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Mini Review

Treatment options with ancient vs novel antibacterial therapy for notorious gram-negative carbapenem-resistant pathogens

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ABSTRACT

Antimicrobial resistance threatens the health of the public and is increasing day by day in tertiary care hospitals. Several novel antibiotics have been approved to combat critically ill patients, but bacteria, specifically the gram-negative bacteria *E. coli*, *A. baumannii, P. aeruginosa, and K. pneumonia*, rapidly evolve to develop resistance against these antibiotics. These Gram-negative pathogens are present as MDR, XDR, CRE, and MBL by producing many different kinds of enzymes active against antibiotics to develop resistance. Ancient antibiotics such as colistin and fosfomycin were considered for the treatment of CRE because no novel therapy was available, but in February 2015, the FDA sanctioned ceftazidime and avibactam, a novel β-lactamase inhibitor. CAZ/AVI is the superlative choice of therapy to use as Colistin spare agent, and it is also choice of therapy against MDR, gram-negative rods as carbapenem spare agents to stop the irrerational use of Carbapenems.

Key words: Multidrug resistance (MDR), Extensive drug resistance (XDR), Carbapenem resistance enterobacterales (CRE), Ceftazidime and Avibactam (CAZ/AVI)

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INTRODUCTION

Antimicrobial resistance (AMR) has been globally threaded for all health care professionals (HCPs) for the last one and half decades as critical care clinicians, and infectious disease experts face a novel weird challenge in the treatment of chronic infections[1,2]. According to the BBC, 1.2 million people die each year globally due to the emergence of resistance. Multidrug resistance (MDR), extensively drug-resistant (XDR), pan drug-resistant (PDR), and carbapenem-resistant Enterobacterales (CRE) are innovative terminologies used when gram-negative microbes such as *E. coli,* Klebsiella pneumonia, Acinetobacter baumannii, and Pseudomonas aeruginosa adopt resistance against antibiotics[3]. Most tertiary care hospital-acquired infections are nosocomial infections caused by these Gram-negative pathogens. Urinary tract infections (UTIs), nosocomial pneumonia (NP), bloodstream infections (BSIs), nosocomial infections such as ventilator-associated pneumonia (VAP), and complicated intra-abdominal infections are caused by these gram-negative rods[4]. More than 70% of hospital-acquired infection hosts are gram-negative bacteria[5].

AMR not only increases the mortality rate but also increases the economic burden globally[6,7]. The principle of bacterial resistance has multiple factors. Irrational use of antibacterial agents, unfitting empiric coverage, delay in precise diagnoses, and early de-escalation of treatment are all contributing factors to emerging resistance. Currently, some limited antibacterial agents are nominal in treating serious infections, which further exacerbates the difficulty. Drug-resistant Gram-negative bacteria are flattering more rampant among nosocomial infections. *E. coli, K. pneumonia, and P. aeruginosa* are the major hosts of hospital-associated infections and quickly change their genetics because of the variety of mechanisms and develop resistance against antibacterial agents[8]. The objective of this mini-review is to describe the best clinical strategies for treating patients with MDR gram-negative infections, regardless of their resistance level.

ANCIENT ANTIBACTERIAL AGENT

Colistin

In 1949, Y. Koyama fermented colistin (Polymyxin E) from Bacillus species, and after one decade in 1959, it was first used for clinical purposes[9,10]. It has significant activity against Gram-negative bacterial infections caused by *P. aeruginosa, A. baumannii, K. pneumonia, E. coli,* and carbapenem-resistant Enterobacteriaceae[11,12]. Due to the lower availability of antibacterial agents for the treatment of MDR, XDR, PDR, and CRE, colistin is considered for treatment with more effective bactericidal activity[1,13]. Colistin attacks and binds to the lipopolysaccharide (LPS)

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section of the exterior membrane of gram-ve rods and damages it as a magnitude[14]. For the last few years, colistin has been used as a first-line therapeutic agent in CRE- and carbapenem-resistant Acinetobacter baumannii (CRAB) and carbapenem-resistant Pseudomonas aeruginosa (CRPA)[15]. The International Network for Optimal Resistance Monitoring (INFORM) monitoring the novel combination of colistin and ceftazidime and avibactam (CAZ-AVI) in Enterobacteriaceae. CAZ-AVI is a more potent and vigorous agent with a greater than 94% susceptibility rate, and Colistin was 82%[16]. Mostly colistin and carbapenem are both used as combination therapy for combating resistance. In patients with low-risk blood stream infections, monotherapy with colistin is acceptable[17].

The adverse effect of colistin is related to organ toxicity, such as eyelid ptosis, hearing dysfunction, visual abnormalities, vertigo, misperception, hallucinations, attacks, any body part effect or loss of function, and rarely neuromuscular barrier leading to lung failure and is essential for ventilator care[18–20]. There is a higher risk of nephrotoxicity from colistin, which is a more serious adverse effect[19,21,22]. Kalin and his coworkers included 45 patients in their study, of whom 15 received a greater dose of colistin (2.5 mg/kg every 6 h), 20 received a normal dose (2.5 mg/kg every 12 h), and 10 received a small dose, as determined by creatine clearance. For high, normal, and low doses of colistin, the nephrotoxicity rates were 40%, 35%, and 20%, respectively[23]. Proteinuria andoliguria may also be observed in patients with colistin nephrotoxicity[18,24].

TIGECYCLINE

Tigecycline is a protein synthesis inhibitor and belongs to the tetracycline modification of a new class known as a glycylcycline antibiotic. Tigecycline works on ribosomal unit 30s to inhibit the activity and disrupt the microbe activity, but it is inherited resistance against the most notorious gram-negative pathogen *P. aeruginosa*[25]. Tigecycline is indicated in cIAIs, cSSSTIs, and community-acquired pneumonia (CAP). In 2011, Karaiskos reported that the susceptibility ratio of tigecycline was near 100% in 22005 isolates of carbapenem-resistant gram-ve rod isolates, but resistance is on the upsurge, as evaluations now show that practically 50% of isolates are nonsusceptible to tigecycline[26]. Currently, the usage of this antibacterial agent daily decreases because the emergence of resistance is increasing and the susceptibility ratio is decreasing in comparison to colistin, but tigecycline is still recommended in critically ill patients due to its renal-friendly property[27,28].

CRE is treated with a high dose of colistin, tigecycline, and fosfomycin as a combination regimen, these produce therapeutic effects[29]. In cases where alternatives are not available and tigecycline is used as a target therapy, high doses should be used to achieve adequate PK/PD results against polymicrobial infections[30].

Fosfomycin

Fosfomycin was invented in 1969 and is active against gram +ve and gram –ve microbes with cell wall synthesis inhibitors. The mechanism of action of this antibiotic is the same as penicillin. Fosfomycin has excellent results against gram +ve (MRSA) and gram –ve (ESBL) pathogen causes. UTIs and LRTIs have excellent tissue penetration, such as lungs and cerebrospinal fluid[3,31]. Fosfomycin is not tremendously cast off against MDR infections and bloodstream infections by CRE, and in patients receiving anti-XDR treatment, fosfomycin is still considered a recoup treatment for CR infections or a breakthrough infection treatment[32,33].

In a limited study of 48 critically ill patients with MDR infections who received fosfomycin at a dose of 8 g every 8 h for 14 days (mostly in a combination regime with tigecycline or colistin), the all-cause 28-day death rate was 37.5%[32]. When used to treat severe or systemic infections beyond the urinary tract, intravenous fosfomycin will most likely be combined with an antibiotic drug from another class (fluoroquinolones, glycopeptides, or glycolipopeptides). The intravenous fosfomycin combination partner was chosen based on the indication and the patient's particular clinical state. According to the kind of infections and microorganisms, fosfomycin can be coupled with any other antibiotic class. The primary reason for combining fosfomycin with a second antibiotic is to avoid the establishment of fosfomycin resistance and to expand the antibacterial spectrum. Combination treatment may potentially provide additive or synergistic activity/efficacy as well as appealing pharmacokinetic features for hard-to-reach compartments[34,35].

Ceftazidime and Avibactam (CAZ/AVI)

MDR-negative pathogens are a serious universal public health alarm. Carbapenem has become more widely used and reliant, as ESBL-producing pathogens are becoming more prevalent. There is

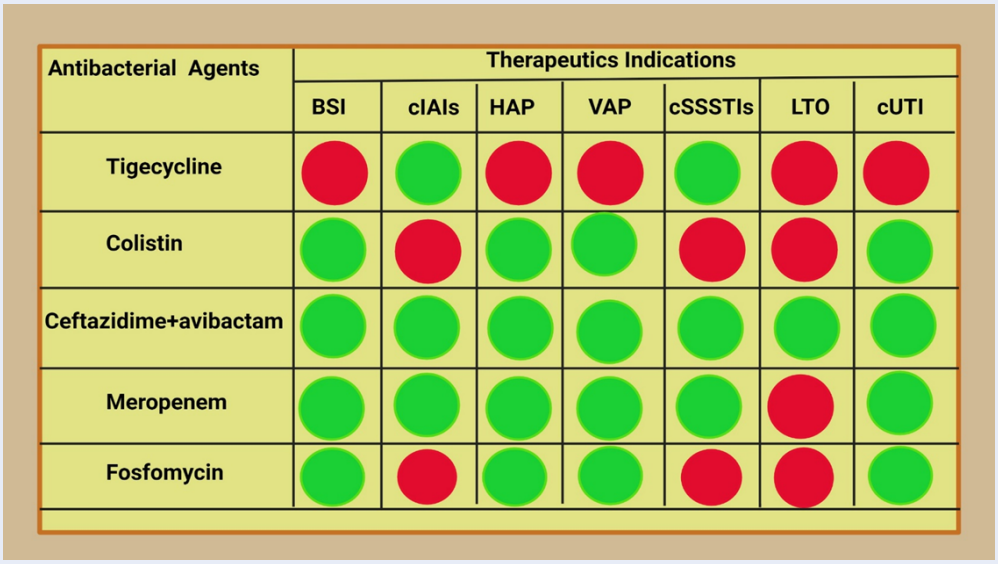

Figure 1: **Therapeutic indication of antibacterial agents**. (**i**) Tigecycline is indicated in cIAIs and cSSSTIs, and CAP. (**ii**) Colistin is not indicated in cIAIs, limited treatment options (LTO) and cSSSTIs. (**iii**) CAZ+AVI is indicated in all targeted areas, specifically those cases who are reported with CRE and in LTO. (**iv**) Meropenem is not indicated in LTO, and (**v**) fosfomycin is not indicated in LTO, cSSSTIs, and cIAIs. (This figure created on Biorender.com).

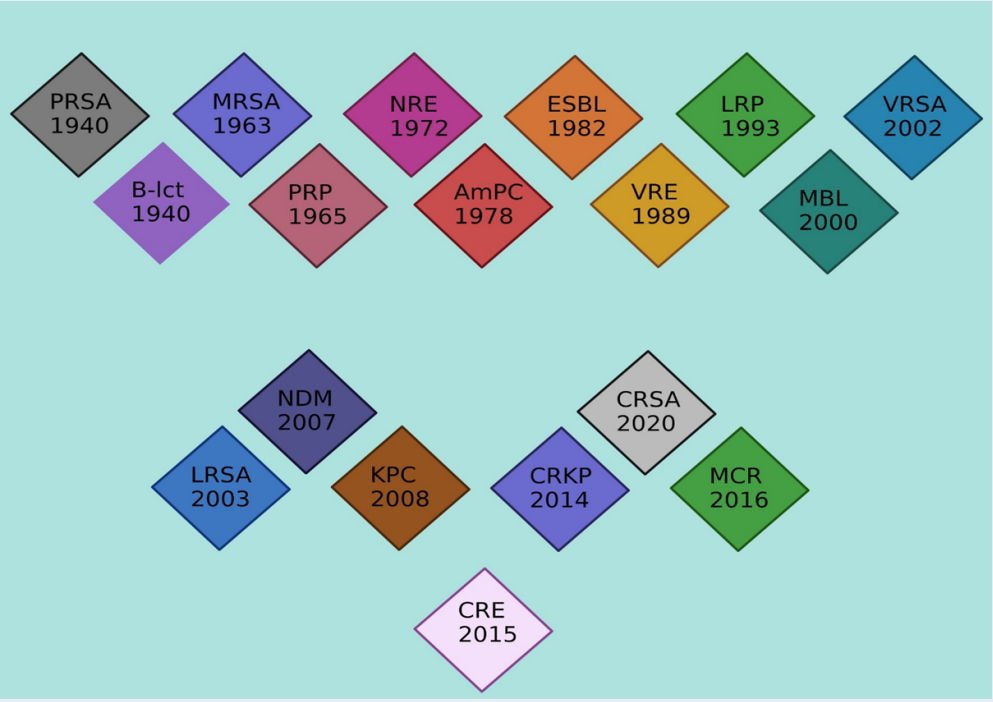

Figure 2: **Developmental eras of bacterial resistance strains from 1940 to continue rapidly.** (This figure created on Biorender.com).

Table 1: Show the global trials of antibiotics in different areas of infections to evaluate the therapeutic effects of CAZ/AVI, colistin, tigecycline, and fosfomycin (registered at https://www.clinicaltrials.gov/)

Sr No.	Disease	Intervention	Phase	Enrollment	NCT Number	Status
1	cUTI	CAZ/AVI	II	97	NCT02497781	Completed
2	cIAI	CAZ/AVI	II	83	NCT02475733	Completed
3	Systemic infection	CAZ/AVI	I	35	NCT01893346	Completed
4	cUTI, cIAI	CAZ/AVI	III	345	NCT01644643	Completed
5	Cystic fibrosis	CAZ/AVI	IV	12	NCT02504827	Completed
6	Nosocomial pneumonia, VAP	CAZ/AVI Meropenem	III	969	NCT01808092	Completed
7	cUTI, Acute pyelonephritis	CAZ/AVI Cipro, Doripenem, sulfamethoxazole/trim	III	598	NCT01595438	Completed
8	Cystic Fibrosis Pulmonary Manifestations	Colistin Tobramycin Powder	III	26	NCT03341741	Completed
9	Critical Illness	Colistin	I	20	NCT02408185	Completed
10	VAP	Colistin meropenem	III	232	NCT01292031	Completed
11	VAP	Colistin + Imepenem	IV	133	NCT02683603	Completed
12	Pneumonia, Blood stream infections	Colistin + Meropenem	III	467	NCT01597973	Completed
13	IAIs, Skin disease	Tigecycline	—–	116	NCT01789905	Completed
14	Antibiotic resistance	Tigecycline	IV	30	NCT01342731	Completed
15	cIAIs, cSSSTIs and CAP	Tigecycline		3172	NCT01072539	Completed
16	Bacterial skin disease	Tigecycline	IV	550	NCT00368537	Completed
17	Neonatal Sepsis	Fosfomycin	II	120	NCT03453177	Completed
18	UTI, Bacteriuria	Fosfomycin	IV	82	NCT03235947	Completed
19	UTI	Fosfomycin, Ciprofloxacin	IV	461	NCT01803191	Completed
20	ESBL infections	Fosfomycin, Meropenem, Ceftriaxone	III	161	NCT02142751	Completed

a growing concern about carbapenemase-producing pathogens (gram –ve) and a near need for new antimicrobials [36–38].

According to in vitro experiments, avibactam (novel beta-lactam inhibitor) can restore ceftazidime (third generation cephalosporin) antimicrobial activity against numerous Enterobacteriaceae that produce ESBL, AmpC, KPC, and OXA-48 and drug-resistant P. aeruginosa isolates [39]. Caz/Avi is intravenously administered in HAP, VAP, cIAI, cUTI, acute pyelonephritis, and LTO [40]. The biological activity of avibactam is broad, barring Ambler class A (TEM-1, CTX-M-15, KPC-2, KPC-3), C (AmpC), and D (OXA-10). It is not active against class B enzymes such as MBL [41–45].

Caz/Avi was tested alongside isolates of *P. aeruginosa* and *Enterobacteriaceae spp. in vitro*. There were 99% inhibition rates for 36,380 isolates of Enterobacteriaceae species. MDR isolates accounted for 99.2%, and XDR isolates accounted for 97.8%. *P. aeruginosa* isolates, including MDR and XDR strains, were inhibited in 97.1% of cases [46]. In 2013, the REPRISE clinical phase 3 trial was conducted and monitored the therapeutic effects of CAZ/AVI in the field of different organ infections resistant to ceftazidime-resistant *P. aeruginosa* and *Enterobacteriaceae*, and the combination therapy showed the best therapeutic yield against these resistant pathogens [47].

In the case of critically ill patients such as HAP and VAP, CAZ/AVI has been approved for treating pneumonia caused by gram-negative pathogens [6]. CAZ/AVI have linear PK/PD, and human protein binding is nearly 8 to 10% [48]. We consider CAZ-AVI to be the most important addition to our arsenal since it is the first stationary combination to be marketed with activity in contrast to KPC and OXA producers. Safety, clinical response, and survivability reports derived from genuine use are very encouraging in life-threatening and nonthreatening conditions. CAZ/AVI must be used as combination therapy and as monotherapy [49–51].

In patients with a high hazard of MDR infections, CAZ-AVI is strong in empiric regimens since it also covers ESBL-producing *Enterobacteriaceae* and has substantial magnitudes against *P. aeruginosa*. On the basis of local epidemiological data, the presence of MBL-producing agents should be balanced with other antibiotics (colistin and tigecycline). To avoid irrational use, CAZ-AVI empiric use should be kept for patients with greater risk influences for infection by KPC- or OXA-48 fabricators.

Role of ASPs in the prevention of antimicrobial resistance

Antibiotic policies, antibiotic management programs, and antibiotic control policies are some of the terminology used to define antimicrobial steward programs (ASPs). Overall, these all narrate the healthcare institution's continual attempt to improve antibiotic usage among hospitalized patients to enhance patient outcomes, assure cost-effective therapy, and prevent undesirable consequences associated with antibacterial agent usage, such as antimicrobial resistance [52]. A collaborative strategy is needed, with an infectious disease physician and a clinical pharmacist with infectious disease training serving as key team members. It is necessary to work closely with a clinical microbiologist, an information system specialist, an infection control professional, and a hospital epidemiologist. The IDSA also created a recommendation for the development and operation of antimicrobial stewardship programs (ASP) in public sector hospitals [53,54]. According to ASPs after diagnosing the infection severity with the *in vitro* result and choosing the right antibiotic, complete treatment of duration with strong follow-up may reduce the hospital stay along with minimizing the antibiotic resistance.

CONCLUSION

The judicial use of antibiotics, with complete treatment of duration, minimizes the resistance. CAZ/AVI is the best emperic and after in-vitro evidence choice of therapy against CRE cases and it is also choice of therapy against MDR cases as carbapenem spare agents for stop the irrerational useage of Carbapenem.

ABBREVIATIONS

None.

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All authors in this current article sufficiently contributed to the conceptualization, design of the manuscript, editing, and revision. Moreover, each author declares that this or comparable content has not been submitted to or published in any other publication. All authors read and approved the final manuscript.

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COMPETING INTERESTS

The authors declare that they have no competing interests.

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