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Review

Multidrug resistance efflux pump expression in uropathogenic Gram-negative bacteria in organ transplant recipients

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Abstract

Urinary tract infections (UTIs) are common in healthcare settings and communities; and are predominantly caused by Gram-negative bacteria, which account for > 70% of UTI cases. *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* are the most common bacterial agents responsible for UTIs. The emergence of antibiotic resistance poses a challenge for UTI treatment; and efflux pump overexpression contributes to Gram-negative bacterial resistance. This comprehensive review summarizes the current understanding of multidrug resistance (MDR) efflux pump expression in prevalent Gram-negative bacteria that demonstrate resistance to antibiotics predominantly used for UTI treatment. This review examines the available data, and offers insights into the role of efflux pumps in conferring MDR to UTI-causing bacteria. Understanding these resistance mechanisms is crucial for developing effective strategies to combat antibiotic resistance in UTI management. Furthermore, this review emphasizes the need to characterize efflux pump–mediated antimicrobial resistance in solid organ transplantation cases. Solid organ transplant recipients are particularly vulnerable to UTIs caused by MDR bacteria, posing a serious threat to their health and recovery. Identifying the efflux pump profiles of these bacterial strains can guide appropriate antibiotic choices and optimize treatment outcomes in transplant recipients. By consolidating existing knowledge on efflux pump expression in antibiotic-resistant Gram-negative bacteria associated with UTIs, this review acknowledges gaps and identifies the future scope of research that should address the growing challenge of MDR UTIs, particularly in high-risk populations such as solid organ transplant recipients.

Key words: efflux pump; expression; *E. coli*; *K. pneumoniae*; *P. aeruginosa*; AMR.

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Introduction

The unjustified use of antibiotics in healthcare settings has substantially increased the incidence and prevalence of antibiotic-resistant microorganisms worldwide, thereby posing a challenge for treating patients infected with multidrug-resistant (MDR) microbes. One mechanism underlying antibiotic resistance is the ability of microorganisms to reduce the intracellular concentration of the drug by either decreasing drug uptake or extruding it through efflux pumps. Recent studies have depicted a strong association between the overexpression of MDR efflux pumps and an increase in clinical cases of MDR bacterial infections [1].

Efflux pumps—present in all living organisms—are crucial in bacterial drug resistance. These proteinaceous transporters located in the cytoplasmic membrane have been conserved through evolution and predate the use of antibiotics [2]. Efflux pump systems are primarily categorized into prokaryotic (bacterial), eukaryotic (fungal, protozoal, and cancer cells), and those that mediate resistance in both. [3]. There are five major families of efflux pumps in prokaryotes that are involved in efflux pathways, of which the ATP-binding cassette family utilizes ATP hydrolysis as an energy source to drive transport. The other four families include the major facilitator superfamily (MFS), multidrug and toxin extrusion family, small MDR family, and resistance-nodulation-division (RND) family which use the proton motive force as its energy source. The most abundant efflux pumps in bacteria are

RND and MFS pumps, which are present in both Gram-positive and Gram-negative bacteria (Figure 1) [2].

Urinary tract infections (UTIs) are the most common bacterial infections in humans. More than 70% of UTI cases are caused by Gram-negative bacteria; with *Escherichia coli* (*E. coli*), *Klebsiella pneumoniae* (*K. pneumoniae*), *Enterococcus* sp., *Enterobacter* sp., *Pseudomonas aeruginosa* (*P. aeruginosa*), and *Proteus mirabilis* being the most common bacterial agents [4]. A UTI is defined as the overgrowth of bacteria (> 10^5 CFU/mL) in a patient's urine samples; accompanied by symptoms such as fever, chills, dysuria, and suprapubic flank or allograft pain. Several risk factors predispose patients to UTIs, including older age, female gender, prolonged use of a urinary catheter, acute organ rejection, and receiving a kidney from a deceased donor. Community- or healthcare-acquired UTIs are clinically categorized as complicated or uncomplicated, with this classification influencing the choice of antimicrobial agents for treatment. Uncomplicated UTIs can often be managed with outpatient antibiotics and generally have good outcomes. In contrast, complicated UTIs present with serious, life-threatening sepsis and multiorgan involvement. Complicated UTIs have high morbidity, a high chance of treatment failure, typically require long courses of antibiotics, and often necessitate further diagnostic workup. These UTIs primarily occur in men, pregnant women, older adults, immunocompromised individuals, those with urinary catheters, those with impaired kidney function, or kidney transplant recipients. They are frequently caused by atypical organisms owing to obstruction, hydronephrosis, kidney stones, or colovesical fistula [5].

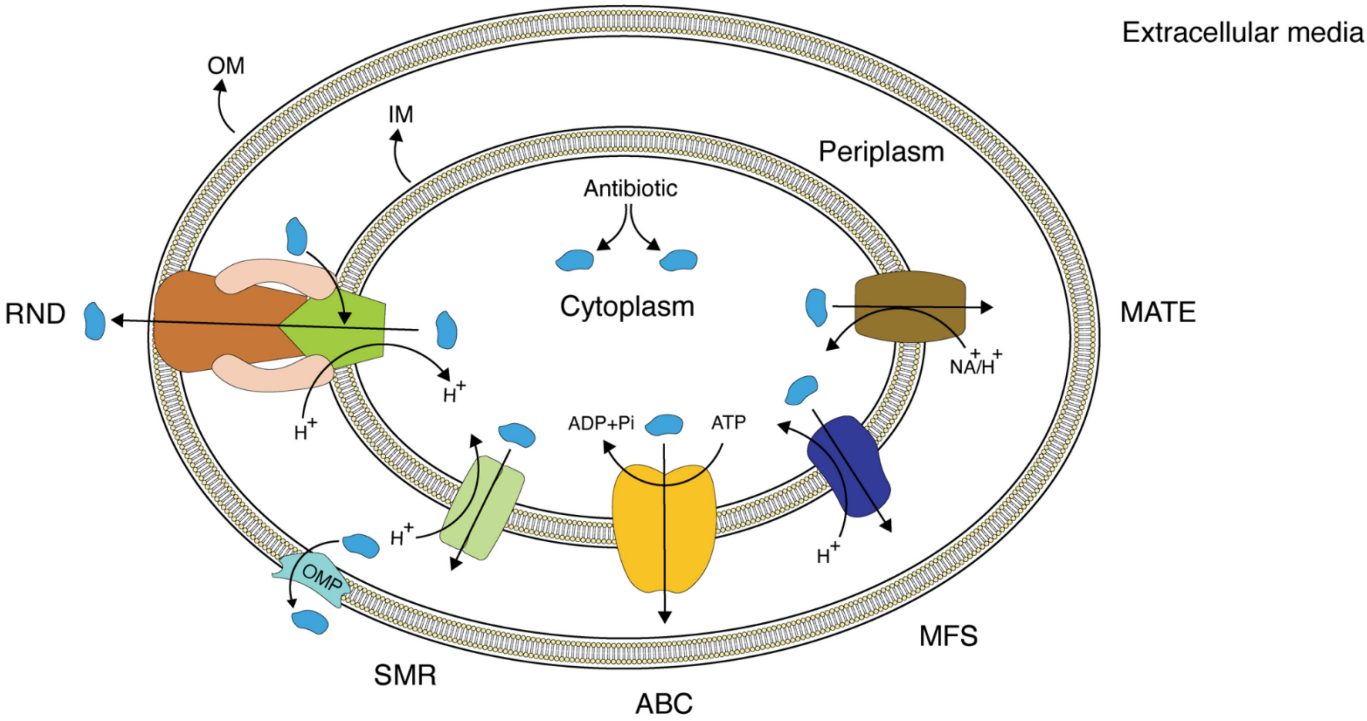
In many countries, routine therapy involves antibiotics such as β-lactams, trimethoprim, nitrofurantoin, and quinolones. The antibiotic choice is influenced by the microbiological spectrum and antibiogram of each hospital. The high rate of antibiotic resistance and the emergence of MDR pathogens in UTIs are immensely attributed to the widespread prescription of empirical antibiotic therapies without prior antibiotic susceptibility testing, thereby leading to ineffective treatment [6].

This review examines the literature on antimicrobial resistance mediated by the overexpression of efflux pumps in prevalent uropathogenic Gram-negative bacteria and discusses antibiotic resistance in kidney transplant recipients.

Role of efflux pumps in antimicrobial resistance in Gram-negative bacteria

Most serious bacterial infections are related to MDR Gram-negative organisms, potentially because of

Figure 1. Bacterial drug efflux pumps along with their energy sources [2].



ABC: ATP-binding cassette; IM: inner membrane; MATE: multidrug and toxin extrusion; MFS: major facilitator superfamily; OM: outer membrane; OMP: outer membrane protein; RND: resistance-nodulation-division; SMR: small multidrug resistance.

their cell envelope consisting of two membranes that prohibit the entry of drugs and other compounds. Some efflux pumps are tripartite and span this envelope to expel compounds over this barrier. Although not all transporters form such assemblies, these pumps can cooperate to move the efflux substrates into the periplasm and then outward via a tripartite machine. Table 1 summarizes some major efflux pumps and their specific substrates found in prevalent Gram-negative bacteria causing UTIs [7].

Efflux pump expression among uropathogenic *E. coli*

E. coli is the predominant agent responsible for approximately 80% of all symptomatic and asymptomatic UTI cases [8]. It is prevalent in the general population and kidney transplant recipients, with frequencies ranging from 21% to 73% [9]. Antibiotic-resistant uropathogenic *E. coli* is a major etiological factor in UTIs. In many countries, trimethoprim-sulfamethoxazole—predominantly used first-line antibiotic for treating uncomplicated UTIs—has recently shown signs of developing resistance [5].

The overexpression of efflux pumps, such as AcrAB-TolC, has been linked to MDR in *E. coli*. The AcrAB-TolC complex is a tripartite efflux pump composed of AcrA, a fusion protein; AcrB, a cytoplasmic membrane transporter protein; and TolC, an outer membrane channel [10]. Quinolones and fluoroquinolones are popularly used to treat UTIs, and their widespread usage has increased resistance among uropathogenic *E. coli*. This resistance is correlated with decreased antibiotic uptake owing to changes in outer membrane porin proteins and the presence of efflux pumps [6]. Several studies have shown the overexpression of the AcrAB-TolC efflux pump in fluoroquinolone-resistant *E. coli* [11].

Yasufuku *et al*. demonstrated a considerable correlation between the AcrAB-TolC and MdfA efflux systems, and resistance to fluoroquinolone [12]. Additionally, the study illustrated a relationship between the overexpression of the *marA* and *mdfA* efflux pump genes, and resistance to nalidixic acid and sitafloxacin in *E. coli* isolated from patients with UTI. Swick *et al.* measured the expression levels of *acrA*, *acrB*, *tolC*, *mdfA*, and *norE* mRNA in clinical isolates of *E. coli* using real-time polymerase chain reaction (PCR). The overexpression of *acrA* and *acrB* mRNA was strongly correlated with fluoroquinolone and MDR, whereas the expression levels of *tolC*, *mdfA*, and *norE* were not [13].

Furthermore, Suzuki *et al.* reported that the overproduction of AcrAB efflux pumps is linked to resistance against tazobactam-piperacillin in clinical isolates of *E. coli* [14]. Abdelhamid and Abozahra proved that the rising resistance to levofloxacin is associated with the higher expression of the efflux pump-coding *acrA* and *mdfA* [15]. They examined *E. coli* isolates from urine samples and found that most levofloxacin-resistant isolates overexpressed *mdfA* and *acrA* (82.1% and 78.6%, respectively), supporting the role of efflux pump systems in fluoroquinolone resistance in urinary *E. coli* isolates.

Antibiotic resistance, particularly to fluoroquinolones, is further linked to the upregulation of efflux pump genes such as *marA*, *yhiU*, *yhiV*, and *mdfA*, in patients with UTI [10]. Quantitative real-time PCR analyses showed consistently high expression levels of the *tolC* and *ynfA* efflux pump genes in 75% to 80% of MDR *E. coli* isolates from UTI patients;

Table 1. Examples of efflux pumps found in prevalent Gram-negative bacteria causing urinary tract infection (UTI). Adapted from [7].

Efflux pump family	Efflux pump	Regulator	Organisms	Substrates (class)	Resistance to specific antibiotics [a]
ABC	MacAB-Tolc	PhoPQ	*E. coli*	Macrolides	EM
MFS	EmrAB- Tolc	EmrR	*E. coli*	Cotrimoxazole	/
	MdfA, MdtM	/		Tigecycline, Chloramphenicol	DC, CM
	QepA	QepR		Fluoroquinolones	FQ
	TetA	TetR		Tigecycline	TC
RND	AcrAB- Tolc	AcrR	*E. coli, K. pneumoniae*	B- lactams, Fluoroquinolones	KF, CM, FQ, P
	MexAB-OprM	Nalc/NalD	*P. aeruginosa*	Quinolones	CM, CP, TC, SM
	OqxAB	OqxR	*E. coli, K. pneumoniae*	Chloramphenicol, Fluoroquinolones	CM, NT, NF, CP, LEV
SMR	EmrE	/	*E. coli, P. aeruginosa*	Quaternary Ammonium Compounds	Quaternary Ammonium Compounds
	KpnEF	/	*K. pneumoniae*	Benzalkonium Chloride, Chlorhexidine	CT, EM, RF, TC, SM

[a] CM: chloramphenicol; CP: ciprofloxacin; CT: colistin; DC: doxycycline; EM: erythromycin; FQ: fluoroquinolones; KF: cephalosporins; LEV: levofloxacin; NF: norfloxacin; NT: nitrofurantoin; P: penicillin; RF: rifampicin; SM: streptomycin; TC: tetracycline. "/" indicates no transcription regulators found or no resistance to a specific antibiotic.

meanwhile, *mdfA* and *norE* were only occasionally expressed [16].

Nitrofurantoin is a common treatment for lower UTIs, with clinical efficacy comparable to cotrimoxazole, ciprofloxacin, and amoxicillin. A plasmid-mediated OqxAB efflux mechanism is a vital contributor to nitrofurantoin resistance in *E. coli* [17]. The expression levels of genes coding for RND efflux pumps (*acrA*, *acrB*, and *acrD*) and genes of the MFS efflux pump (*emrA*, *emrD*, and *emrY*) were reported to be high in colistin-resistant *E. coli* isolated from female patients with UTI [18]. A study examining the frequency of RND efflux pump genes—including *AcrAB-TolC*, *AcrAD-TolC*, and *AcrFE-TolC*—in *E. coli* and *K. pneumoniae* isolates using traditional PCR showed that 68% of *E. coli* and 90% of *K. pneumoniae* isolates were MDR. The results indicated low resistance to piperacillin, aminoglycosides, and carbapenem; but high resistance to β-lactams and cephalosporin [19].

Tigecycline is a last-line treatment for MDR Enterobacteriaceae. Sato *et al.* measured the expression of *acrA* and *acrB* in tigecycline-non-susceptible *E. coli* clinical isolates, revealing that all non-susceptible isolates exhibited higher expression of these genes compared to tigecycline-susceptible isolates [20].

Efflux pump expression among *K. pneumoniae*

K. pneumoniae—a Gram-negative bacterium—is responsible for various infections, including pneumonia, UTI, bacteremia, and liver abscesses. Previously, such infections were common in immunocompromised individuals; however, hypervirulent strains also affect healthy individuals. *K. pneumoniae* strains are increasingly developing antibiotic resistance, and thus complicating treatment. A significant factor contributing to this resistance is the expression of efflux pumps [21].

The overexpression of the AcrAB-TolC efflux pump mediates resistance to several frequently used antimicrobial agents. MDR in *K. pneumoniae* is often driven by the overexpression of *acrAB* and *oqxAB* genes, regulated by *RamA* and *RarA*, respectively [22].

The AcrAB-TolC efflux pump system in MDR *K. pneumoniae* strains is particularly responsible for resistance to antibiotics such as fluoroquinolones (e.g., ciprofloxacin), tetracycline, and beta-lactam antibiotics [21]. The combination of AcrAB efflux pump overexpression, porin deficiency, and the presence of extended-spectrum β-lactamases may contribute to the MDR phenotype observed in some epidemic *K. pneumoniae* strains [23].

Furthermore, many species within the Enterobacteriaceae family, including *K. pneumoniae*, have the AcrAB efflux mechanism; which utilizes the outer membrane protein TolC to reduce susceptibility to a broad range of antibiotics, including macrolides, fluoroquinolones, chloramphenicol, trimethoprim, and tetracyclines [24].

In *K. pneumoniae*, the AcrAB and OqxAB efflux pumps have been linked to resistance against nitrofurantoin [25]. Tigecycline resistance, in particular, is strongly associated with the overexpression of the AcrAB-TolC efflux system [26]. Moreover, reduced susceptibility to piperacillin-tazobactam and ceftolozane/tazobactam has been attributed to the activity of the AcrAB efflux pump in tigecycline-non-susceptible *K. pneumoniae* strains [27].

Studies have shown that most carbapenem-resistant *K. pneumoniae* isolates from urine samples of patients with UTI exhibited elevated expression levels of acrB, oqxB, or both; as determined by quantitative reverse transcription polymerase chain reaction (qRT-PCR) [28].

Ciprofloxacin resistance in clinical isolates of *K. pneumoniae* is linked to the overexpression of transcriptional regulators *marA*, *soxS*, and *rarA*; as well as efflux pump genes *acrAB* and *OqxAB* [29]. A high prevalence of *oqxA* (95%) and *oqxB* (98%) was detected in fluoroquinolone-resistant *K. pneumoniae* isolates from hospitalized patients, with high expression of *oqxA* observed in ciprofloxacin-resistant strains [30].

Efflux pump expression in *P. aeruginosa*

P. aeruginosa is another Gram-negative bacterium that often causes UTIs, along with other infections [4]. There is a significant correlation between the expression of efflux pumps in *P. aeruginosa* and its resistance to various antibiotics. RND efflux pumps, in particular, play a key role in MDR. Zahedi Bialvaei *et al.* reported a remarkable association between the overexpression of RND efflux pumps, such as MexAB-OprM, MexCD-OprJ, MexEF-OprN, and MexXY (-OprA); and resistance to several antipseudomonal antibiotics, including ticarcillin, ciprofloxacin, and meropenem [31].

Considerably, carbapenems are effective antibiotics for treating resistant *P. aeruginosa* infection. However, *P. aeruginosa* has developed multiple resistance mechanisms. For example, the overexpression of MexAB-OprM, MexCD-OprJ, MexEF-OprN, and MexXY-OprM efflux pumps; along with

carbapenemase production, has been linked to high levels of carbapenem resistance [32]. Similar findings were demonstrated by Yousefi *et al.,* showing that these efflux pump systems were overexpressed in most carbapenem-resistant and MDR *P. aeruginosa* strains isolated from clinical specimens [33].

In addition to efflux pump overexpression, carbapenem resistance in *P. aeruginosa* strains is associated with the downregulation of *oprD* and overexpression of *MexAB-OprM* [34]. Overactivity of *mexA*, *mexB*, and *mexC* has been detected in extensively drug-resistant *P. aeruginosa* clinical isolates, contributing to the carbapenem resistance phenotype [35]. Furthermore, resistance to levofloxacin and piperacillin-tazobactam was significantly correlated with elevated expression of *mexB* in MDR *P. aeruginosa* strains [36].

Infection and antibiotic resistance status in kidney transplant recipients

Kidney transplantation substantially improves patients' quality of life and life expectancy, making it the preferred medical procedure for those with advanced and chronic renal failure. However, despite advancements, post-transplant infections remain a leading cause of mortality among kidney transplant recipients. These patients are vulnerable to various viral, protozoal, fungal, and bacterial infections [37].

Bacterial infections are the primary cause of infection after transplant, posing serious threats, especially due to MDR Gram-negative bacteria. For example, extended-spectrum beta-lactamase (ESBL)-producing *E. coli* and *K. pneumoniae* often cause bacteremia and intra-abdominal infections in liver and kidney transplant recipients. In addition, pathogens such as *P. aeruginosa*, *Burkholderia* spp., *Stenotrophomonas* spp., and *Acinetobacter baumannii* are critical threats to these individuals. Recipients of liver, lung, kidney, and heart transplants are particularly susceptible to infections caused by carbapenemase-producing Enterobacterales, primarily *K. pneumoniae* [38].

UTI is the most common infection leading to hospitalization among kidney transplant recipients. The prevalence of post-transplant UTIs in these recipients is 12% to 75% [8]. A meta-analysis by Hosseinpour *et al.* reported an overall prevalence of UTIs of 35% among kidney patients and identified various risk factors for increased susceptibility to infection, such as older recipient age, female gender, deceased donor status, UTI history, prolonged catheter use, acute rejection episodes, ureteral stent use, diabetes, abnormal urinary tract anatomy, and hypertension. *E. coli* (39%) was identified as the most common bacterium responsible for UTIs in kidney transplant recipients. Other common pathogens detected in urine cultures included *Enterococcus* spp. (16%), *Klebsiella* spp. (14%), *Staphylococci* spp. (12%), *Enterobacter cloacae* (8%), and *Pseudomonas aeruginosa* (6%) [9].

Numerous factors, such as exposure to surgical trauma, intensive immunosuppressive regimens, long-term urinary catheterization, ureteral stents, and prolonged hospitalization, have been linked to an increased rate of infectious complications in kidney transplant recipients compared to the general population. However, reports on the connection between UTI incidence and acute rejection episodes have been conflicting. Some studies have not established a clear link between acute rejection episodes and UTI frequency; while others confirm an association between the frequency of UTIs and acute rejection phase. For example, Hosseinpour *et al.* found that patients who had experienced an acute rejection period were at higher risk of UTIs. Treating acute rejection typically requires intensive immunosuppression, which in turn increases the risk of posttransplant infection [9].

Antimicrobial resistance is a global healthcare concern, particularly for vulnerable groups such as pediatric, elderly, and immunocompromised individuals, including transplant recipients. Solid organ transplant recipients are at higher risk of developing healthcare-associated infections caused by resistant microbes, especially in the early posttransplant period [38]. After solid organ transplants, patients are often treated with prophylactic antibiotics and immunosuppressive medications, increasing their susceptibility to antimicrobial resistance owing to prolonged antimicrobial exposure. This contributes to considerable public health challenges, including increased healthcare costs and worse patient outcomes [39].

Rani *et al.* compared the antimicrobial resistance genes in the urinary metagenome of kidney transplant recipients with healthy cohorts using metagenomic shotgun sequencing. They discovered a higher prevalence of antimicrobial resistance genes, predominantly MDR efflux pumps among kidney transplant recipients. In contrast, healthy individuals exhibited a low abundance of these MDR efflux pumps. These MDR efflux pumps may enhance bacteria survival in the high-stress environment of transplantation [40].

Literature gap

Kidney transplantation remains the most effective treatment for patients with end-stage kidney disease. However, infection is the leading cause of mortality ≤ 1-year post-transplantation, with UTIs being the most frequently reported infection [9]. Infections caused by resistant microbes are a major cause of admission to the intensive care unit and are closely associated with increased morbidity and mortality [5]. This highlights the need for effective diagnostic approaches for improving prognosis and preventing treatment failure in these patients. The best therapeutic approach remains controversial, particularly when managing UTIs caused by MDR and highly drug-resistant uropathogenic Gram-negative bacteria. Therefore, standardizing the treatment protocol for UTIs mediated by MDR bacteria is crucial.

Despite the prevalence of antimicrobial resistance in kidney transplant recipients, this population has limited data on MDR efflux pump-mediated resistance. No data have been published from transplant programs in Saudi Arabia, despite the high volume of solid organ transplants in the country. There is a gap in understanding the association between efflux pump-mediated resistance and clinical outcomes in kidney transplant recipients in Saudi Arabia. This review highlights the importance of surveying and characterizing antibiotic resistance profiles, focusing on correlating these profiles with efflux pump expression to better understand the virulence of circulating uropathogenic Gram-negative bacteria in kidney transplant patients in Saudi Arabia and globally.

Future directions

Considering the global scarcity of related research and the common occurrence of MDR bacteria associated with UTIs in kidney transplant recipients, future research should focus on investigating the relationship between antibiotic resistance and the expression of efflux pump genes in prevalent uropathogenic Gram-negative bacteria. Using qRT-PCR to analyze specimens from kidney transplant recipients will be a valuable approach. Studies in Saudi Arabia and other regions can provide critical insights on clinical practice and improving outcomes in organ transplant recipients.

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Conflict of interests

No conflict of interests is declared.

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