carbapenemase-producing pathogens and is active against MDR Gram-negative bacteria causing HAP, VAP, cUTI, and bloodstream infections.[45] Experimental evidence suggested that it has a potential for use in lung infections associated with carbapenem-resistant Gram-negative bacilli (*P. aeruginosa, A. baumannii, and K. pneumoniae*).[64] Clinical studies will be necessary to confirm its efficacy in respiratory infections.

Ceftobiprole

Ceftobiprole, a broad-spectrum cephalosporin, has a potent bactericidal activity, causing cell lysis or death by binding to PBP, inhibiting transpeptidation and formation of the bacterial cell wall. Against isolates MRSA, VISA, and VRSA, MIC of 2 mcg/mL has been observed. It is also observed to have activity against various Gram-negative isolates such as *Citrobacter* spp., *E. coli, Enterobacter* spp., *Klebsiella* spp., *Serratia marcescens*, and *P. aeruginosa*. Noninferiority of ceftobiprole compared to ceftriaxone (with or without linezolid) is also established in hospitalized patients with CABP.[65]

Newer macrolide: Solithromycin

It is a fluoroketolide "fourth-generation" macrolide antibiotic that has activity against the common agents in CABP such as *S. pneumoniae, Haemophilus influenzae*, and atypical pathogens, including those resistant to other macrolide antibiotics. Phase II and III trials have demonstrated that it is noninferior to moxifloxacin in the treatment of CABP and has milder adverse event than other macrolide antibiotics.[66]

Newer aminoglycosides: Plazomicin

This protein synthesis inhibitor exhibits dose-dependent bactericidal activity against Gram-positive bacteria (e.g., MRSA), including aminoglycoside-resistant isolates. It is also active against MDR *Enterobacteriaceae*, including CRE and aminoglycoside-resistant Gram-negative isolates. USFDA has approved it for use in cUTI in 2018.[67] CARE study was a Phase III study that compared colistin and plazomicin in CRE-associated bloodstream infections. Plazomicin compared to colistin was associated with improved outcomes (all-cause mortality/significant disease-related complications: 14.3% vs. 53.3%) and microbiological clearance by day 5 (85.7% vs. 46.7%), suggesting potential for use in CRE infections.[68] Its wide spectrum of activity against resistant Gram-positive and Gram-negative infections suggests its possible future use in CABP.

Newer fluoroquinolones: Levonadifloxacin (WCK 771 and WCK 2349)

The WCK 771 and WCK 2349 are L-arginine salt and L-alanine ester prodrug of levonadifloxacin, respectively. These are currently under development for the treatment of MRSA-associated ABSSSIs and hospital-acquired bacterial pneumonia.[69] This new benzoquinolizine subclass of FQs has potent antimicrobial activity against Gram-positive bacteria, including MRSA, VISA/glycopeptide-intermediate *S. aureus* (GISA), and levofloxacin/moxifloxacin-resistant *Staphylococci*. Its coverage of significant respiratory pathogens such as *H. influenzae* and *Moraxella catarrhalis*, *in vivo* efficacy for *S. pneumoniae* infections, and activity against atypical respiratory pathogen, *M. pneumoniae*, are good, with potencies comparable to and matching with the best drugs for the respective indications in its class. Activity against anaerobes and atypical organisms such as *Mycoplasma genitalium*, *Mycoplasma hominis*,

M. pneumoniae, and *Ureaplasma* spp. has also been demonstrated.[70,71] A recent study has demonstrated that the ratios of ELF concentration and concentration in AMs relative to plasma concentration were 7.66 and 1.58, respectively, suggesting better lung penetration.[72] Achievement of such good levels in lung combined with its broad-spectrum activity covering Gram-positive, Gram negative, and atypical pathogens, makes levonadifloxacin a potent antibiotic for the treatment of CABP.

Newer tetracycline: Eravacycline

This tetracycline is structurally similar to tigecycline, showing more potent activity than tigecycline against Gram-positive, Gram-negative, and anaerobic bacteria. It has no activity on *P. aeruginosa*.[52] Achievement of ELF and AM concentration greater than plasma by 6-fold and 50-fold suggests that it is a good candidate for use in respiratory infections.[73]

Newer pleuromutilin: Lefamulin

Pleuromutilin (from fungi *Pleurotus mutilus,* i.e., *Clitopilus scyphoides*) binds to the peptidyl transferase site on 23S RNA of the 50S ribosome and inhibits the bacterial protein synthesis. Retapamulin, one of the early agents in the class, was approved by the USFDA in 2006 for topical use to treat impetigo.[63] Lefamulin is the first antibiotic from this class to be used for systemic treatment of bacterial infections in humans. Its broad-spectrum of activity covers Gram-positive and atypical organisms associated with CABP (*S. pneumoniae, H. influenzae, M. pneumoniae, L. pneumophila,* and *C. pneumoniae*), with an expanded Gram-positive spectrum including *S. aureus* (MRSA, VISA, and heterogeneous strains) and vancomycin-resistant *E. faecium*. In a Phase III study in patients with CABP, it has shown similar activity to moxifloxacin with or without linezolid. Currently, it is undergoing review by the USFDA for its use in CABP.[74]

Newer oxazolidinone: Tedizolid

Tedizolid offers potential advantages of once-daily dosing, shorter duration of therapy, and increased tolerability over linezolid. It is approved by the USFDA in the management of ABSSSIs. Its MIC is lower than linezolid against MRSA isolates and is active against linezolid-resistant isolates as well.[75] It is currently under investigation for efficacy in nosocomial pneumonia (ClinicalTrials.gov Identifier: NCT02019420) and for diabetic foot, bone, and joint infections.

Newer lipoglycopeptide: Telavancin

Telavancin is active against Gram-positive aerobic and anaerobic bacteria including MRSA, VISA, and non-Van-A strains of vancomycin-resistant *Enterococci*. It is approved for use in cSSTI and HAP.[76] With achievement of ELF and AMs at concentrations up to 8 fold and 85 fold of MIC90 for *S. aureus*, it promises to be better antibiotic for Gram-positive respiratory infections.[77]

Newer Outer Membrane Protein Targeting Antibiotics: Murepavadin

Murepavadin is a first molecule from the novel class - Outer Membrane Protein Targeting Antibiotics. It has a potent *in vitro* activity against carbapenemase-producing and colistin-resistant *P. aeruginosa*. Intravenous formulation of murepavadin is currently under clinical for nosocomial pneumonia due to *P. aeruginosa* (ClinicalTrials.gov Identifier: NCT03582007).[78]

CONCLUSION

The current evidence suggests that *S. pneumoniae* is a common bacterial pathogen, but Gram-negative and atypical bacteria are also frequently encountered in CABP. CABP has a significant presence and has adverse outcomes despite the availability of effective antibiotics. Limitations of currently available antibiotics such as high level of resistance and attainment of inadequate concentration in the lung epithelial lining as well as in AMs can lead to the failure of therapy. The ideal antibiotic demands broad-spectrum of activity along with adequate lung penetration and comparable safety. Among newer antibiotics, antibiotics such as nemonoxacin, levonadifloxacin, solithromycin, eravacycline, and lefamulin have potential to be more efficacious than existing antibiotics. Successful use of such newer antibiotics can extend the benefits of reducing morbidity and mortality associated with CABP.

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Conflicts of interest

Authors Jaishid Ahdal and Rishi Jain are the salaried employees of Wockhardt Ltd., Mumbai, India. Other authors have no conflicts of interests.

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