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Drug-related problems among patients with infectious disease admitted to medical wards of Wollega University Referral Hospital: Prospective observational study

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Abstract

Introduction: Drug-related problems can affect the treatment outcomes of hospitalized patients and outpatients that lead to morbidity and mortality. Despite this, there were scanty of studies among patients with infectious diseases in Ethiopia. As the result, this study was tried to assess the magnitude and determinants of drug therapy problems among infectious disease patients admitted to the medical wards of Wollega University Referral Hospital.

Methods: A prospective observational study was conducted from May to August 2019. The prevalence and types of drug-related therapy problems were studied using the Pharmaceutical Care Network Europe Foundation classification system, and adverse drug reaction was assessed by using the Naranjo algorithm. Multivariable logistic regression analysis was used to determine the predictors of drug-related problems, and a significant association was declared if p-value < 0.05.

Result: Of the 172 study participants, 106 (61.6%) were males, and the patient's mean age was 39.1 ± 14.31 years. Over the study period, 123 (71.51%) patients had drug-related problems. Need for additional drug therapy was the widely occurred drug-related problem that accounts for 107 (22.77%), and the most common drug-associated with the drug therapy problem was ceftriaxone (77 (44.77%)). This inappropriate use of ceftriaxone might be due to the preference of physicians to prescribe this broad spectrum antibiotic in which it was prescribed for the majority of the infectious disease etiology. Polypharmacy (adjusted odds ratio (AOR) = 2.505, 95% confidence interval (CI): 1.863–11.131), length of hospital stay $\geqslant$ 7 days (AOR = 4.396, 95% CI: 1.964–7.310), and presence of co-morbidity (AOR = 2.107, 95% CI: 1.185–4.158, p = 0.016) were determinants of drug-related problems.

Conclusion: The magnitude of drug-related problems was found to be high. Hence, the clinical pharmacy service should be established to tackle inappropriate indications, ineffective drug therapy, and adverse drug events in the study area.

Keywords

Drug-related problems, infectious diseases, medical ward, admitted patients, Ethiopia

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Background

Drugs that are used for the prevention and cure of the disease may have an impact on the patients if used incorrectly and they result in any drug therapy problem (DTP). The untoward effects of drugs are a result of the nature and property of the drugs or their improper use, which is referred to as medication errors.[1–4] Drug-related problems (DRPs) have been defined as any problems involving drug therapy which can affect desired health outcomes. This includes inappropriate dosage, adverse

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drug reaction (ADR), needs additional drug therapy, ineffectiveness, unnecessary drug therapy, and non-compliance.[5]

Nowadays, DTP is one of the public health problems worldwide, and about 10%–20% of inpatients will have at least one ADR during their hospital stay.[6] It was estimated that around 5%–10% of hospital admissions were due to DTPs, in which more than half of them are preventable.[7] DTP is becoming a major safety issue for hospitalized patients and outpatients that can decrease the quality of life for the patients, prolonged hospitalization, affects health care budgets, and even death.[1,8]

Penicillin and cephalosporins among the antibiotics cause different skin reactions in 3.1% of the total hospital admission, and the rate of hospital mortality was estimated to be 6.4%. It has been estimated that 3% to 14% and 5% of total hospital admissions to medical wards are related to ADR.[6,8] Generally, ADR is the most common cause of patient morbidity, mortality, and increase health care costs.[9] The majority of DTPs have happened during the medication use process; however, inadequate follow-up of the patients' therapy by health care providers is also one of the causes of DRP.[10] As a result of complex today's therapy, it is paramount to identify the cause and magnitude of the DTP.[11]

DTPs are the most common causes of patients' re-admissions, and it was found that incorrect techniques, unnecessary drug, and dose too high were among the DTPs that cause patients hospitalization. The major classes of drugs involved in this problem were beta-lactamase systemic antiinfective.[12,13] If the patients' DTPs were not resolved, patients' hospitalization, mortality, and morbidity may be increased.[10,11] DTPs can also affect health care providers and patients family as a result of increased health care costs and loose confidence from health care services.[14]

In Nekemte referral hospital nearby to our study area, about half of antibiotics was prescribed inappropriately.[15] Inappropriate use of antibiotics can result in bacteria resistant to antibiotics in infectious disease patients.[16] The prevalence of antimicrobial resistance is higher in communities that use non-prescription antibiotics more frequently.[17] The emergence of antimicrobial resistance, the main cause of morbidity and mortality from otherwise treatable infections, is largely attributed to the use, overuse, or misuse of antimicrobials.[18]

The increases in emerging antibiotic resistance and the decrease in the discovery of novel drugs have made a major problem to health policymakers and health care workers.[19] The irrational use of antibiotics and the emergence and transmission of antibiotic-resistant pathogens cause large health care costs annually. More than half of penicillin and cephalosporins were used inappropriately in hospitals.[20] These inappropriate use of antibiotics have been associated with increased mortality, side effects, and the development of resistant bacteria, which hold a threat to the generation.[21] Carbapenems are the most effective drugs used to treat infections caused by ESBL-producing *Enterobacteriaceae*. Despite this, inappropriate use can result in its resistance.[22] Irrespective of their use β-lactamase producing gram-negative bacteria is a leading cause of antimicrobial resistance.[23] Similarly, *Mycobacterium tuberculosis* has developed multi-drug resistance due to genetic mutations.[24]

As compared with outpatients, hospitalized patients were more prone to different DRPs as a result of polypharmacy, hospital-acquired infections, presence of comorbid cardiovascular disease, and chronic therapeutic regimens, which can affect the patient's treatment outcomes.[2,10,25]

The old practices of pharmacy in which the pharmacists were only involved in the dispensing of drugs as prescribed by medical doctors were not ensured the appropriateness of drug therapy. Therefore, clinical pharmacists need to be actively involved in the management of the disease to avoid any of DTPs.[10] Pharmaceutical care was the best way of identifying and resolving DTP, and the participation of clinical pharmacists in health care has decreased medication errors.[2,3] To date, in our study area, the clinical pharmacy service was not implemented to decrease the incidence of DTPs.

Although in recent years in Ethiopia much effort has been put into the initiation of clinical pharmacy services to stimulate the delivery of uniform and structured care, prospective data on DTPs and its predictors among patients with medical wards are limited. Therefore, this study tried to identify the magnitude and determinants of DRPs among infectious disease patients admitted to the medical wards of Wollega University Referral Hospital (WURH).

Methods

Study area, design, and period

A prospective observational study was conducted at WURH from May to August 2019. WURH is found in Nekemte town, which is located 330 km to the west of Finfinne, the capital city of Ethiopia. This hospital serves as a teaching hospital, treatment, and research center.

Study participants and eligibility criteria

Patients ⩾ 18 years who were admitted to the non-intensive care unit (ICU) of medical wards and with more than 48 hours of length of stay were included. Patients who refused to participate, re-admitted during the data collection period, and developed ADR due to genetic factors were excluded.

Study variables and outcome endpoints

The DTP was the primary outcome. ADR was assessed by using the Naranjo algorithm of the ADR probability scale[26] Hill-Bone Compliance to High Blood Pressure Therapy Scale (HB-HBP) was used to measure medication adherence.[27–30] For this study purpose, a nine-item medication-taking subscale was selected. Each item is a 4-point Likert-type scale

(none of the time, some of the time, most of the time, and all of the time). The total scores on this subscale range from 9 to 36 with higher scores reflecting poorer adherence to drug therapy. The median split was used and dichotomized into two groups: 1 = Adherent to the treatment and 0 = Non-adherent to the medication

Sample size and sampling technique

Single population proportion formula was used to calculate the required sample size by considering the following assumptions: Proportion of DRP 75.51%,[9] 95% confidence level, and 5% margin of error (absolute level of precision)

$$n = \frac{(Z\alpha/2)2p(1-p)}{d2}$$

$$z = 1.96$$

$$P = 75.51\% \ (0.7551)$$

$$d = 0.05$$

$$n = \frac{(1.96)2(0.755)(0.245)}{(0.05)2} = 284.24 \sim 284$$

where n = sample size, P = proportion of drug related problems (p) = 50%, Z = standardized normal distribution value at the 95% confidence interval (CI): 1.96, and d = the margin of sample error tolerated = 5%.

The expected number of populations in the study period (N), based on the average number of patients coming to the hospital in 3 months was 346. The corrected sample size (nf) was calculated by using correction formula as follows

$$nf = \frac{(n*N)}{(n+N)}$$

$$nf = \frac{(284*346)}{(284+346)}$$

$$nf = 156.05$$

After adding a 10% contingency, it becomes 171.65∼172. A convenient sampling technique was used to include study participants.

Data collection process and management

Data were collected by using a semi-structured data collection tool adapted from previous literature and contextualized to our area. One medical doctor, two nurses, and three pharmacists were recruited for data collection; one clinical pharmacist was assigned to supervise the data collection process. The appropriateness of drug therapy was assessed by using Medscape, Up-to-date, lexicom, and Micromedex and different guidelines. DRP registration format was used to identify and record different types of DRPs.[31] To assess the outcomes of DTPs, the patient's laboratory investigations, including thyroid function test (T3 T4, and thyroid-stimulating hormone), blood glucose level, blood pressure, serum cholesterol level, liver function test (alanine aminotransferase and aspartate aminotransferase level), renal function test (creatinine clearance and blood urea nitrogen), blood count test (hematocrit, platelets, and white blood cell), serum electrolytes, and uric acid level, were recorded and compared with the values against their respective reference measures. The pretest was conducted in nearby hospital named Nekemte referral hospital. The pretest was done for nine of the patients to check the acceptability and consistency of the data collection tool 2 weeks before the actual data collection.

Data processing and analysis

The data were entered into a computer using EPI-info 3.5.4 software. On daily bases, data checking and cleaning were done by investigators. The analysis was done using statistical software for social sciences (SPSS) 24.0. Multivariable logistic regression was used to analyze the variable by using crude odds ratio and adjusted odds ratio (AOR) with 95% CI. All variables associated with the DRPs at a p-value ⩽ 0.25 on the bivariate analysis were entered into a multivariable logistic regression analysis to control for confounders. Finally, the predictors of DRPs were declared if a p-value is ⩽ 0.005.

Operational definitions

Drug-related problem: Includes ADR, non-adherence, inappropriate indication and dose, and ineffective drug therapy.

Polypharmacy: The daily consumption of five or more medications.[11]

Comorbidity: The presence of two or more diseases.[32]

Results

Socio-demographic and clinical characteristics of study participants

Over the study period, a total of 172 patients with bacterial infectious diseases were admitted to the medical wards of WURH. A total of 106 (61.6%) were male with a mean age of 39.1 ± 14.31 years. The majority of the study participants, 117 (68%), had a history of at least once admission to health care, and over a quarter (70.3%) of them have/had antibiotic use within the past 6 months. Almost all (91.3%) of the respondent's reason for admission was the infectious origin on the bases of clinical approaches (Table 1).

Table 1. Socio-demographic factors and clinical characteristics of the infectious diseases patients admitted to the medical ward of WURH from June to August, 2019.

Variables		Frequency (n)	Percentage (%)
Sex	Male	106	61.6
	Female	66	38.4
Age (years)	18–34	68	39.5
	35–54	72	41.9
	⩾55	32	18.6
Residence	Urban	95	55.23
	Rural	77	44.77
Previous medication and admission history	Previous history of admission	43	25.0
	Recent history of Antibiotic use	81	47.1
Infectious diseases reason for admission	Community acquired pneumonia	58	33.72
	Acute febrile illness (AFI)	46	26.74
	Diabetic foot infection	26	15.11
	Urinary tract infections (UTI)	21	12.21
	Bacterial meningitis	13	7.56
	Others[a]	8	4.65
Presence of comorbidity	Yes	63	36.63
	No	109	63.37
Length of hospital stay (days)	<7	99	57.56
	>7	73	42.4
Number of medications per patient	<5	116	67.44
	>5	56	32.56

AFI: acute febrile illness; UTI: urinary tract infections.
[a]Helminthic infection, post-partum sepsis, giardia, osteomyelitis, extrapulmonary and disseminated tuberculosis, and human immune virus.

Incidence and characterization of DRPs

The prevalence of actual or potential DRPs among subjects put on at least a single form of antibiotic was found to be 123 (71.51%). A total of 470 DRPs were identified on average, 2.73 DRPs per patient. The three leading categories of DRPs found to be a culprit among the sample were need additional drug therapy (107 (22.77%)), unnecessary drug therapy (99 (21.06)), and ineffective drug therapy (96 (20.42%)). The rest too were non-adherence (89 (18.94%)) and adverse drug events (79 (16.81%)).

The common drugs involved in DRPs

During their hospitalizations, Ceftriaxone (77 (44.77%)) was the most common drug related to DRPs which are followed by gentamycin (65 (37.79%)) and vancomycin (44 (25.58%)) (Table 2).

Factors associated with DRPs

The output of the multivariable logistic regression analysis found that a significant association was obtained between the patient's duration of hospital stay, polypharmacy, and presence of comorbidity with the presence of DRPs. Patients who had ⩾7 days length of hospital stays were 4.4 times more likely to have DRPs than patients who had <7 days (AOR = 4.396, 95% CI: 1.964–7.310, p = 0.037). Patients who had prescribed ⩾5 drugs (polypharmacy) were 2.5 times more likely to have DRPs than patients prescribed with <5 drugs (AOR = 2.505, 95% CI: 1.863–11.131, p = 0.01). Finally, patients who had comorbidity had 2 times more likely to had at least one DRPs than patients who hadn't comorbidity (AOR = 2.107, 95% CI: 1.185–4.158, p = 0.016)(Table 3).

Discussion

Different factors are associated with the occurrence of DRPs in infectious disease patients.[33,34] This study was tried to identify the magnitudes and determinants of this DRP among infectious disease patients admitted to medical wards.

The prevalence of DRP in our study patients was 123 (71.51%), which was higher than the study done in Gondar (66%), Zewditu Memorial Referral Hospital (31.57%), Northern Sweden (66%), and Hong Kong (21%).[1,11,33,35] In addition, the prevalence was lower than the Dessie Referral Hospital (75.51%) and Kenya (93.8%).[9,36] However, comparable findings were reported from Tikur Anbesa Specialized Hospital (70.4%) and Jimma University Specialized Hospital (73.5%).[32,37] The difference in magnitudes of DRP observed across different countries might be due to a variation in DRPs classifications and study settings. Despite this difference observed, the interventions should be done to resolve DRPs to improve patients' treatment outcomes, and future researchers should use similar DRPs classification systems to generate evidence-based recommendations.

Table 2. Common drugs associated with the occurrence of DRPs among infectious diseases patients admitted to the medical ward of WURH from June to August, 2019.

Individual Drugs	Class of drug	Mechanism of action	Frequency (n)	Percentage (%)
Ceftriaxone	Cephalosporin	Inhibits bacterial cell wall synthesis by binding to trans peptidases	77	44.77
Gentamycin	Aminoglycoside	Inhibit protein synthesis	65	37.79
Vancomycin	Glycopeptide	Inhibits cell wall synthesis by binding to the D-Ala-D-Ala	44	25.58
Cotrimoxazole	Sulfonamide	Blockade of folic acid enzymes	31	18.02
Omeprazole	Proton pump inhibitor	Inhibition of the H^+/K^+-ATPase	27	15.69
Ibuprofen	NSAID	Inhibition of the cyclooxygenase enzymes COX-1 and COX-2	19	11.05
Prednisolone	Corticosteroid	Inhibition of cytokine production	15	8.72
Cloxacillin	Penicillin	Inhibition of bacterial cell wall synthesis by binding to the penicillin binding proteins (PBPs)	11	6.39
Cimetidine	Histamine 2 blocker	Blocks histamine 2-receptor	9	5.23
Enalapril	ACEI	Inhibits the ACE	7	4.07
Others			8	4.65

NSAID: non-steroidal anti-inflammatory agents; ACE: angiotensin-converting enzyme.
[a]Ampicillin, ciprofloxacin, acetylsalicylic acid, captopril.

In the present study, need additional drug therapy (107 (22.77%)), unnecessary drug therapy (99 (21.06)), and ineffective drug therapy (96(20.42%)) were the most commonly occurred DRPs. This was similar to the finding of Hiwot Fana Specialized University Hospital in which inappropriate indication was the commonly occurred DRPS.[4] In Jimma University Specialized Hospital, non-compliance was the least prevalent type of DRP.[32] In addition, a study from the University of Gondar showed inappropriate dosage was the most commonly occurred type of DTP 39.1%.[33] According to the finding of Dessie Referral Hospital, needs additional drug was the most common DTP and the ineffective drug was the least.[12] In Adama Hospital Medical College Adama Hospital Medical College, drug interaction, non-adherence, and adverse drug interaction were the most commonly occurred DRPs.[38] Ineffectiveness was the widely occurred DRPs according to the study conducted in Newton Paiva University Center, Brazil.[39]

In our study, the most common drugs associated with at least one of the DRPs were ceftriaxone (77 (44.77%)), gentamycin (65 (37.79%)), and vancomycin (44 (25.58%)). Similarly, the study conducted in Dessie Referral Hospital revealed that antibiotics, cardiovascular drugs, and non-steroidal anti-inflammatory drugs were the most common class of drugs associated with DRPs. Specific to the drugs ceftriaxone, spironolactone, enalapril, and furosemide were highly associated with DRPs.[9] On the contrary, the study conducted in the University of Gondar showed that the most common agents associated with DRPs were omeprazole, heparin, and acetylsalicylic acid.[33] In Zewditu Memorial Referral Hospital, the most common drugs related to DRPs were ampicillin, phenobarbital, and diazepam.[1]

The study conducted in Jimma University Specialized Hospital among heart failure patients revealed that beta-blockers, angiotensin-converting enzyme inhibitors, statins, and antithrombotic were commonly related to DRPs.[7] Cardiovascular drugs and psychotropic drugs were commonly associated with DRPs in northern Sweden.[35] The study done in Singapore showed that the drugs most implicated were beta-blockers, non-steroidal anti-inflammatory agents (NSAIDs), and angiotensin-converting enzyme (ACE) inhibitors.[40] The variety of drugs related to DTPs were due to availability, patient and physician preferences, and different treatment guidelines within different countries.

Identifying factors contributing to DTPs is crucial for the reduction of unwanted effects of DRPs in infectious disease patients.[32] In our study, polypharmacy was one of the predictors of DRP. Patients who took $\geqslant$5 drugs were 2 times more likely to develop DRPs as compared with patients who took $<$5 drugs. This was similar to the study of Tikur Anbesa Specialized Hospital,[41] University of Gondar Teaching Hospital,[33] Hiwot Fana Specialized University Hospital,[4] Dire Dawa,[41] Zewuditu Memorial Hospital,[1] Jimma University Specialized Hospital,[32] Netherlands,[42] India,[43] and Switzerland.[44]

In the present study, patients whose hospital stay was $\geqslant$7 days were 4.4 times more likely to have DRPs than patients whose hospital stay $<$7days. This was consistent with that of the University of Gondar.[33] On the contrary, in Jimma University Specialized Hospital, the length of hospital stay did not predict the occurrence of DRPs.[32] This is due to the patients who had prolonged hospital stays may develop different nosocomial infections that need complex therapeutic management.

In our study, patients who have comorbidity were 1.8 times more likely to have DRPs than patients who have not comorbidity. This was consistent with the finding of the University of Gondar and Hong Kong,[11]and inconsistent to Tikur Anbessa Specialized Hospital, Jimma University

Table 3. Multivariate logistic regression analysis result of factors associated with DRPs among patients with infectious disease admitted to Medical Wards of WURH from June to August, 2019.

Variables	Category	DRPs		COR (95%CI)	AOR (95%CI)	p-value
		Yes (n = 123)	No (n = 49)			
Sex	Female	47 (35.6%)	19 (41.46)	1		
	Male	76 (64.4%)	30 (58.54)	1.024 (0.894–6.523)[a]		
Age (years)	18–34	42 (34.146)	26 (53.06)	1		
	35–54	53 (43.089)	19 (15.447)	1.727 (0.924–5.856)[a]		
	>55	28 (22.764)	4 (8.163)	4.33 (1.034–11.973)[a]		
Area of residence	Urban	66 (53.658)	29 (59.183)	1		
	Rural	57 (46.341)	20 (40.816)	1.252 (0.740–3.542)[a]		
Presence of comorbidity	No	70 (56.910)	39 (79.591)	1	1	0.016
	Yes	53 (43.089)	10 (20.408)	2.952 (0.274–6.740)[a]	2.107 (1.185–4.158)[b]	
Polypharmacy (n ⩾ 5)	No	77 (62.601)	39 (79.59)	1	1	0.010
	Yes	46 (37.398)	10 (20.408)	2.329 (0.957–9.694)[a]	2.505 (1.863–11.131)[b]	
Length of hospital stay (days)	<7	58 (43.94)	41 (42.45)	1	1	0.037
	⩾7	65 (56.06)	8 (57.55)	5.743 (1.580–13.572)[a]	4.396 (1.964–7.310)[b]	

AOR: adjusted odds ratio; CI: confidence interval; COR: crude odds ratio.
[a]Shows significant at p-value 0.25.
[b]Shows statistically significant at p-value 0.05.

Specialized Hospital, and Hiwot Fana Specialized University Hospital.[4,32,37] These differences may be due to differences in category of comorbidities (renal, vascular, and metabolic disorders) and the number of diseases taken as comorbidity in different areas in which having two comorbidities is not like having five or more. This is because the more disease presents, the more drugs are prescribed for their specific indication which can have the chance of drug-drug interaction and the unsafe drug might be prescribed. In our study, some comorbidities maybe were unnoticed or not really reported by the patient or not yet diagnosed, and thus an underlying bias in data collection may be present.

In the current study, socio-demographic variables like the area of residence, sex, and age did not have an association with the presence of DRP. This was similar to Hiwot Fana Specialized University Hospital, Adama Hospital Medical College, East Ethiopia, and Zewuditu Memorial Referral Hospital.[1,4,38] On the contrary, the study done in Jimma University Specialized Hospital indicated that age >50 years were predictors of DRP.[7] In Bahir Dar, Northwest Ethiopia, younger ages were associated with inappropriate antibiotics.[16]

Strength and limitation of the study

As the limitations, the impacts of the DRPs on the disease outcome of the infectious disease patients were not measured. Besides, we only evaluate DRPs among infectious disease patients admitted to the medical ward which lacks generalizability. As the strength, the study was prospective, and information on different organ function tests (renal, liver), a diagnostic test of electrocardiography, and laboratory tests of serum electrolytes and complete blood count were used to assess any DRPs.

Conclusion

The magnitude of DRPs in infectious diseases admitted to the medical ward in WURH was found to be high. Unnecessary drug therapy and non-adherence were the most and the least prevalent DRPs, respectively. Antibiotics were the common class of drugs associated with DRPs. Ceftriaxone, gentamycin, and vancomycin were the most common individual drugs agents encountered in DRPs. Polypharmacy, comorbidity, and duration of hospital stay were determinants of DRPs. Hence, WURH should establish a system for reporting DRPs in the medical ward of the hospital as it may enhance to start interventions. To prevent the inappropriate use of drugs, especially antibiotics, different health care professionals should work together. In addition, the clinical pharmacy service should be established to tackle any DRPs in our study area. The role of clinical pharmacists should also be geared to identify, solve, and prevent DRPs rather than overlapping on the already existing dispensing pharmacists.

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Author contributions

FB and GF contribute in the proposal development, methodology, analysis, and preparing the first draft of the manuscript. KB, DD, and JS contributed to the methodology and editing of the manuscript. The final revised manuscript was approved by all authors before submission.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

Ethical approval was obtained from the Research Ethics Review Committee (RERC) of the Institute of Health Sciences of Wollega University with reference number 025CHRT/11. Before the study was undergone, permission was obtained from the medical director of the WURH.

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Informed consent to participate

The benefit and harm of the study were explained to patients participated in the study and written informed consent was obtained from participants. The name of patients and health care providers were not written on the questionnaire to ensure confidentiality.

Informed consent for publication

No individual person's personal details, images, or videos are being used in this study.

Data availability

The materials used while conducting this study are obtained from the corresponding author on reasonable request.

Trial registration

The study was registered researchregistry.com with a unique reference number of "researchregistry5698.

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Supplemental material

Supplemental material for this article is available online.

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