

Assessing Antibiotic Use Pattern by Severity of Clinical Presentation among COVID-19 Inpatients in a Tertiary Care Hospital - A Retrospective Study

Vipin Kumar Jain¹, Sarfaraz Alam Khan², Girish B. Ramteke³, Megha Jain⁴, Ritesh Kumar Upadhyay⁵, Dileep Dandotiya⁶

¹Associate Professor, Department of Pharmacology, Chhindwara Institute of Medical Sciences, Chhindwara (M.P.)

²Professor and Head, Department of Pharmacology, Chhindwara Institute of Medical Sciences, Chhindwara, (M.P.)

³Professor and Dean, Birsa Munda Government Medical College, Shahdol, (M.P.)

⁴Associate Professor, Department of Dentistry, Chhindwara Institute of Medical Sciences, Chhindwara, (M.P.)

⁵Associate Professor, Department of Community Medicine, Government Medical College, Singrauli (M.P.)

⁶Assistant Professor, Department of Community Medicine, Chhindwara Institute of Medical Sciences, Chhindwara, (M.P.)

Received: 01-09-2025 / Revised: 15-10-2025 / Accepted: 21-11-2025

Corresponding author: Dr. Megha Jain

Conflict of interest: Nil

Abstract

Introduction: COVID 19 is an infectious disease caused 772 million confirmed cases and over 7 million deaths worldwide as per WHO. There is lack of data on drugs used in COVID-19 patients with few studies evaluating the treatment patterns as per severity.

Objectives: 1: To study the drug utilization pattern in COVID- 19 patients. 2. To study the antibiotic utilization according to severity of the disease in covid-19 patients.

Methodology: This retrospective, single-centre observational drug utilization study was conducted in patients admitted in our tertiary care centre between 1st April 2021 to 31 December 2021. Data was analysed for demographic details, clinical features and severity based on SpO₂ % along with different class of drugs prescribed like anti-inflammatory, anti-viral, antibiotics. Further antibiotics utilized in severe and other non-severe (mild, moderate) group were classified in different groups.

Results: Out of 243 patients, 44% were mild and 12% were in severe category. The most common age group was 51-60 years (29%) and males were predominated. Overall, in Antibiotics, 48.97% patients were received piperacillin and tazobactam, 46.50% were received doxycycline, 37.8% received azithromycin. In this study prescriptions having >8 drugs per encounter were 41% and >10 drugs per encounter were 51.85 %.

Conclusion: Overprescribing of antibiotics along with off label use of drugs was encountered in most cases which may be attributed to limited research in drugs utilised in COVID-19 patients. Polypharmacy needs to be addressed for promoting rational use of drugs.

Keywords: COVID-19, Drug Utilization, Antibiotics, Polypharmacy.

This is an Open Access article that uses a funding model which does not charge readers or their institutions for access and distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>) and the Budapest Open Access Initiative (<http://www.budapestopenaccessinitiative.org/read>), which permit unrestricted use, distribution, and reproduction in any medium, provided original work is properly credited.

Introduction

Novel corona virus causing corona virus disease 2019 (COVID-19) has considerable impact on health care systems all over the world and caused approximately 777 million confirmed cases and over 7 million deaths worldwide as per WHO. [1] COVID-19 is very contagious and has a wide spectrum of presentations from asymptomatic to severe illness including sepsis induced shock and involvement of multi organ failure associated with

ARDS (acute respiratory distress syndrome). [2] Male sex and genetic predisposition to covid-19 infection with progression to severity and response to medicines are under investigation as potential contributors. [3,4,5] There is a lack of data on drug use (monotherapy and polytherapy) in COVID-19 patients. Few studies have been done in United States which evaluated the treatment patterns of first year of pandemic including pregnant women

and as per disease severity levels. [6,7] The government of India, Ministry of Health and Family Welfare, Directorate general of Health Services (Emergency medical Relief (EMR) Division), recommended treatment as per severity level for mild to moderate cases and for moderate to severe cases of COVID-19 which included hydroxychloroquine and low molecular weight heparin and steroid respectively. [8] The antibiotics were largely used in COVID-19 patients to treat superimposed or co-infection caused by relevant bacteria. During the peak of first wave of COVID-19, it was found that antimicrobial especially azithromycin used in excess to other medicine in outdoor patients in spite of negative recommendation by central competent authority. [9] It was a well-known fact that widespread use of antibacterials with various other drugs can cause possible adverse events which raise concern and attention to clinician. [10] Polypharmacy is very common in medical practices, more so in critical patients. It has been reported to increase risk of hospital admission and adversely affect the clinical outcome along with the increased adverse drug events in COVID-19 patients. [11] There are limited research available for understanding the drug utilization in COVID-19 patients, therefore we conducted a retrospective study to assess the drug utilization pattern in admitted cases of COVID-19. Additionally with the knowledge of population characteristics and antibiotic prescribing details, there is possibility of developing a hypothesis related to specific antibiotic utilization pattern and improve patient care and minimize the adverse drug reactions in COVID-19 patients.

Material and Methods:

Participants and data sources: This retrospective, single-centre observational drug utilization study enrolled 243 patients who had been admitted at our institute a tertiary care centre of southwest India between 1st April 2021 to 31 December 2021. Patient confirmed positive for COVID-19 disease by detection of SARS-CoV-2 RNA nucleic acid amplification with probe detection (RT-PCR) as per WHO interim guidance [12] were only included in the study whereas COVID -19 (RT-PCR negative) patients were excluded. The predefined information of patients was extracted from medical record department (MRD) in a patient profile form which was designed to gather demographic details like age, gender, date of admission (DOA), date of discharge (DOD), past medical history, underlying comorbidities, diagnosis and treatment which included sign and symptoms, chest computed tomographic (HRCT chest) scans and details of medicines like dose, duration, frequency, route. The different outcomes like discharge, discharge on

request (DOR), leave against medical advice (LAMA), shifted to COVID Care Centre (CCC) and home quarantine along with the total duration of stay in hospital after admission were also observed. Patients were classified into mild, moderate and severe category based on AIIMS/ICMR-COVID-19 National Task Force/ Joint Monitoring Group (Dte.GHS) Ministry of Health & Family Welfare, Government of India guidelines of 17th May 2021. [13]

Medication and outcomes: We further categorized utilized drugs in Anti-inflammatory, Antibiotics, antivirals, anticoagulants, antiplatelets, steroids, antiulcer and other class of drugs like insulin and oral antidiabetic, drugs for cough, antihistaminics, antimalarial, anthelmintic etc. We had evaluated the total number of drug classes, along with number of drugs per prescription. Most common drug prescribed, and most common prescribed class of drug was found out to know which drug is consumed most. Further in present study, antibiotics were classified into β -lactam group, tetracycline group, macrolides and fluoroquinolone group to evaluate their utilization pattern.

After that we found out the statistical significance in all groups of antibiotics which were utilized in severe and other non-severe (mild, moderate) group by applying chi-square statistical test. we had evaluated the number of patients who were received broad spectrum and higher antibiotics after escalation from empirical treatment due to worsening of their clinical condition, higher oxygen requirement and ventilatory support.

Data Analysis: All data was entered in Microsoft excel. Analysis was done by SPSS software 23.0 and expressed in actual numbers, mean with SD, percentage and applying chi-square statistical test to compare the variables between the severity groups.

The present research aimed to observe pattern of prescription of COVID-19 after obtaining clearance from the institutional ethical committee.

Observation and Results:

Out of 243 patients enrolled in our study, males were 75.31 % and 24.69% were females. Age group predilection was 51-60 year (29%), followed by 41-50 year (20.58%), 31-40 year (19.34%) and least were the 0-10-year age group affecting only one patient. The mean age was 40.66 ± 34.579 . [Table1] The stay in hospital for period of less than 10 days was 44 % followed by 32 % for less than 5 days, 16 % for up to 15 days. Out of total 243 patients 4 patients (1.65%) admitted for more than 25 days. The mean number of stay in hospital was 7.71days.

Table 1: Distribution of Age-group and Gender of the patients

Age/gender	Male (%)	Female (%)	Total
0-10	0	1 (0.41)	1 (0.41)
11-20	3 (1.23)	3 (1.23)	6 (2.47)
21-30	23 (9.47)	5 (2.06)	28 (11.52)
31-40	34 (13.99)	13 (5.35)	47 (19.34)
41-50	38 (15.64)	12 (4.94)	50 (20.58)
51-60	52 (21.40)	19 (7.81)	71 (29.21)
61-70	27 (11.11)	5 (2.06)	32 (13.17)
71-80	6 (2.47)	2 (0.82)	8 (3.29)
Total	183 (75.31)	60 (24.69)	243

Table 2: Distribution of the Patient Symptoms

Patient Symptoms	N (%)
Fever	158 (65.02)
Cough	160 (65.84)
Shortness of breath	135 (55.55)
Common Cold	22 (9.05)
Chest Pain	11 (4.53)
Ghabrahat	4 (1.65)
Loose motion	2 (0.82)
Headache	1 (0.41)
Vomiting	6 (2.47)
Bodyache	4 (1.65)
Weakness	32 (13.17)
Sore throat	13 (5.35)
Oedema in legs	1 (0.41)
Decrease appetite	3 (1.23)
Loss of taste	1 (0.41)
Pain in legs	1 (0.41)
Dizziness	1 (0.41)
Loss of smell	1 (0.41)
Abdominal Pain	1 (0.41)

In our study, total 19 different type of symptoms were present in covid-19 infected patients, and the most common symptom was the cough 65.84% followed by fever and shortness of breath 65.02% and 55.55% respectively. 13.17% patients have

generalized Weakness and 9 % have common cold as primary symptoms. Sore throat was present in 5.35% of patients and Chest pain which was nonspecific in nature was present in 4.53 % of covid-19 patients in our study. [Table 2]

Table 3: Distribution of Number of drugs per prescription

No of drugs per prescription	No of prescriptions (243)	Percentage (%)
≤6	17	6.99
7-10	100	41.15
>10	126	51.85

Out of total patients, HRCT data was available for 41.97 %. Of these 5.35% had HRCT score of 10/25, 4.93% had score of 14/25, and 4.11% patients had score of 17/25 and only two patients have score more than 20/25. The average number of drugs per prescription were 11.01% in our study. In our study prescriptions having <6 drugs per prescription were 6.99%, >8 drugs per

encounter were 41% and >10 drugs per encounter were 51.85 %. [Table 3] Total 68% patients were discharged from hospital in stable condition and 13.17% left against medical advice, 9.05% were shifted to covid care centre, 5.35% were discharged on request, 2.88% were sent to home isolation, 1.23% were gone absconded and one patient discharged against medical advice.

Table 4: Antibiotics distribution among all admitted patients (n=243)

Antibiotics	N (%)
Piperacillin and Tazobactam	119 (48.97)
Doxycycline	113 (46.50)
Azithromycin	92 (37.8)
Meropenem	70 (28.81)
Cefotaxime	15 (6.17)
Ceftriaxone	13 (5.35)
Amoxicillin / Clavulanic acid	3 (1.23)
Levofloxacin	3 (1.23)
Total	428 (100)

Under Antibiotic usage, in our study, 48.97% patients received piperacillin and tazobactam followed by 46.50% doxycycline, 37.8% azithromycin and 28.81% Meropenem. Third

generation cephalosporin, ceftriaxone and cefotaxime were utilised by 6.17 % and 5.35% respectively. Fluoroquinolone antibiotics was least utilized (0.82 %). [Table 4]

Table 5: Association between different groups of antibiotics as per severity

Antibiotics	Mild	Moderate	Severe	Total (n=428)	P value
β Lactam group	78	106	36	220	0.000014
Tetracycline group	51	47	15	113	
Macrolide group	64	18	10	92	
Fluoroquinolones group	1	1	1	3	

Mild- SpO₂ >93%, Moderate - SpO₂ 90%≤93%, Severe- SpO₂ <90%

Out of 243 patients, 107 (44%) were mild, 106 (43%) were moderate and 30 (12%) were in severe category. [Table 5]

After classifying antibiotics in different groups, β lactam group received by 220 patients, tetracycline group received by 113 patients followed by macrolide group and fluoroquinolones group which received in 92 patients and three patients respectively. Further analysis of antibiotics utilization in Covid-19 patients done by categorizing the patients into mild, moderate and severe category in between antibiotic groups. Out of 220 patients who received β lactam group

antibiotics, 36/220 patients were severe and 106/220 were moderately affected with covid-19 and 78/220 were mild category patients. Total 113 patients received doxycycline in tetracycline group. Out of this, 15/113 belonged to severe category of patients and 47/113 were of moderate category and 51/113 were of mild category.

In macrolide group total 92 patients received azithromycin in oral dose form although 10/92 of them were severe patients. A High positive correlation was found among the utilization of antibiotics in different category of illnesses. [Table 5]

Table 6: Distribution of various ADRs (n=42)

ADR	N (%)
High blood pressure	10, Mild-6, Moderate-4
Hyperglycaemia in diabetic patients	14 (Moderate)
Hyperglycaemia in Non-diabetic patients	4, Mild-3, Moderate-1
Diarrhoea	4 (Mild)
Rashes	3 (Mild)
Hypoglycaemia	1 (Moderate)
Abdominal pain (Spasmodic)	1 (Mild)
Blood in stool	1 (Moderate)
Nasal bleeding	1 (Moderate)
Haematuria	1 (Mild)
Pain in sinus area	1 (Moderate)
Irritability	1 (Mild)

In present study, total 42/243 (17.28%) ADRs were recorded and identified as 11 different types. [Table 6]

Greater percentage of ADRs were shared by metabolic related ADRs like increased blood sugar and high blood pressure 42.85% and 23.80% respectively followed by 7.14 % related to nasal

bleeding, haematuria and blood in stool. Diarrhoea and rashes present in 9.52% and 7.14% respectively.

Discussion: In our study, male population was more than the female. Another study also reported the similar findings. [14] However no gender difference was observed in other study. [15] The most affected age category in our study was 51-60 year (29.21%) which is similar to other studies, and this may be due to presence of comorbidities mostly like hypertension and diabetes and other cardiovascular disorders as well as probably this age group is common earning age group in our study. [16] Severity percentage of patients in our study was 12.35% similar to findings of another study. [17]

In our study prescriptions having >8 drugs per encounter were 41% and >10 drugs per encounter were 51.85 % which were indicating polypharmacy trend in accordance with findings of another study. [18] One of the Chinese studies found that treating physician tried good number of drugs and combinations to treat covid-19 infection in a single hospital setup. [15] This polypharmacy trend might be due to no specific treatment recommended at that time of pandemic and further advancements and changes were continuing and this may be one of the reasons for polypharmacy in our study. [19] Average number of drugs/prescriptions was 11.01 (2676/243) which was higher than WHO recommended range (1.6-1.8) although other study reported it to be 6.97. [18]

In Covid -19 infected patients, chief complaints during hospital visit were fever, cough, cold and shortness of breath in all over world. During first year of pandemic in June 2020 and December 2020 the common complaint was fever, cough, generalised weakness and cold. Afterwards loss of taste and smell all along with fever, cough and cold were commonly found in patients with covid -19 infection due to different mutations in virus. In our study, the most common symptom was the cough 65.84% followed by fever 65.02% which was similar to finding of other studies. [20,15]

In this study most widely used antibiotic was β -lactam group 77.78% followed by Doxycycline 46.50% and Azithromycin 37.8% which is similar to findings of other studies [20, 21] although different from another study. [17] During first wave of pandemic of covid-19 Azithromycin was widely used in treatment as compared to doxycycline in second wave. [17]

In present research, antibiotics were escalated to broad spectrum and higher category based on patients' clinical condition and oxygen saturation status along with the need of oxygen supplement by various methods including Nasal prongs,

NRBM (Nonrebreather Mask), BiPAP and invasive ventilatory support. Out of 243 patients, seven patients who were started on I.V. (intravenously) piperacillin and tazobactam later on shifted to meropenem due to fall in oxygen saturation and worsening of their clinical condition. Similarly, eight patients initially put on I.V. ceftriaxone, with due course in hospital have been developed increased HRCT score probably by developing COVID-19 pneumonia, further shifted to meropenem in five patients and piperacillin and tazobactam in three patients. Due to mild nature of disease as per severity, three patients, in initial days of admission started on oral antibiotics like azithromycin and doxycycline later on changed to higher antibiotic class like piperacillin and tazobactam and ceftriaxone by I.V. route.

In our study based on guidelines patients' severity categorised into 3 level: mild, moderate and severe. [13] Highly positive co-relation was found among the utilization of antibiotics in different category of illnesses. The result is significant at $p < 0.05$.

In present study nearly all patients received more than one group of antibiotics however non-severe group of patients were more likely to receive it which was in contrast to findings of another study [20] where use of antibiotics was more in severe group compared to non-severe group. In our study this may be due to, being a tertiary care setup all admitted patients with low O₂ saturation and ill state received empirical antibiotic treatment. There are studies which recommended empirical antibacterial treatment in view of superinfection which were quite common in covid-19 patients having low oxygen saturation and can cause increase mortality. [22] Although there are few studies which were stressed out to evade the use of antibacterials primarily the combination of broad-spectrum antibiotics. [23] It was found that β -lactam group of antibiotics were predominated over all other groups of antibiotics in our study. The viral infection can cause serious lung injury by bacterial superinfection and co infection which warn initiation of empirical antibiotic therapy in patients of covid -19.

In previous studies it was found that relevant bacterial pathogen was common for causing Community acquired pneumonia and hospital acquired pneumonia before and after pandemic.

Therefore, utilization of β -lactam group of antibiotics with either a macrolide like azithromycin or a fluoroquinolone preferred, or β -lactam group of antibiotics can be used as monotherapy in these [covid-19] patients. [24, 25] In our study the occurrence of ADRs may be due to polypharmacy and widespread use of antibacterials along with corticosteroids and Blood

thinners supported by findings of another research. [15]

Conclusion:

Polypharmacy was prominently observed in more than 50 % of the patients. Most widely used antibiotics were β -lactam group followed by tetracycline and macrolide group respectively. Although COVID-19 is a viral disease, but antibiotics have been used to prevent secondary bacterial infections.

References:

1. Organization W.H. WHO Coronavirus (COVID-19) Dashboard. Accessed June 2025. <https://data.who.int/dashboards/covid19/cases?n=c>
2. Zaim S, Chong JH, Sankaranarayanan V, Harky A. COVID-19 and Multiorgan Response. *Current Problems in Cardiology*. 2020;45(8):100618–100618.
3. Jin JM, Bai P, He W, Wu F, Liu XF, Han DM, Liu S, Yang JK. Gender Differences in Patients With COVID-19: Focus on Severity and Mortality. *Front Public Health*. 2020 Apr 29; 8:152.
4. Fricke-Galindo I, Falfán-Valencia R. Genetics Insight for COVID-19 Susceptibility and Severity: A Review. *Front Immunol*. 2021 Apr 1; 12:622176.
5. Charitou T, Kontou PI, Tamposis IA, Pavlopoulos GA, Braliou GG, Bagos PG. Drug genetic associations with COVID-19 manifestations: a data mining and network biology approach. *Pharmacogenomics J*. 2022 Dec;22(5-6):294-302.
6. Westhoff WJ, Smith LH, Wyszynski DF, Hernandez-Diaz S. COVID-19 pharmacotherapy utilization patterns during pregnancy: International Registry of Coronavirus Exposure in Pregnancy. *Pharmacoepidemiol Drug Saf* 2022; 31:804–9.
7. Lin KJ, Schneeweiss S, Tesfaye H, et al. Pharmacotherapy for hospitalized patients with COVID-19: treatment patterns by disease severity. *Drugs* 2020; 80:1961–72.
8. Clinical Management Protocol: COVID-19. Ministry of Health & Family Welfare, Government of India directorate general of health services (EMR division), Available from: <https://www.mohfw.gov.in/pdf/ClinicalManagementProtocolforCOVID19>. Pdf accessed June 2025
9. Douglas, M., Moy, S., and Hernandez, N. (2021). Impact of COVID-19 on Outpatient Antimicrobial Prescribing Patterns in New York City. *Infect. Dis. Clin. Pract. (Baltim Md)*. 29 (6), e352–e355.
10. Fan Z, Chen L, Li J, et al. Clinical Features of COVID-19-Related Liver Functional Abnormality. *Clin Gastroenterol Hepatol* 2020; 18:1561-6.
11. Potemski F, Bilimoria K: Polypharmacy in the age of COVID-19: medication management during a pandemic. *University of Toronto Medical Journal* 2021, 98(1).
12. World Health Organization. Clinical management of severe acute respiratory infection when Novel coronavirus (2019-nCoV) infection is suspected: Interim Guidance. January 28, 2020.
13. [https://www.aiims.edu/images/pdf/notice/C_OVID_Management_Algorithm_170521%20\(1\).pdf](https://www.aiims.edu/images/pdf/notice/C_OVID_Management_Algorithm_170521%20(1).pdf) Accessed June 2025.
14. Caruso PF, Angelotti G, Greco M, Albini M, Savevski V, Azzolini E, Briani M, Ciccarelli M, Aghemo A, Kurihara H, Voza A. The effect of COVID-19 epidemic on vital signs in hospitalized patients: a pre-post heatmap study from a large teaching hospital. *Journal of Clinical Monitoring and Computing*. 2022 Jun;36(3):829-37
15. Sun F, Kou H, Wang S, Lu Y, Zhao H, Li W, Zhou Q, Jiang Q, Cheng Y, Yang K, Zhuo L, Xu Y, Wu D, Zhan S, Cheng H. An analytical study of drug utilization, disease progression, and adverse events among 165 COVID-19 patients. *Ann Transl Med*. 2021 Feb;9(4):306.
16. Vittoe SE, Govil P, Baglivo A, Beebe E, Garry EM, Gatto NM, Lasky T, Chakravarty A, Bradley MC, Perez-Vilar S, Rivera DR, Quinto K, Clerman A, Rajpal A, Frajzyngier V. A Descriptive Cohort Study of Drug Utilization Patterns Among Patients Hospitalized With Coronavirus Disease 2019 in the United States, January 2021-February 2022. *Open Forum Infect Dis*. 2023 Jul 10;10(7):ofad339.
17. Ramanath KV, Venugopal S, Shadakshari A, Pradhan NK, Abhinavi B, Kaur H, Jacob L. Drug Utilization Evaluation in COVID-19 Hospitalized Patients: A Retrospective study. *Journal of Advances in Medicine and Medical Research*. 2022;34(20): 319-337.
18. Manjhi PK, Singh SK, Kumar R, Singh S, Priya A, Nishi. Drug Utilisation Study among COVID-19 Inpatients in a Tertiary Care Hospital in Eastern India. *International Journal of Current Research and Review*. 2021;13(11),S210-214.
19. General Office of the National Health Commission. General Office of Administration of Traditional Chinese Medicine. Diagnostic and treatment protocol for Novel Coronavirus Pneumonia (trial third version). January 22, 2020.
20. Hema K, Moulika P, Kukunuri DK, Saidhulu G. Evaluation of Drug Utilisation pattern and clinical presentation in Covid19 patients based

- on the disease severity. *Int. J. Nov. Tren. Pharm. Sci.* 2021;11(2): 25-33.
21. Orlando V, Coscioni E, Guarino I, Mucherino S, Perrella A, Trama U, et al. Drug-utilisation profiles and COVID-19. *Sci Rep* 2021; 11:8913.
22. Uyeki TM, Bernstein HH, Bradley JS, Englund JA, File TM, Fry AM, Gravenstein S, Hayden FG, Harper SA, Hirshon JM, Ison MG, Johnston BL, Knight SL, McGeer A, Riley LE, Wolfe CR, Alexander PE, Pavia AT. Clinical Practice Guidelines by the Infectious Diseases Society of America: 2018 Update on diagnosis, treatment, chemoprophylaxis, and institutional outbreak management of seasonal influenza. *Clin Inf Dis.* 2019;68: 895–902.
23. Jin YH, Cai L, Cheng ZS, et al. A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (standard version). *Mil Med Res* 2020; 7:4.
24. Metlay JP, Waterer GW, Long AC, Anzueto A, Brozek J, Crothers K, Cooley LA, Dean NC, Fine MJ, Flanders SA, Griffin MR, Metersky ML, Musher DM, Restrepo MI, Whitney CG. Diagnosis and Treatment of Adults with Community-acquired Pneumonia. An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America. *Am J Respir Crit Care Med.* 2019 Oct 1;200(7):e45-e67.
25. Metlay JP, Waterer GW. Treatment of Community-Acquired Pneumonia During the Coronavirus Disease 2019 (COVID-19) Pandemic. *Ann Intern Med.* 2020 Aug 18;173(4):304-305.