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Antimicrobial Susceptibility Pattern in Opportunistic Pathogens Isolated from Immunocompromised Patients

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ABSTRACT

Background: Brought with the advancements in transplantation science and the development of immunosuppressive agents, immunocompromised patients characterized with defective immunity have increased throughout the world with increased risk for opportunistic infections. This study provides an overview of the antimicrobial susceptibility pattern among opportunistic pathogens isolated from immunocompromised patients.

Methods: Clinical and laboratory records of immunocompromised patients [patients with chronic kidney disease neutropenia, diabetes, rheumatic heart disease acquired immune deficiency syndrome hepatitis B, hepatitis C, who were subjected to microbiological culture analysis in the Department of Clinical Microbiology, KIST Medical College and Teaching Hospital, for 2 years (January 2019 and December 2020) were analyzed.

Results: Out of 8,402 immunocompromised patients, 954 (11.4%) patients were subjected to microbiological culture analysis. Among 954 patients, 253 (26.5%) patients [median(interquartile range) age: 52(31-67) years; male 138 (54.5%)] were infected. A total of 295 pathogens were isolated from 1,331 cultured samples. Infections due to *Escherichia coli* (n=71, 24.1%), *Klebsiella* spp. (n=55, 18.6%), *Acinetobacter calcoaceticus-baumannii complex* (n=35, 11.9%), *Candida albicans* (n=30, 10.2%), and *Staphylococcus aureus* (n=28, 9.5%) were frequently observed. Among the bacterial isolates (n=239), 81.6% (n=195) of bacteria were ß-lactamase producers, 51.0% (n=122) were multi-drug resistant, 9.2% (n=195) were extensively-drug resistant, 0.8% (n=195) were pan-drug resistant, and 35.7% (n=10) of *S. aureus* were methicillin-resistant *Staphylococcus aureus*.

Conclusions: The majority of infection in immunocompromised patients is caused by Gram-negative bacteria, and is often associated with a higher number of ß-lactamase producers and multi-drug resistant organisms. Prescriptions of antibiotics on the grounds of antimicrobial stewardship might help to reduce the burden of antimicrobial resistance.

Keywords: Antimicrobial resistance; immunocompromised host; opportunistic infections.

INTRODUCTION

Immunocompromised hosts, who possess a weak immune system either as a result of genetically heterogeneous impairment in immune systems or due to organ transplantation, are relatively at an increased risk for opportunistic infections as compared to immunocompetent hosts.[1-3] Such infections are often associated with an increase in disease severity, prolonged hospital admission, and increased mortality.[4]

The prolonged and aggressive antibiotic treatment in the immunocompromised hosts has expanded the global

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health risk.[5] The rapid emergence of antimicrobial-resistant microbes and failure to discover the newer antimicrobial agents to treat the infection associated with multidrug-resistant (MDR), extensively-drug resistant (XDR), pan-drug resistant (PDR), methicillin-resistant *Staphylococcus aureus* (MRSA), and ß-lactamase producers has prompted immunocompromised hosts to be at particularly high risk for developing and dying of sepsis.[6-8]

In this article, we have presented the prevalence, organism profile, and antimicrobial susceptibility pattern among opportunistic pathogens isolated from immunocompromised patients.

METHODS

A hospital-based retrospective study was conducted in the Department of Microbiology of Kist Medical College and Teaching Hospital (KISTMCTH), Gwarko, Lalitpur. The study was approved by the Institutional Review Committee (Ref. number: 0770788) of KISTMCTH. Patients with immunocompromised conditions such as chronic kidney disease (CKD), neutropenia, rheumatic heart disease (RHD), diabetes, hepatitis B (HB), hepatitis C (HC), and acquired immunodeficiency syndrome (AIDS), of any age and sex, visiting the hospital from February 1, 2019, to January 31, 2021, were traced and analyzed for microbiological culture and sensitivity.

Microbiological samples such as blood, urine, sputum, and other body fluids obtained from the immunocompromised patients were subjected to culture. All samples were inoculated onto blood agar, chocolate agar, and MacConkey agar, except for the urine samples, which were inoculated on cysteine lactose electrolyte-deficient agar. The inoculated agar plates were aerobically incubated at 35 ± 2°C for 24 hours. Fastidious bacteria such as *Streptococcus* spp. were identified by gram staining (Gram-positive cocci), catalase test (catalase non-producing), bile esculin test (esculin hydrolyzed by *Enterococcus* spp.), and bacitracin and optochin sensitivity test. *Moraxella* spp were also identified by gram staining (Gram-negative coccobacilli), catalase test (catalase-producing), oxidase test (oxidase-producing), and nitrate reduction test (nitrate-reducing). Conclusively, all of the isolated microbial colonies were identified based on the colony characteristics, gram staining, and biochemical tests following the standard microbiological guidelines.[9]

After identification, antimicrobial susceptibility testing was performed by Kirby Bauer disc diffusion method on Mueller-Hinton agar as per the guideline of The Clinical and Laboratory Standards Institute.[10]

MDR was defined as acquired non-susceptibility to at least one agent in three or more antimicrobial categories, XDR was defined as non-susceptibility to at least one agent in all but two or fewer antimicrobial categories (i.e. bacterial isolates remain susceptible to only one or two categories) and PDR was defined as non-susceptibility to all agents in all antimicrobial categories.[7] The ß-lactamase producer was defined as the bacterium that had resistance to any one group of ß-lactam antibiotics, such as penicillin derivative, cephalosporins, monobactams, and carbapenems.[10] MRSA was defined as resistance (a zone size ≤ 19mm) of *S. aureus* to cefoxitin.[10]

Data analysis was performed using the Statistical Package for the Social Sciences software version 17.0.

RESULTS

Out of 8,402 immunocompromised patients investigated over a 2-year period, patients with immunocompromised conditions such as neutropenia (n=5628, 67.0%), diabetes (n=1983, 23.6), CKD (n=542, 6.5%), RHD (n=204, 2.3%), hepatitis B (n=26, 0.3%), hepatitis C (n=13, 0.2%), and AIDS (n=6, 0.1%) were found. Among them, 954 (11.4%) patients were clinically suspected for infection and hence underwent a subsequent panel of microbiological investigations to confirm the presence of microbial infections (Table 1).

A total of 1,331 clinical samples from 954 immunocompromised patients were processed for microbiological findings. There were 619 (46.6%) blood, 372 (27.9%) urine, 228 (17.1%) sputum, and other infrequent body fluids that were processed for culture analysis (Table 2). Out of 954 microbiologically analyzed patients, 253 (26.5%) patients (mean age: 48.9 ± 23.9, male sex: 138 [54.5%]) were infected with microbes. Concerning the infected immunocompromised patients, there were 124 (42.0%) patients with CKD, 60 (20.3%) with neutropenia, 59 (20.0%) with diabetes, 6 (2.0%) with RHD, 3 (1.0%) with hepatitis B, and 1 (0.3%) with hepatitis C (Table 2). Samples such as sputum (n=99, 33.6%), urine (n=95, 32.2%), and blood (n=38, 12.9%) were most commonly positive for the microbiological culture. There were 207 (70.2%) patients likely to be infected by one species identified, 26 (8.8%) patients likely to be infected by two of the species identified, and 20 (6.8%) patients likely to be infected by at least 3 species (Table 2).

Table 1. Demographics of immunocompromised and infected patients.

Variables		Immunocompromised patients		
		Total (*n* = 8402) *n* (%)	Microbiologically analyzed (*n* = 954) *n* (%)	Infected (*n* = 253) *n* (%)
Age (years)	Mean	41.1 ± 22.3	42.9 ± 24.0	48.9 ± 23.9
	Median (Q1-Q3)	41 (24-59)	42 (23-63)	52 (31-67)
Age groups (years)	< 10	849 (10.1)	84 (8.8)	15 (5.9)
	10-20	560 (6.7)	77 (8.1)	15 (5.9)
	20-30	1506 (17.9)	168 (17.6)	32 (12.6)
	30-40	1176 (14.0)	127 (13.3)	34 (13.4)
	40-50	1109 (13.2)	112 (11.7)	23 (9.09)
	50-60	1197 (14.2)	107 (11.2)	33 (13.0)
	≥ 60	2005 (23.9)	279 (29.3)	101 (39.9)
Gender	Male	4040 (48.1)	507 (53.1)	138 (54.5)
	Female	4362 (51.9)	447 (46.9)	115 (45.5)
IMC state	AIDS	6 (0.1)	2 (0.2)	0 (0)
	HB	26 (0.3)	9 (0.9)	3 (1.19)
	HC	13 (0.2)	5 (0.5)	1 (0.4)
	RHD	204 (2.4)	17 (1.8)	6 (2.37)
	CKD	542 (6.5)	282 (29.6)	124 (49)
	Neutropenia	5628 (67.0)	459 (48.1)	60 (23.7)
	Diabetes	1983 (23.6)	180 (18.9)	59 (23.3)

IMC = immunocompromised, AIDS = Acquired immunodeficiency syndrome, CKD = Chronic Kidney Disease, RHD = Rheumatic Heart Disease, HB = Hepatitis B, HC = Hepatitis C

Table 2. Culture results based upon the type of samples.

Samples	Samples		Type of infection		
	Processed *n* (%)	Positive culture *n* (%)	1 microbe *n*	2 microbe *n*	≥ 3 microbe *n*
Blood	619 (46.6)	38 (12.9)	33	3	2
Others	21 (1.6)	3 (1.0)	3	0	0
Urine	372 (27.9)	95 (32.2)	73	10	12
Sputum	228 (17.2)	99 933.6)	88	8	3
Wound	12 (0.9)	5 (1.7)	4	1	0
Pus	20 (1.5)	11 (3.7)	5	4	2
CSF	19 (1.4)	-	-	-	-
Ascitic fluid	19 (1.4)	1 (0.3)	0	0	1
Pleural fluid	10 (0.7)	1 (0.3)	1	0	0
Catheter tips	11 (0.8)	-	-	-	-
Total	1331	253	207	26	20

The majority of infections were caused by *E. coli* (n=71, 24.1%), *Klebsiella* spp. (n=55, 18.6%), *Acinetobacter calcoaceticus-baumannii complex* (*ACB complex*) (n=35, 11.9%), *C. albicans* (n=30, 10.2%), and *S. aureus* (n=28, 9.5%). There were 239 (81.0%) cases of bacterial infection, 44 (14.9%) of fungal infections, and 12 (4.1%) of polymicrobial infections (≥ 3 three different species, specifically in the urine samples, which were neither identified nor tested for sensitivity) (Table 3).

Table 3. Organisms isolated from different clinical samples.

Pathogens	Sputum (n=114)	Urine (n=109)	Blood (n=45)	Wound (n=6)	Pus (n=13)	Ascitic fluid (n=2)	Pleural fluid (n=1)	Others (n=5)
ACB complex (n=35)	23	1	6	1	2	1	0	1
Pseudomonas spp. (n=18)	9	7	1	0	0	1	0	0
Proteus spp. (n=2)	0	2	0	0	0	0	0	0
Salmonella spp. (n=2)	0	0	2	0	0	0	0	0
Klebsiella spp. (n=55)	31	15	3	2	4	0	0	0
Enterobacter spp. (n=8)	3	2	2	0	1	0	0	0
Escherichia coli (n=71)	14	50	3	1	1	0	1	1
Citrobacter spp. (n=8)	5	0	3	0	0	0	0	0
Moraxella spp. (n=1)	1	0	0	0	0	0	0	0
Staphylococcus aureus (n=28)	5	0	18	0	4	0	0	1
Streptococcus spp. (n=2)	0	1	1	0	0	0	0	0
Enterococcus spp. (n=9)	0	4	4	0	1	0	0	0
Candida albicans (n=30)	18	10	0	2	0	0	0	0
Candida non-albicans (n=13)	4	5	2	0	0	0	0	2
Aspergillus spp. (n=1)	1	0	0	0	0	0	0	0
Multiple organisms (n=12)	0	12	0	0	0	0	0	0

ACB complex = Acinetobacter calcoaceticus-baumannii complex

Table 4. Antibiotic resistance profile of the Gram-negative bacterial isolates.

Antibiotics	*E. coli* (n=71)	*Klebsiella* spp. (n=55)	*ACB complex* (n=35)	*Pseudomonas* spp. (n=18)	*Citrobacter* spp. (n=8)	*Enterobacter* spp. (n=8)
Ampicillin	86.0	92.0	100.0	100.0	100.0	100.00
Amoxicillin-Clavulanic acid	57.1	62.5	100.0	-	12.5	66.7
Ceftriaxone	86.4	55.3	95.5	50	100.0	100.0
Cefotaxime	74.5	48.1	81.3	-	100.0	100.0
Ceftazidime	67.8	100.0	100.0	28.6	100.0	100.0
Cefepime	100.0	100.0	100.0	-	100.0	-
Nalidixic Acid	93.5	0	-	-	-	100.0
Ciprofloxacin	83.6	43.2	62.5	0	100.0	37.5
Ofloxacin	91.1	48.3	95.2	100.0	100.0	-
Norfloxacin	79.4	0	-	-	-	0
Norfloxacin	100.0	100.0	-	-	-	-
Gentamicin	27.7	16.7	36.7	14.3	100.0	28.8
Amilkacin	18.4	58.9	39.4	12.5	12.5	-
Meropenem	4.3	25.0	100.0	28.6	100.0	-
Imipenem	55.6	71.4	90.9	-	100.0	-
Tetracyclin	-	100.0	100.0	100.0	-	-
Cotrimoxazole	80.3	42.3	78.8	100.0	87.5	75.0
Chloramphenicol	-	75.0	18.2	-	0	0
Colistin	0	4.0	0	-	0	0
Polymixin B	0	0	0	-	0	0
Nitrofurantoin	5.17	66.7	-	-	-	100.0
Piperacillin/Tazobactem	50.0	66.7	10.0	25.0	-	-
Tigecycline	0	0	42.1	-	0	0

Table 5. Antibiotic resistance profile of the Gram-positive bacterial isolates.

Antibiotics	*S. aureus* (n=28)	*Enterococcus* spp. (n=9)
Penicillin	100.0	71.43
Ampicillin	92.6	33.33
Amoxycilli-clavulanic acid	100.0	-
Cloxacillin	20.0	-
Cefoxitin	33.4	-
Cefotaxime	75.0	100.00
Ceftriaxone	100.0	75.00
Ceftazidime	100.0	100.00
Cefepime	100.0	-
Ciprofloxacin	37.5	100
Ofloxacin	100.0	83.33
Levofloxacin	11.11	-
Gentamicin	53.9	100.00
Amikacin	84.6	100
Clindamycin	50.0	-
Erythromycin	60.0	-
Chloramphenicol	6.3	12.50
Cotrimoxazole	29.4	100.00
Meropenem	91.7	100.00
Imipenem	100.00	-
Cefotaxime-clavulanic acid	100.00	-
Vancomycin	0	0
Tigecycline	0	0

Out of 239 bacterial isolates, 195 (81.6%) organisms were ß-lactamase producers, 122 (51.0%) were MDR, 22 (9.2%) were XDR, 2 (0.8%) were PDR, and 10 (35.7%) *S. auresu* were MRSA (Fig 1).

Bacteria-specific drug susceptibility profile has been summarized in Table 4 and Table 5. Hundred percent of *E. coli* and *Klebsiella* spp. were resistant to cefepime and levofloxacin, while absolute non-resistance was observed for polymixin B and tigecycline. Similarly, the *ACB complex* showed 100% resistance to ampicillin, amoxicillin clavulanic acid combination, ceftazidime, cefepime, meropenem, and tetracycline, and 100% sensitivity to both colistin and polymixin B. Absolute (100%) resistance in *Pseudomonas* spp. was also observed for ampicillin, ofloxacin, tetracycline, and cotrimoxazole (Table 4). Absolute resistance for ampicillin, cefotaxime, ceftriaxone, ceftazidime, nalidixic acid, ciprofloxacin, and ofloxacin was observed for *Proteus* spp. *Salmonella* spp., and *Moraxella* spp. Hundred percent of *S. aureus* were resistant to penicillin, ceftriaxone, ceftazidime, cefepime, ofloxacin, imipenem, amoxicillin-clavulanic acid, and cefotaxime-clavulanic, while 100% sensitivity was observed for tigecycline and vancomycin (Table 5). *Streptococcus* spp. exhibited 100% resistances to penicillin, cefoxitin, cefotaxime, ceftazidime, ofloxacin, gentamicin, cotrimoxazole, and meropenem. Such higher incidences of antibiotic resistance could be due to fewer (n=2) *Streptococcus* spp.

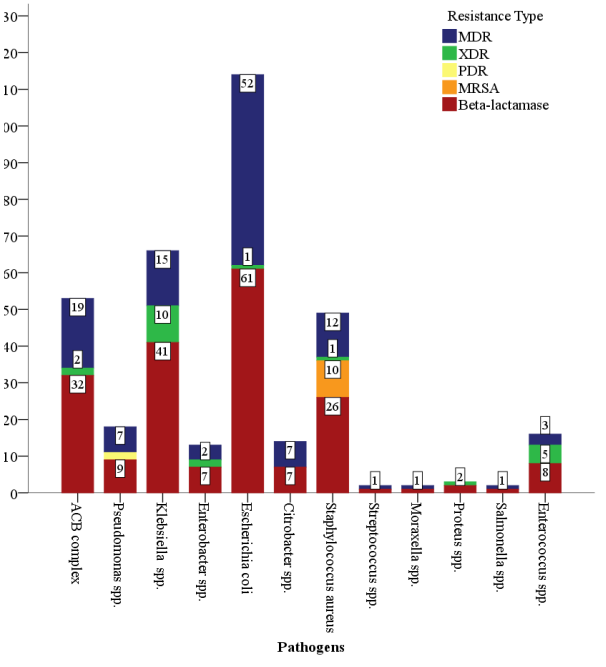

Fig 1. Types of antibiotic resistance.

DISCUSSION

With the varying patterns of infection in immunocompromised patients,[1] the facilities of late prognosis and/or prolonged aggressive treatment practices have created challenges for practitioners, either by changing drug susceptibilities or by evolving standards for empirical use of the antimicrobial agents against pathogens.[6] Despite such facts, there are still limited numbers of studies concerning the burden of microbial infection and/or superinfection among immunocompromised patients. Therefore, we aimed to analyze the prevalence of opportunistic infections, organism profile, and antimicrobial susceptibility patterns among immunocompromised patients.

The mean age of the immunocompromised patients in this study was 41.1 years±22.3, which is inconsistent with the findings of Trivedi et al.[11] (55 years±14.8). The immunocompromised patients of the age group ≥ 60 years (34.2%) were mostly infected, which could be attributed to the significant loss of innate immune and poor T-cell function.[12] In this study, the majority of males (54.5%) with the immunocompromised condition were infected. This could be attributed to the behavioral factors such as higher levels of drinking and smoking among men compared to women and sex-based immunological differences, mediated by sex hormone and X chromosome.[13]

The culture positivity rate in this study was higher for the patients with CKD (42.0%) as compared to the patients with neutropenia (20.3%), diabetes (20.0%), RHD (2.0%), hepatitis B (1.0%), and hepatitis C (0.3%). In contrast to our findings, several studies reported varying incidences of bacterial infection in patients with neutropenia (21.3-35.4%),[14,15] CKD (13.8-17.2%),[13] diabetes (19.4-63.4%),[11,16] hepatitis B (28.1-36.8%),[17,18] and hepatitis C (38.3-78.6%).[19,20] The increased rate of bacterial infections in patients with CKD from our study could be accredited to dialysis-related problems like repeated skin puncture and reduced immunity.[21] Additionally, the observation of fewer microbial infections in hepatitis-infected patients and no microbial infections in HIV-infected patients in this study was due to the lower frequency of hepatitis-infected and HIV-infected patients visiting the hospital.

We observed respiratory tract infections (39.43%) as the obvious source of infection in immunocompromised patients, which contrasts with the finding of Adhikari et al.,[22] who had reported urinary tract infection (36.57%) to be the commonest infection among such patients. Though the lower incidence of bloodstream infection (16.57%) from our study was similar to the findings from several studies,[15,22] it was inconsistent with the findings of Taj et al.[14] (46.01%), who have reported a higher rate of bloodstream infections in immunocompromised patients. The probable reason for the lower rate of bloodstream infection in our study could be accountable to the fact that many patients could have received empirical antibiotics before blood culture analysis.[14]

Most of the immunocompromised patients from this study were infected with *E. coli* (24.1%), *Klebsiella* spp. (18.6%), *ACB complex* (11.9%), *C. albicans* (10.2%), and *S. aureus* (9.5%). Similar pathogens were also isolated from the National Kidney Center of Nepal during a study in CKD patients[22] and several other studies conducted in diabetic patients[11] and neutropenic patients.[13] Wisplinghoff et al.[23] mentions that infections in immunocompromised hosts are commonly associated with *S. pneumoniae*, *H. influenzae*, and *S. aureus* and most often with *Salmonella* spp., *Pseudomonas* spp., and *Mycoplasma* spp. Such infections may be due to abnormalities in either cell-mediated immunity or defects in antibody or complement response developed against the pathogen in the immunocompromised host, nevertheless, resulting in pneumonia, chronic or disseminated fungal or viral infections, and severe mycobacterial disease.[24]

Our study revealed a variable degree of resistance to many of the routinely used drugs. Tetracycline (100%), cefepime (100%), ampicillin (95.8%), and ceftazidime (94.9%) had the highest overall resistance rate for Gram-negative bacteria. Similarly, Gram-positive bacteria showed absolute non-sensitivity to cefepime, ceftazidime, ceftriaxone, cefotaxime-clavulanic acid combination, and imipenem. Such higher resistances to antibiotics among bacteria could be due to the modification in their cell permeability; drug degradation/alteration by enzymes such as beta-lactamase, aminoglycoside-modifying enzymes, or acetyltransferases; and efflux pump expression, which results in reduced intracellular drug accumulation.[25,26] In this study, while Gram-negative bacteria showed better sensitivity towards polymyxin B (100%), colistin (99.08%), and tigecycline (92.7%), Gram-positive bacteria showed better sensitivity towards vancomycin (100%), tigecycline (100%), and chloramphenicol (92%). An absolute resistance of *E. coli* and *Klebsiella* spp. to cefepime and levofloxacin was observed. Both of them were sensitive to polymyxin B and tigecycline. *ACB complex* showed 100% resistance to ampicillin, amoxiclav, ceftazidime, cefepime, meropenem, and tetracycline, and 100% sensitivity to both colistin and polymixin B. A study mentions *ACB complex* as a highly antimicrobial-resistant pathogen, and accredited its potency to its property of clonal expansion.[27] A high level of resistance in ß-lactam antibiotics was also observed in a study by Shrestha et al.,[7] who had reported 35% of *E. coli* and *K. pneumoniae* to be a ß-lactamases producers. Nevertheless, such ability of Gram-negative bacteria to alter the outer membrane, either by changing the hydrophobic properties or by mutations in porins, which hinders the passage for drugs, makes them more resistant to antibiotics than Gram-positive pathogens.[28] Concerning the Gram-positive bacteria in this study, hundred percent of *S. aureus* were sensitive to vancomycin and tigecycline. While *Enterococcus* spp. was moderately resistant to ampicillin and ofloxacin in this study, other *Streptococcus* spp. was resistant to

them.

The incidence rate of MDR (51.0%), XDR (9.2%), PDR (0.8%), and MRSA (35.7%) were comparable to the findings of Shrestha et al.,[7] who had also reported the incidence rate of MDR, XDR, PDR, and MRSA to be 40%, 10%, 0%, and 30%, respectively. Very high incidences of ß-lactamase producers (81.6%) observed in this study were discordant with the findings of Shrestha et al.,[7] who had reported 35% of *E. coli* and *Klebsiella* spp. as the ß-lactamase producers.

This study suffers from several limitations. Firstly, patients, who have cancer and are on chemotherapy, or who have had a solid organ transplant such as kidney or heart transplant, and are taking medication to keep their transplant were not included. Secondly, this is a single-center cross-sectional study comprising the Nepalese population who visited the study site seeking medical care, and therefore the findings may not be generalizable in the worldwide context. Hence, further well-designed studies with a larger sample size are required.

CONCLUSIONS

This study showed an infection rate of 26.5% in immunocompromised patients. *E.coli*, *Klebsiella* spp., *ACB complex*, *C. albicans*, and *S. aureus* are the frequently encountered organisms, most of which are ß-lactamase producers and multi-drug resistant. Bacterial infections showing considerable resistance to the commonly used antibiotics call for the strategies to prescribe antibiotics on the grounds of antimicrobial stewardship principles in order to reduce morbidity and mortality in immunocompromised patients.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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