Archives of Medicine©
14 (4) 2022 : 001-006 • MINI REVIEW

Evidence-based approach to fever and fever of unknown origin in Fiji

Abhijit Gogoi*, Judith Apondi Oremo, Ivor Xavier Tsika, ElisonJimmy, Alphones Kuma, Muhammed Ilyas Harun, Mercy Gogoi
Umanand Prasad School of Medicine and Health Sciences, The University of Fiji, Saweni, Lautoka, Fiji

SUMMARY

While Fiji a South Pacific Country is an archipelago of more than 300 islands. With an approximate population of 889, 953, Fiji faces a growing burden of several communicable diseases and non-communicable disease including fever of unknown origin. Surveillance data suggest that Fever has become increasingly common in rural areas of Fiji and is more frequent amongst acute respiratory infections, dengue and viral infections. Appropriate measures are taken by the Ministry of Health Fiji to reduce the potential for relapse and reinfection in clinical cases, by encouraging proper hand hygiene of food and drink handlers, water and sanitation agencies to review current sanitation practices and vaccination policy targeting epidemiologically relevant populations. This article initial aim is to examine fever of unknown origin around the Pacific and Fiji but due to limited data available we mainly focus on cases of diseases that have at least fever as one of the associated symptoms in 2018 within the four divisions of Fiji namely the Northern Central, Eastern and Western regions. A retrospective study with data obtained from the Fiji Ministry of Health 2018 and National Notifiable Disease Surveillance System Weekly Bulletin. Acute respiratory infection is the leading cause of FUO and fever in Fiji with an average of 64% cases in 2018 followed by Dengue at 14%. Patient in significant numbers continue to present fever/FUO due to a wide range of diseases. Future prospective data collection is recommended to identify the cause and trends, which inform the Ministry of Health and future research priorities hence allowing the development of appropriate policies and clinical guidelines for management of fever/FUO.

Keywords: Antibiotic; Fiji; Pacific; Dengue Fever ; Fever of Unknown Origin (FUO) ; Pyrexia of Unknown Origin (PUO) ;Viral infections (Viral illness infection); Acute Respiratory Infection (ARI)

Address for correspondence:

Dr. Abhijit Gogoi
Umanand Prasad School of Medicine and Health Sciences, the University of Fiji, Saweni, Lautoka, Fiji
E-mail: abhijitgg25@gmail.com

Word count: 2345 **Tables:** 04 **Figures:** 08 **References:** 22

Received: 25 March, 2021, Manuscript No. ipaom-22-12523; **Editor Assigned:** 28 March, 2022, Pre QC No. P-12523; **Reviewed:** 17 Apr, 2022, QC No. Q-12523; **Revised:** 22 March, 2022, Manuscript No. R-12523; **Published:** 27 April, 2022.

INTRODUCTION

Fevers of unknown origin still remain one of the most difficult diagnostic challenges in medicine. While technology such as F-fluorodeoxyglucose positron emission tomography (FDG-PET) [1] exists, clinicians often have to ordernon-clue based imaging and specific testing early in FUO work up. Fever of unknown origin may be caused by over 200 malignant/neoplastic, infectious [1]. rheumatic/ inflammatory, and miscellaneous disorders, therefore test ordered may be inefficient/misleading. Neurons in both the preoptic anterior and posterior hypothalamus receive two kinds of signals to control the human body temperature. One signal from the peripheral nerves transmit information from warmth or cold receptors in the skin and the other transmit signal from temperature of the blood bathing the region. These two are integrated by thermoregulatory center of the hypothalamus to maintain the normal temperature [2]. Normal human body temperature ranges between 36.5°C to 37.5°C. Other sites of the body have the following normal temperature, mouth 36.8°C, axilla 35.4°C, rectum 37.7°C and ear 36.8°C [3-5]. Fever, also known as pyrexia is defined as an elevation of the human body temperature that exceeds the normal daily variation (35.5°C-37.5°C) and occurs in conjunction with an increase in the hypothalamic set point, that is 37°C to 39°C. Fever is caused by infections either bacterial [6]. viral or fungal that affects the ears, lungs, throat, skin bladder or kidney. Other causes of fever include heat exhaustion, sunburn, conditions that causes inflammation such as rheumatoid arthritis, adverse drug reactions of medications, vaccination and immunizations, blood clots, autoimmune disorders, hormone disorders and illegal drug use. Classified in two ways, acute or chronic fever and continuous, intermittent, remittent or relapsing fever. Acute fever occurs in less than 7 days and is characteristics of infectious diseases such as malaria and viral-related upper respiratory tract infection. Chronic or persistent fevers is fever that occurs and lasts for more than or equal to two weeks' duration and are typical of chronic bacterial infections such as tuberculosis, viral infections such as HIV, cancers and connective tissue diseases. However, any cause of acute fever can become persistent [6] or chronic if untreated. Continuous fever or sustained fever **(Fig. 1-4)** is defined as fever that does not fluctuate more than about 1°C during 24 hours, but at no time touches normal and are characteristic features of lobar and gram-negative pneumonia, typhoid, acute bacterial meningitis, urinary tract infections, among others [7,8]. Pyrexia of Unknown Origin (PUO)also known as fever of unknown origin (FUO) was first defined by Petersdof in

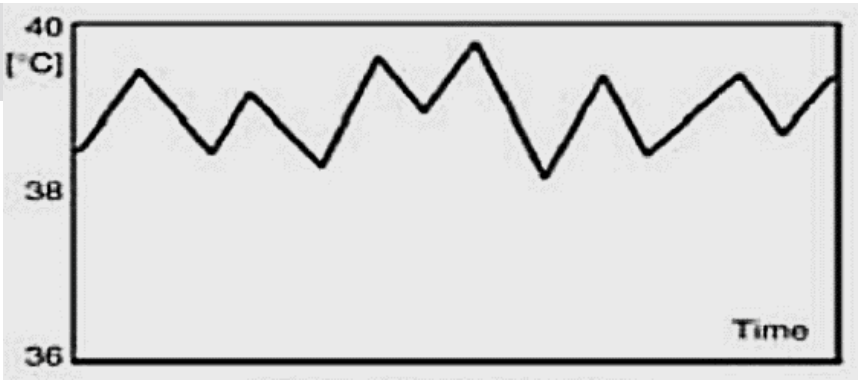


Fig. 1. Continuous Fever Pattern Seen in Viral Pneumonia, Typhoid and Meningitis

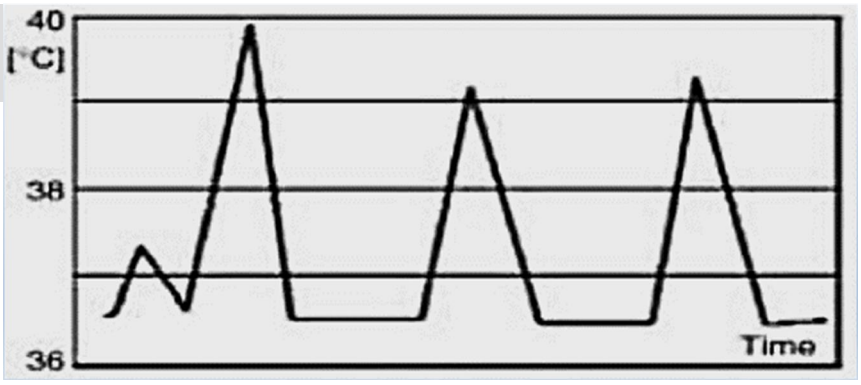


Fig. 2. Intermittent Fever Pattern as seen in Malaria, Leptospirosis, Sepsis and TB.

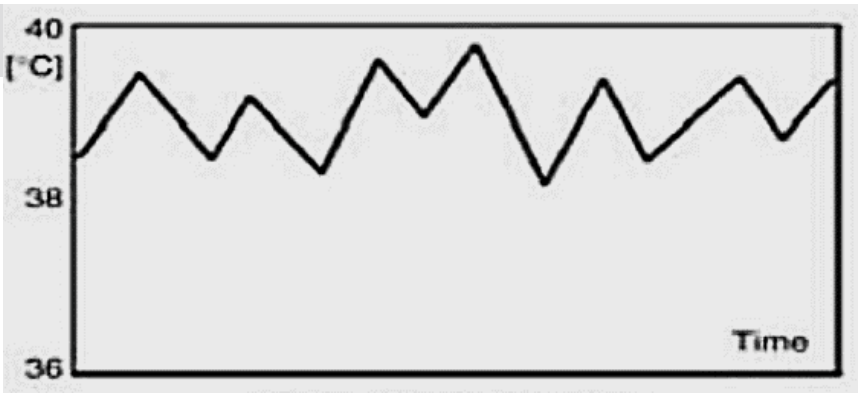


Fig. 3. Remittent Fever Pattern: Seen in rheumatic fever

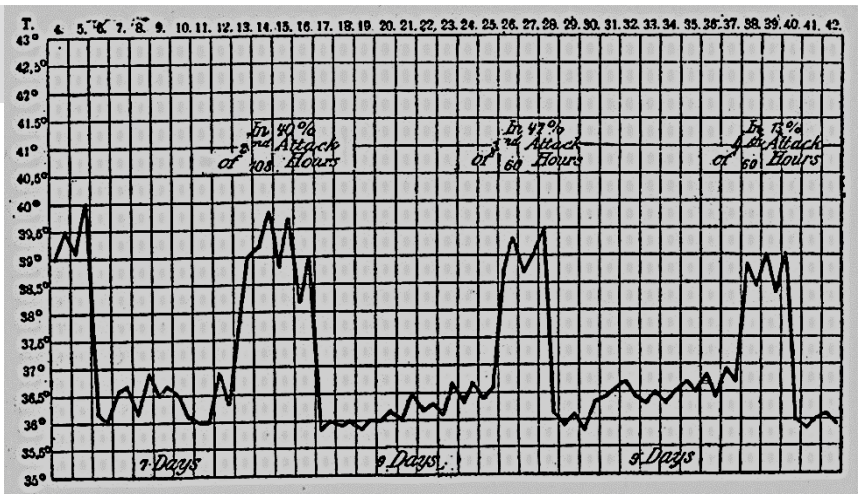


Fig. 4. The Pattern of Relapsing fever as seen in Malaria and Lymphoma

1961 but over the year was refinedto any fever greater than or equals to 38.3°C several occasion with the duration of more than three weeks the least with no known diagnosis after many laboratory tests despite one week of inpatient investigations or three outpatient visits [9]. Infections account for approximately 25 to 30% of cases usually the most likely cause of FUO [10,1] followed by neoplasm and noninfectious inflammatory [11]. FUO can also be

Fig. 5. Pie Graph of Infected Patients of Northern Division 2018.

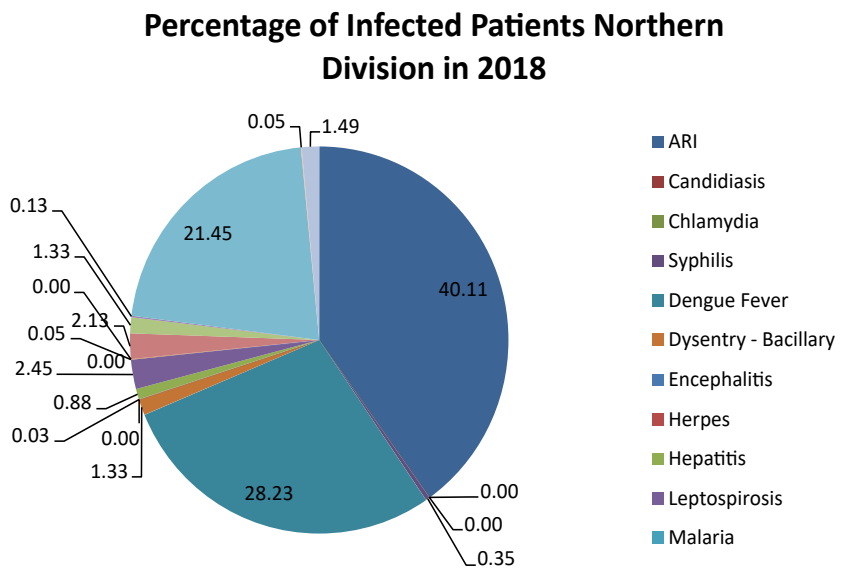


Fig. 6. Pie Graph of Infected Patients of Eastern Division 2018.

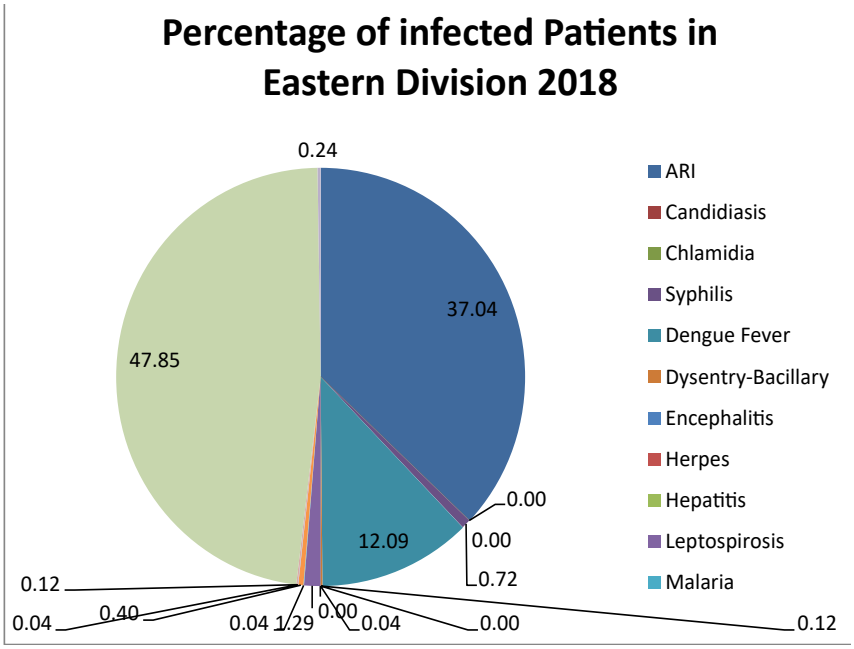


Fig. 7. Pie Graph of Infected Patients of Central Division 2018.

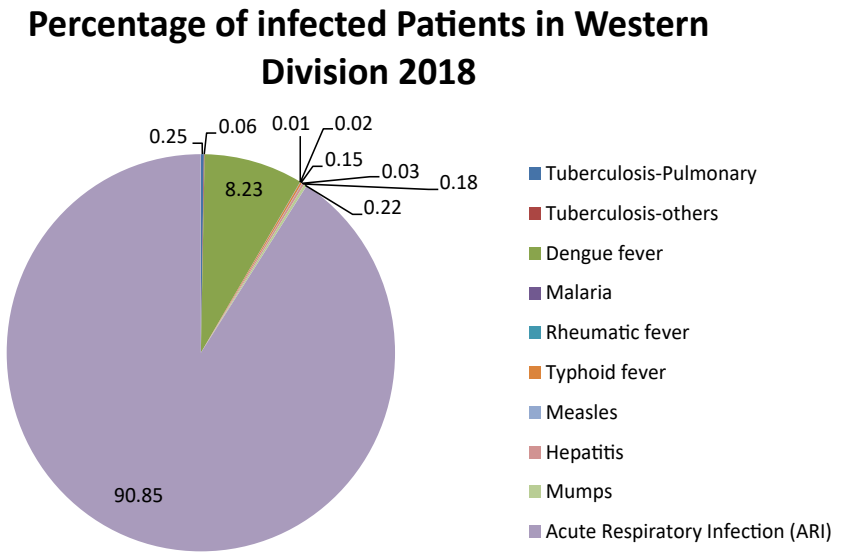
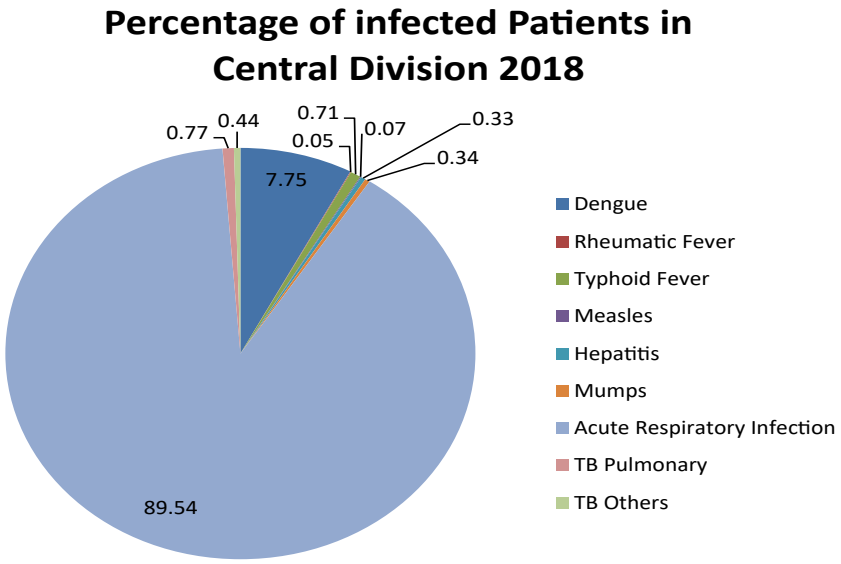


Fig. 8. Pie Graph of Infected Patients of Central Division 2018.



Tab. 1. Shows the total number and percentage of persons infected with different disease causing PUO/fever in the Northern division in the year 2018. ARI having the highest outcome at 40.11% and herpes being the lowest outcome at 0.03%. Other disease such as Chlamydia showed insignificant data.

Causes of PUO/Fever	Number Infected	Percentage
ARI	1,509	40.11
Syphilis	13	0.35
Dengue Fever	1,062	28.23
Dysentery– Bacillary	50	1.33
Herpes	1	0.03
Hepatitis	33	0.88
Leptospirosis	92	2.45
Amebiasis	2	0.05
Typhoid Fever	80	2.13
TB Pulmonary	50	1.33
TB Others	5	0.13
Viral Illness Infection	807	21.45
Rheumatic Fever	2	0.05
Meningitis	56	1.49
Total	3,762	100.00

Tab. 2. Shows the total number and percentage of persons infected with different disease causing PUO/fever in the Eastern division in the year 2018.Viral Illness having the highest outcome at 47.85% and herpes, malaria and pulmonary TB being the lowest outcome at 0.04%. Other diseases such as Chlamydia showed insignificant data.

Causes PUO	Number Infected	Percentage
ARI	922	37.04
Syphilis	18	0.72
Dengue Fever	301	12.09
Dysentery-bacillary	3	0.12
Herpes	1	0.04
Leptospirosis	32	1.29
Malaria	1	0.04
Typhoid Fever	10	0.40
TB Pulmonary	1	0.04
TB Others	3	0.12
Viral Illness Infection	1191	47.85
Meningitis	6	0.24
Total	2489	100.00

classified to intonosocomial, neutropenic, classic, and Human Immunodeficiency Virus (HIV)-associated FUO [12]. PUO mortality is low, antipyretics or antimicrobials therapy early on may delay diagnosis hence treatment before diagnosis not suggested [13]. In 2011, Fiji, had a concern over the rapid rise in reported cases of typhoid fever, leptospirosis along dengue fever locally known as the "three plagues" [6]. The three plagues are common etiologies of fever of unknown origin in Fiji. Other causes of FUO in Fiji includes dengue, rheumatic fever, measles, hepatitis, mumps, acute respiratory infections (ARI), TB, meningitis, viral illness Infections among others.

METHODOLOGY

Several research on FUO studies since the early 19thcentury to date has led to understanding and clinical implementation. This research is a retrospective study,with focus on available data on FUO and Fever caused by infection, using this criterion was more effective because

Tab. 3. Shows the total number and percentage of persons infected with different disease causing PUO/ fever in the Western division in the year 2018. ARI having the highest outcome at 90.85% and malaria being the lowest outcome at 0.01%. Other disease such as Chlamydia showed insignificant data.

Causes of PUO	Number Infected	Percentage
Tuberculosis-pulmonary	91	0.25
Tuberculosis-others	24	0.06
Dengue fever	3,044	8.23
Malaria	3	0.01
Rheumatic fever	6	0.02
Typhoid fever	54	0.15
Measles	11	0.03
Hepatitis	68	0.18
Mumps	82	0.22
Acute Respiratory Infection (ARI)	33,602	90.85
Total	36985	100.00

Tab. 4. Shows the total number and percentage of persons infected with different disease causing PUO/ fever in the Central division in the year 2018. ARI having the highest outcome at 89.54% and Rheumatic fever being the lowest outcome at 0.05%. other disease such as Chlamydia showed insignificant data

Causes of PUO	Number Infected	Percentage
Dengue	1655	7.75
Rheumatic Fever	11	0.05
Typhoid Fever	152	0.71
Measles	14	0.07
Hepatitis	71	0.33
Mumps	72	0.34
Acute Respiratory Infection (ARI)	19115	89.54
TB Pulmonary	165	0.77
TB Others	94	0.44
Total	21349	100.00

most data on Fever and FUO in Fiji is due to infection, all age groups were included due to the elderly being susceptible to infection compared to young persons [14]. Data collected also included HIV and this was guided by a study that proved opportunistic infection and HIV can cause FUO, patient under HAART may have FUO at a smaller percentage compared to those not receiving HAART [15] and in Japan, HIV was the commonest cause of FUO due to increase in HIV patients [16]. Sources of information of this research were taken from online sources and reference textbooks and the main source of information data regarding diseases relating to FUO and fever were taken from the Ministry of Health, National Notifiable Disease Surveillance System Weekly Bulletin 2018 [17-22]. All data were tabulated and charts generated for data analysis was done using Microsoft Excel software. Herpes, hepatitis, denguewas tracked separately from other viral illness because they are of concern and endemic in Fiji.

DISCUSSION

In this study there are a significant number of cases of fever and fever of unknown origin in Fiji. The Western and Central division recorded the highest case of fever/FUO at 36,985 and 21349 in 2018 respectively this can be due to several factors as geographic condition and urbanization and accessible medical facilities. While the Northern and Eastern division recorded the lowest cases 3762 and 2489 respectively. Acute respiratory infection cases were the main reason of fever/FUO in Northern, Western and Central division **(Fig. 5-8)** followed by dengue except in the Eastern) where the main reason was viral illness, RI and dengue respectively. Dengue fever has been reported in Fiji over the years since the 19th century [2] as epidemic, to date there are still cases though controlled through vector borne clean up campaigns [3]. and public awareness on prevention. Acute Respiratory Infection can be caused by a number of pathogen ranging from bacterial, viral and fungal infection which are more influenced by the humid climatic condition, living conditions and other environmental factors such factories in those area. Others infections such as syphilis, dysentery – Bacillary, herpes, leptospirosis, amebiasis, meningitis hepatitis, measles, tuberculosis, rheumatic fever, mtyphoid fever, measles, hepatitis, mumps causes fever/FUO but this depend on the location climatic influence. Chlamydia, causes of FUO/Fever was insignificant in this study and some viral illness can cause acute respiratory infection. Other fever cases associated with fever of unknown origin such as TB, meningitis and typhoid fever were reported but were not as significant as that of acute respiratory infections and dengue fever. n ranging from bacterial **(Tab. 1-4)**.

CONCLUSION

The management of PUO should be supportive until the cause has been determined. Therapeutic trials of antimicrobials or steroids are not recommended because they can mask symptoms and signs of the underlying disease process. The overall mortality of fever of unknown origin is very low as compared to the rest of the world. In two situations empirical treatment is appropriate: antituberculous therapy for suspected miliary or CNS TB and antimicrobials for patients with suspected infective endocarditis and signs of sepsis. Empirical treatment for TB should always be discussed with a specialist, as the risk of drug resistance needs to be evaluated for each patient, together with the need for early adjunctive steroid therapy for CNS and pericardial TB (at differing dosing regimens).

In management the best approach is to address the patient's expectations of diagnosis and treatment. It is very important to warn the patients about the need methodical stepwise approach to investigation, which can be sometimes frustrating for both the patient and physician and as most of the time it doesn't lead to a firm diagnosis. Undiagnosed patients should be reassured that their prognosis is likely to be good, despite possible continuation of symptoms. Prospective research can be carried out to give more specific out of fever and FUO in Fiji, which will contribute much in research of Fever and FUO and formulation of specific guideline through the policy makers. A thin line lies between acute respiratory infection and viral illness infection.

CONFLICTS OF INTEREST

All authors declare that they have no conflict of interest.

DATA AVAILABILITY

The data used for the research is available on request email juditho@unifiji.ac.fj

FUNDING

No funding although research was performed as part of the employment at Umanand Prasad School of Medicine and Health Sciences, The University of Fiji.

ACKNOWLEDGMENTS

We thank the Fiji Ministry of Health and Medical Service for approval, support and for providing access to historical health records, and to UPSM&HS staff for their support and technical assistance

REFERENCES

1. **Beović B, Doušak M, Ferreira-Coimbra J, et al.** Antibiotic use in patients with COVID-19: A 'snapshot' Infectious Diseases International Research Initiative (ID-IRI) survey. *J Antimicrob Chemother*. 2020;75:3386-3390.
2. **Liu C, Wen Y, Wan W, et al**. Clinical characteristics and antibiotics treatment in suspected bacterial infection patients with COVID-19. *Int Immunopharmacol*. 2021;90:107157.
3. **Seaton RA, Gibbons CL, Cooper L, et al.** Survey of antibiotic and antifungal prescribing in patients with suspected and confirmed COVID-19 in Scottish hospitals. *J Infect Chemother.* 2020;81:952-960.
4. **Adebisi YA, Jimoh ND, Ogunkola IO, et al.** The use of antibiotics in COVID-19 management: A rapid review of national treatment guidelines in 10 African countries. *Trop Medi Health.* 2021;49:1-5.
5. **Jing R, Vunnam RR, Schnaubelt E, et al.** Co-infection of COVID-19 and influenza A in a hemodialysis patient: A case report. *BMC Infect Dis*. 2021; 21:1-6.
6. **Narendrakumar L, Joseph I, Thomas S.** Potential effectiveness and adverse implications of repurposing doxycycline in COVID-19 treatment. *Expert Rev Anti-Infect Ther*. 2021;19:1001-1008.
7. **Pani A, Lauriola M, Romandini A, et al.** Macrolides and viral infections: Focus on azithromycin in COVID-19 pathology. *Int J Antimicrob Agents.* 2020;56:106053.
8. **Ulrich H, Pillat MM.** CD147 as a target for COVID-19 treatment: Suggested effects of azithromycin and stem cell engagement. *Stem Cell Rev Rep*. 2020;16:434-440.
9. **Echeverría-Esnal D, Martin-Ontiyuelo C, Navarrete-Rouco ME, et al.** Azithromycin in the treatment of COVID-19: A review. *Expert Rev Anti-Infect Ther.* 2021;1:147-163.
10. **Sai Disha K, Rashmi Puranik, Sudheesh N, et al.** Structure-based identification of small molecules against influenza A virus endonuclease: An *in silico* and *in vitro* approach. *Pathog Dis.* 2020;78:ftaa032.
11. **Lin C, Li Y, Zhang Y, et al.** Ceftazidime is a potential drug to inhibit SARS-CoV-2 infection *in vitro* by blocking spike protein–ACE2 interaction. *Signal Transduct Target Ther*. 2021;6:1-4.
12. **Karampela I, Dalamaga M.** Could respiratory fluoroquinolones, levofloxacin and moxifloxacin, prove to be beneficial as an adjunct treatment in COVID-19? *Arch Med Res.* 2020;51:741-742.
13. US Food and Drug Administration. Drug Safety Communication: FDA warns about increased risk of ruptures or tears in the aorta blood vessel with fluoroquinolone antibiotics in certain patients. 2018.
14. **Al-Azzam S, Mhaidat NM, Banat HA, et al.** An assessment of the impact of coronavirus disease (COVID-19) pandemic on national antimicrobial consumption in Jordan. *Antibiotics.* 2021;10:690.
15. **Van Gorp GA, Sanders PJ, Van Waardenburg DA, et al.** COVID-19 pneumonia successfully managed with high-flow nasal cannula in a 15-year-old boy. *BMJ Case Rep CP*. 2021;14:e239682.
16. **Beraldo RF, Marcondes MB, Dos Santos MN, et al.** COVID-19 in a patient with liver cirrhosis. *Am J Med Case Rep*. 2021;22:e929948-1.
17. **Haraszti S, Sendil S, Jensen N**. Delayed presentation of acute generalized exanthematous pustulosis following treatment with cefepime in a patient with COVID-19 without the use of hydroxychloroquine. *Am J Med Case Rep.* 2020;21:e926901-1.
18. **Min JY, Jang YJ.** Macrolide therapy in respiratory viral infections. *Mediat Inflamm*. 2012.
19. **Batiha GE, Zayed MA, Awad AA, et al.** Management of SARS-CoV-2 infection: Key focus in macrolides efficacy for COVID-19. Front Med. 2021;8.
20. **Gyselinck I, Janssens W, Verhamme P, et al.** Rationale for azithromycin in COVID-19: An overview of existing evidence. *BMJ Open Respir Res*. 2021;8(1):e000806.
21. **Sultana J, Cutroneo PM, Crisafulli S, et al.** Azithromycin in COVID-19 patients: Pharmacological mechanism, clinical evidence and prescribing guidelines. *Drug Safety.* 2020;43:691-698.
22. **Arshad S, Kilgore P, Chaudhry ZS, et al.** Treatment with hydroxychloroquine, azithromycin, and combination in patients hospitalized with COVID-19. *IntJ Infect Dis*. 2020;97:396-403.