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Review

The use of fosfomycin in the treatment of carbapenem-resistant Acinetobacter infections

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ABSTRACT

Multi-drug resistant (MDR) *Acinetobacter baumannii* is now a major pathogen responsible for morbidity and mortality in intensive care units. Fosfomycin has been used as a "salvage" therapy in these cases. Resistance to colistin, which was frequently used in the treatment of *Acinetobacter baumannii* infections in previous years, has pushed the use of fosfomycin to the forefront of research. The purpose of this review was to draw attention to the potential risk of MDR Acinetobacter infections in Türkiye.

Keywords: *Acinetobacter baumannii*, carbapenem resistance, fosfomycin.

Species of the genus Acinetobacter are obligate aerobe, non-motile, Gram-negative coccobacilli, oxidase-negative, generally nitrate-negative, and non-fermentative that are commonly found in nature. Acinetobacter species are also most commonly associated with hospital settings. They can last a very long time in both dry and humid environments, on food, and on human hands.[1] *Acinetobacter baumannii, (A. baumannii)* one of the Acinetobacter species, plays a significant role in healthcare-related infection (HRI).[2] It is one of the most important opportunistic pathogens responsible for serious nosocomial infections in various hospital units, particularly intensive care units (ICU). Due to trauma, mechanical ventilation, and interventional procedures, it frequently causes pneumonia, endocarditis, meningitis, bacteremia, skin and wound infections, peritonitis, and urinary tract infections.[2,3]

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Currently, multidrug resistance (MDR) *A. baumannii* is a major cause of morbidity and mortality in ICU. In these cases, fosfomycin has been used as a "salvage" treatment. Resistance to colistin, which was commonly used in the treatment of *A. baumannii* infections in previous years, has resulted in the use of fosfomycin. The purpose of this review was to draw attention to the potential threat of MDR Acinetobacter infections in Türkiye.

ACINETOBACTER INFECTIONS: EPIDEMIOLOGY, COLONIZATION, AND MICROBIOLOGY

While *A. baumannii* was found to be sensitive to a wide range of antibiotics in the 1970s, it now exhibits extensive resistance to first-line drugs. Since the early 1980s, hospital outbreaks caused by *A. baumannii* have been reported in many European and Asian countries, most notably in England, France, Germany, Italy, Spain, and the Netherlands.[1-8] Infections with *A. baumannii* are quite prevalent in Türkiye and are among the leading causes of HRI, particularly in ICU.[1,8]

Even in healthy people, it can be found in the flora of moist areas like the groin, between the fingers, and armpits. In fact, it has been reported that in patients with *A. baumannii*

infections, it can colonize the oropharynx, respiratory secretions, and skin and remain viable in nearly any environment.[9] It can colonize many inanimate surfaces, including the hands of healthcare workers in a hospital setting.[1,9]

A. baumannii is the most common clinical agent due to its virulence and multidrug resistance. Furthermore, *A. nosocomialis* and *A. pittii* play important roles in nosocomial infections. Traditional microbiology labs are unable to differentiate between these three species and *A. calcoaceticus*. A. calcoaceticus is an environmental pathogen with little clinical significance. For this reason, these four species are commonly referred to as the *A. baumannii* complex.[6,7]

RISK FACTORS FOR ACINETOBACTER INFECTIONS

It is very difficult to infect healthy people with Acinetobacter species, which are typically low-virulence pathogens. In elderly and immunocompromised individuals, they cause HRIs. Conditions that suppress the host's defense system, such as cancer, burns, and advanced age, facilitate the spread of this infection.[1] Other risk factors include major surgical interventions, prematurity, mechanical ventilation, broad-spectrum antibiotic therapy, and long-term hospitalization.[1,8] Hemodialysis and hypoalbuminemia have also been identified as risk factors in carbapenem-resistant *A. baumannii* infection.[9]

THE SIGNIFICANCE OF RESISTANCE IN ACINETOBACTER INFECTIONS

Acinetobacter spp. is a significant pathogen, particularly in ICUs. Increased antibiotic resistance in this pathogen limits the antibiotics that can be used to treat patients, increases the length of stay in ICUs, and raises mortality. *A. baumannii* is a MDR pathogen. Insensitivity to at least three different antibiotic classes' active ingredients is known as MDR. The presence of resistance to ceftriaxone, ciprofloxacin, and trimethoprim/sulfamethoxazole is sufficient to classify an isolate as MDR. Extensively drug-resistant (XDR) bacteria are those that are resistant to at least one antibiotic in all antibiotic groups, with the exception of one or two antibiotic groups. In other words, extensive drug resistance (XDR) *A. baumannii* isolates are resistant to all antibiotics except colistin and tigecycline. They are becoming more clinically important. While carbapenem-resistant XDR *A. baumannii* isolates are rapidly increasing, with the increased use of colistin, which has re-entered clinical practice for the treatment of these infections, there have been repeated reports of colistin resistance and XDR *A. baumannii* isolates all over the world.[6-8]

The rapid spread of antimicrobial resistance among Gram-negative bacteria, combined with the slow development of new antibiotics, has become a major threat to global public health. MDR Acinetobacter spp. with colonization or as risk factors for infection are susceptible patients who have already colonized or become infected with the organism, the use of broad-spectrum antimicrobial agents, including third generation cephalosporins and carbapenems, length of hospitalization, ICU hospitalization, mechanical ventilation, antimicrobial agent exposure, recently performed surgery, and the severity of the underlying disease.[10]

A. baumannii isolates in ICUs are typically resistant to beta-lactams, aminoglycosides, and fluoroquinolones, including carbapenem. The presence of a long-term urinary catheter, gastrostomy tube, use of carbapenem or piperacillin/tazobactam, or contact with the colonized patient in the ICU lasting more than four days, mechanical ventilation, surgery, and the severity of the underlying disease are all considered significant risk factors in the development of colonization or infection with XDR *A. baumannii* in ICUs.[11]

ANTIMICROBIAL RESISTANCE IN ACINETOBACTER INFECTIONS

It is critical to initiate appropriate antibiotic treatment to prevent antimicrobial resistance. Carbapenems and sulbactam have long been used to treat Acinetobacter spp. infections, but severe resistance rates have recently been reported. Polymyxins have begun to be used as a reliable agent in *A. baumannii* isolates, but improper use has resulted in an increase in colistin resistance rates. It was first presented in the Czech Republic in 1999 by *Acinetobacter* spp. infections have been shown to be resistant to colistin,[12] and an

increasing number of colistin-resistant cases have been reported in subsequent years. Changes in efflux pumps, outer membrane proteins, and penicillin-binding proteins can also lead to beta-lactam resistance, including carbapenem resistance, in *A. baumannii*. Carbapenem-resistant *A. baumannii* hospital outbreaks due to porin loss have been reported in New York and Spain.[13]

Although many antibiotics, such as cephalosporins, β-lactam β-lactamase inhibitor combinations, carbapenems, sulfonamides, fluoroquinolones, and aminoglycosides, were once effective against *Enterobacterales*, current resistance to these antibiotics (extended-spectrum β-lactamase, AmpC β-lactamases, and carbapenemase) makes them insufficient for the treatment of both community-acquired and hospital-acquired infections with *Enterobacterales* species.[14]

FOSFOMYCIN

Fosfomycin, formerly known as "fosfonomycin," is a phosphonic acid derivative isolated from Streptomyces cultures in 1969. It has long been used in the treatment of various infections in many European countries, including our own.[15]

Fosfomycin is a bactericidal antibiotic that irreversibly inhibits an early stage of bacterial cell wall synthesis. Compared to β-lactams and glycopeptides, it inhibits peptidoglycan synthesis earlier. It enters the cytoplasm and begins to exert its bactericidal activity there. Two transport systems are used by fosfomycin to enter the target cell. The first is the hexose-6-phosphate transporter (UhpT) induced by glucose-6-phosphate, while the other is the L-α-glycerophosphate (α-GP) uptake system (GlpT) induced by glyceraldehyde-3-phosphate. When fosfomycin reaches the cytoplasm, it acts as a phosphoenolpyruvate (PEP) analog, binding to the 115th cysteine residues of UDP-GlcNAc enolpyruvyl transferase (MurA). Thus, it inhibits enolpyruvyl transferase, the main enzyme responsible for peptidoglycan synthesis. As a result, it prevents the formation of UDP-GlcNAc-3-O-enolpyruvate from UDP-GlcNAc and PEP during the first step of peptidoglycan synthesis, resulting in bacterial cell lysis and death.[16,17] In addition to its bactericidal effect, fosfomycin has immunomodulatory effects on lymphocytes, monocytes, and neutrophils, altering levels of tumor necrosis factor-alpha (TNF-α), interleukin (IL), and leukotrienes (LT). It suppresses the release of IL-2 by T cells, LTB4 by neutrophils, and IL-8 by monocytes. Fosfomycin has been shown *in vitro* and *in vivo* studies to affect the acute inflammatory cytokine response, modulating TNF-α, IL-1, and IL-6.[18,19] It also reduces bacterial adhesion to the respiratory and urinary tract epithelium.[17]

Fosfomycin has a low molecular weight, is freely soluble in aqueous solution, binds to plasma proteins *in vivo* at a very low rate, and spreads primarily to extracellular fluids (approximately 0.30 l/kg body weight, or a steady-state volume of distribution between 18 and 27 liters). Fosfomycin is well distributed in serum, kidney, bladder wall, prostate, lung, bone, cerebrospinal fluid (CSF), abscess fluid, and heart valves.[18] Fosfomycin achieves very high minimum inhibitory concentration (MIC) values in *A. baumannii* and *Morganella morganii* isolates and should be preferred in fosfomycin combination therapies in *A. baumannii* isolates.[20,21] The synergistic activity of fosfomycin with various antibiotics in nonfermentative bacteria has mostly been studied in isolates of *A. baumannii* and *Pseudomonas aeruginosa*. The synergy between fosfomycin and colistin has been reported at rates ranging from 12.5 to 50% in *A. baumannii* isolates producing OXA-23.[22,23] In another study, a 75% synergy between fosfomycin and sulbactam was found in *A. baumannii* isolates.[22] No significant results were obtained in combinations of fosfomycin with polymyxin B or minocycline in XDR *A. baumannii* isolates (synergistic activity 16%, Fractional inhibitory concentration index [FICI] 12%).[24]

The use of intravenous (IV) fosfomycin has been reintroduced in the twenty-first century. In severe infections, IV fosfomycin is administered 3-4 times per day at a dose of 2-24 g, usually in combination with other antibiotics.[19] In the evaluation of clinical trials and meta-analyses using IV fosfomycin, 5.527 patients in 128 studies were treated for sepsis, urinary tract infection, respiratory tract infection, and central nervous system infection. For MDR infections, IV fosfomycin combination therapy (with β-lactam or aminoglycosides) has been used, particularly

after 1990. There were no differences in clinical or microbiological efficacy between IV fosfomycin and other antibiotics in comparative studies (OR: 1.44 [95% CI: 0.96-2.15]) The risk of developing resistance to IV fosfomycin monotherapy was 3.4%; additionally, treatment-related side effects were found to be mild enough not to necessitate treatment discontinuation.[25]

Intravenous fosfomycin is an antibiotic that can be used primarily in combination with other antibiotics (β-lactams, carbapenems, fluoroquinolones, aminoglycosides, and glycopeptides), and to treat infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant *Staphylococcus epidermidis* (MRSE), vancomycin-resistant *Enterococcus* spp. (VRE), MDR *Enterobacterales* and MDR *Pseudomonas aeruginosa* isolates. Furthermore, combining fosfomycin with other antibiotics in treatment will slow the development of fosfomycin resistance over time.[26-30]

In Thailand, 94 patients with carbapenem-resistant *A. baumannii* infection were randomized to receive colistin or colistin-fosfomycin. The first group was given 2×4 gr/day fosfomycin+5 mg/kg/day colistin, while the second was given a 5 mg/kg/day colistin. Microbiological eradication was more effective in the fosfomycin group.[31]

The Clinical and Laboratory Standards Institute (CLSI) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST), two fundamental, widely used standards, both publish the standard for antimicrobial susceptibility testing for fosfomycin.[32,33]

Fosfomycin is a bactericidal antibiotic that inhibits cell wall synthesis; extended-spectrum beta-lactamase (ESBL)-positive *Escherichia coli (E. coli)* and carbapenem-resistant *Klebsiella pneumoniae* are promising due to its broad spectrum of action, which includes MDR and XDR Gram-negative bacteria and Gram-positive bacteria, including MRSA. It has a very high clinical efficacy for the treatment of uncomplicated urinary tract infections. It has been reported that it can be used as a single treatment as well as a combination of antibiotics in the treatment of invasive infections. However, it has been reported in the literature that fosfomycin resistance can develop *in vitro* and *in vivo*, particularly in the presence of transferable resistance mechanisms.[30]

THE IMPORTANCE OF INFECTION PREVENTION AND CONTROL

One of the main risk factors for the occurrence and spread of outbreaks is environmental *A. baumannii* contamination in critical care areas such as ICUs. It has been demonstrated that maintaining environmental cleanliness by using efficient disinfection techniques in ICUs plays a critical role in infection control strategy and prevents outbreaks from developing. The primary infection control measures in the control of *A. baumannii* include hand washing, contact isolation, environmental decontamination, and the proper use of antibiotics.[34-36]

In conclusion, the rapid spread of antimicrobial resistance has become a public health concern.

To prevent nosocomial infections and hospital outbreaks caused by XDR and colistin-resistant *A. baumannii*, screening for resistant bacteria, particularly in ICUs, determining colonization risk scores in patients, and administering chlorhexidine baths to patients for source control will supplement existing infection control measures significantly. Other microorganisms (e.g., carbapenem-resistant *Klebsiella pneumoniae*) have similar risk factors and treatment issues, and the only effective method appears to be full compliance with hand hygiene and infection control measures. Fosfomycin has emerged as a new treatment option for resistant infections, but it should be noted that there is a risk of developing resistance to this agent as well.

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