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Table of Contents

1–6

Antibiotic Knowledge, Perception, and Practice of Intern Doctors in Turkey: A Survey Study (*Original Article*)

AHMET DOĞAN; Azra SÖNMEZ; Beyza DIŞLİ; Hasan Şamil ÇELİK; Chingiz RUSTAMLİ; Ecem Berra NAZLIOĞLU; Zuhat ABDULKERİMOĞLU; Mustafa Talha ALTUNBAŞ; Rumeysa ÖZER

DOI: <https://doi.org/10.71079/ASIDE.IM.1442541>

7–14

Efficacy and Safety of Optic Nerve Sheath Fenestration for Idiopathic Intracranial Hypertension: A Subgroup-Focused Systematic Review and Meta-Analysis (*Original Article*)

Feras Almasoud; Abduljabbar Alabduljabbar; Abdulaziz Alotaibi; Abdulbari Hanash; Yazeed Bader Alaq; Abdulwahab Alshehri; Yousef Almohammadi; Mohammad Alenazi; Abdulmajeed Alharbi; Muhammed Amir Essibayi; David J Altschul; Ahmed Y Azzam

DOI: <https://doi.org/10.71079/ASIDE.IM.1542545>

15–21

Efficacy and Safety of Penehyclidine Hydrochloride in Postoperative Nausea and Vomiting Prevention: A Systematic Review and Meta-Analysis of Randomized Controlled Trials (*Original Article*)

Ahmed Magdy; Eithar Alqady; Mohamed Wagdy; Ahmed T. Shalby; Mahmoud Abdelkader; Karim Osamy; Alaa Anter; Ihab Tarik; Manar Samy; Sherif Eltawansy; Ahmed Hassan

DOI: <https://doi.org/10.71079/ASIDE.IM.04272547>

22–27

Challenges and Infectious Complications in Living Donor Liver Transplantation in Egypt: A Comprehensive Review (*Review Article*)

Ahmed Mohamed Ali Aref; Ahmed H. Abdelwahed; Abdelrahman Nassar; Mohamed Elshennawy; Maryam Massoud; Nada Madkour; Esraa Awad; Fatma Aljalawy; Mohamed Akram Abdelwahab Hassan Khalil; Mohammed Y. Youssef; Omar Nassar; Mostafa Alfishawy

DOI: <https://doi.org/10.71079/ASIDE.IM.05112553>

28–33

Acute Myeloid Leukemia Presenting as Bilateral Proptosis: A Case Report with Literature Review (*Case Report*)

Ahmed Mostafa Youssef; Mohamad Monif Assker; Farah Alkhaleefa; Mahasin Shaheen

DOI: <https://doi.org/10.71079/ASIDE.IM.05122559>



Original Article

Antibiotic Knowledge, Perception, and Practice of Intern Doctors in Turkey: A Survey Study

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ABSTRACT

Background: This study aimed to measure intern doctors' knowledge, attitudes, and perceptions about antibiotic treatment and determine the situation on the subject.**Methods:** A 34-question questionnaire was prepared for the study, and volunteers were administered the questionnaire face-to-face or via a Google form on a mobile WhatsApp application. Prospectively, 221 volunteer physicians participated in the survey conducted between March 15 and 22, 2024, in Turkey.**Results:** Of the participants, 118 (53.4%) were male and 103 (46.6%) were female. The mean age (mean \pm SD) was 24 years (24.46 \pm 1.83). Many participants had good antibiotic knowledge but a poor antibiotic use percentage. The knowledge that misuse of antibiotics causes resistance was quite high, and there were deficiencies in the mechanisms of resistance. The misconceptions identified were stopping treatment when the clinical condition improved, regardless of the duration, or giving treatment every time the fever was high. There was a significant and positive correlation between age level-antibiotic knowledge and age-level-resistance awareness ($r_s=0.190$, $p=0.002$ and $r_s=0.152$, $p=0.007$, respectively). A significant difference was also found between gender-attitude scores ($p=0.004$). There was a significant ($r_s=0.247$, $p=0.003$) and positive correlation between antibiotic knowledge and resistance awareness, and a significant ($r_s=0.610$, $p<0.001$) and positive correlation between antibiotic knowledge and attitude and perception scores.**Conclusion:** To increase the intern doctors' resistance awareness and decrease their wrong attitudes and perceptions, social programs, practical applications, and patient-oriented practices, together with some educational program curriculum changes, are needed.

1. Introduction

Increased antibiotic resistance is directly associated with treatment failure, recurrent infections, cost, increased mortality, and morbidity. This resistance problem has become an increasing public health concern. Globally, there is concern that by 2050, approximately 10 million people will be lost due to resistance problems. The World Health Organization and many countries around the world are trying to develop antimicrobial resistance prevention strategies. Antimicrobial resistance can be easily detected by standard microbiological tests [1, 2, 3, 4]. Pathogens can build resistance to antibiotics in many different ways. In antibiotic treatment management, knowing these resistance pathways and other factors that stimulate resistance to use appropriate antibiotics at appropriate times and doses [5]. The use of antibiotics in animal foods, unnecessary and

excessive usage during the COVID-19 pandemic, and irrational usage of antibiotics on different spectra, such as surgical prophylaxis or inappropriate empirical treatment, especially in our country, are important factors that increase the development of resistance [6, 7, 8, 9]. A lack of time to evaluate patients, different knowledge levels of physicians, febrile patients, fear of complications, parental expectations of antibiotics, and undetailed physical examination findings are other factors that increase inappropriate antibiotic usage [10, 11, 12]. Our country has a very high rate of antibiotic usage. After graduation, intern doctors prescribe antibiotics at a high rate in emergency services and family physicians. Therefore, this study aimed to analyze intern doctors' knowledge, perception, and practices about antibiotics.

2. METHODS

The study was planned as a prospective, observational cross-sectional survey study between March 15-22, 2024 in Turkey, voluntarily. The interns in our center and semester 5 students who had a short transition period to internship were included in the study. Students were personally contacted during the internship or through their phone numbers registered in the hospital data processing and the questionnaire was applied with an information message. The minimum sample size was calculated as 221 with a 5% margin of error, 95% confidence interval, and 50% distribution

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of responses. The following formula was used to calculate the sample size [13]:

$$X = Z \left(\frac{c}{100} \right)^2 r(100 - r)$$

$$N = \frac{Nx}{(N - 1)E^2 + x}$$

$$E = \sqrt{\frac{(N - n)x}{n(N - 1)}}$$

Where n is the sample size, E is the margin of error, N is the population size, r is the fraction of responses, and $Z (c/100)$ is the critical value for confidence level c .

The questionnaire was prepared in a Word file, and a Google survey form was shared with volunteers both face-to-face and via the WhatsApp application through the registered telephone number of the intern. The questionnaire has been validated and previously implemented in other countries such as Pakistan and Uganda [14, 15, 16]. An English-language version of the questionnaire guide was uploaded as a supplementary file. The study questionnaire was composed of five main sections. In the introduction section, general information about the questionnaire was given, and voluntary consent was requested. Demographic data was collected in the first section. In the second section, six questions about general antibiotic knowledge were asked, and in the third section, 10 questions about antibiotic resistance were asked. Participants were asked to respond yes, no, or not sure. In the fourth section, five questions were asked to evaluate resistance awareness. The participants were asked to respond as do not know, partially know, know well, or know very well.

In the last section, 12 questions were asked to evaluate the attitudes and perceptions of intern doctors about antibiotics. The participants were asked to respond to each question as agree or disagree. Except for the demographic section, the responses received for each section were tabulated as frequencies and percentages. In addition, the second and third sections were scored together by giving 1 point for correct answers and 0 points for incorrect answers or unclear answers. Knowledge about antibiotics questions were evaluated out of 6 points. The score for knowledge about antibiotic resistance was assessed out of 10 points (yes=1 point, no=0 points, not sure=0 points). Statistical evaluation was made over a total score of 16 points. The fourth section examining awareness of antibiotic resistance received 15 points (don't know, partially know, know well=2, know very well=3 points). The last section, which examined the attitudes and perceptions of the intern doctors, was evaluated over 12 points according to the correct answer (Agree=1 point for questions 1-4 and 10-12, disagree=1 point for questions 5-9). Students who provided incomplete information, non-volunteers, intern doctors, and those who were not Semester 5 students were not included in the study.

2.1. Ethics approval and consent to participate

The study was approved by the Abant Izzet Baysal University Non-interventional Clinical Research Ethics Committee Unit. Ethical permission was received at the meeting dated February 20, 2024, and numbered 2024/28 (Approval no: BAIBU-28). The study is a survey. An information paragraph was included for all participants in the questionnaire form. In addition, the voluntary basis was highlighted.

2.2. Statistical analysis

SPSS version 23.0 (IBM, New York, USA) was used to analyze the data. The Kolmogorov–Smirnov test and histogram analysis were used to assess the normality of the data. Categorical variables are presented as numbers and percentages and were compared by the chi-square test or Fisher's exact test, if appropriate. A Bonferroni correction was applied to account for multiple comparisons when analyzing associations between demographic variables and knowledge/attitude scores. The Mann-Whitney U test was used to analyze continuous variables (gender and scores) that did not show a normal distribution. Spearman's rho test (r_s) was used to analyze antibiotic knowledge scores and resistance awareness. The significance level was set as $p < 0.05$.

3. Results

Only the age and gender of the participants were questioned in terms of socio-demographic characteristics. Of the study participants, 118 (53.4%) were male, and 103 (46.6%) were female. The mean age (mean \pm SD) was 24 (24.46 \pm 1.83). The resistance awareness score was calculated as Mean (Min-Max) =5.98 (0-15), antibiotic knowledge score=9.79 (1-16), and attitude score=10.93 (2-12). When the responses to the six questions about general antibiotic knowledge and antibiotic usage were analyzed, it was observed that while a high percentage of correct responses were given for general antibiotic knowledge, the percentage of correct responses was low for questions related to antibiotic usage (**Table 1**).

In the second part, where antibiotic resistance knowledge was measured, the students were asked 10 questions. The answers given to the questions about how misuse of antibiotics affects resistance were correct at a high rate. However, the rate of correct responses to questions about resistance mechanisms decreased considerably (**Table 1**).

In the third section, where antibiotic resistance awareness was evaluated, the participants were asked five questions. The participants were generally trusted in their level of knowledge on the awareness and management of antibiotic resistance (**Table 2**).

In the fourth part, 12 questions were asked to evaluate the participants' attitudes and perceptions about antibiotic stewardship. Most of the students reported that they did not consider antibiotic resistance an important problem. In addition, the rate of those who stated that antibiotics should be started in fewer cases was quite high. Another false perception was that antibiotic treatment should be stopped immediately when the patient's clinic is cleared. Again, the number of those who thought that leftover antibiotics should be stored and reused was quite high. The rate of agreement with the correct responses to the other questions about antibiotic management was high (**Table 3**).

The age of the interns and their antibiotic knowledge scores and resistance awareness scores were evaluated separately. A significant but weak positive correlation was found between age and antibiotic knowledge ($r_s=0.190$, $p=0.002$). It was observed that antibiotic knowledge scores increased with increasing age. Similarly, a significant but weak positive correlation was found between age and resistance awareness ($r_s=0.152$, $p=0.007$) (**Figure 1**). It was determined that awareness increased with increasing age. Resistance Awareness, Antibiotic Knowledge, and Attitude Score were evaluated separately according to gender. While a significant difference was found between the attitude scores and gender ($p=0.004$), no difference was observed between the other scores (**Table 4**).

Table 1: Information about antibiotics, usage, and resistance

| Question | Responses | N=221 | % |
|---|-----------|-------|-------|
| Can antibiotics destroy normal flora in the body? | Yes* | 214 | 96.8% |
| | No | 4 | 1.8% |
| | Not sure | 3 | 1.4% |
| Can antibiotics cause allergic reactions? | Yes* | 218 | 98.6% |
| | No | 1 | 0.5% |
| | Not sure | 2 | 0.9% |
| Do you know when to start antimicrobial treatment? | Yes* | 154 | 69.7% |
| | No | 10 | 4.5% |
| | Not sure | 57 | 25.8% |
| Do you know how to choose the best antibiotic? | Yes* | 94 | 42.5% |
| | No | 26 | 11.8% |
| | Not sure | 101 | 45.7% |
| Do you know the appropriate dosage of antibiotics to be given? | Yes* | 57 | 25.8% |
| | No | 60 | 27.1% |
| | Not sure | 104 | 47.1% |
| Do you know when to switch from intravenous antibiotics to oral regimens? | Yes* | 60 | 27.1% |
| | No | 79 | 35.7% |
| | Not sure | 82 | 37.1% |
| Inappropriate use of antibiotics causes antibiotic resistance. | Yes | 220 | 99.5% |
| | No | 0 | 0% |
| | Not sure | 1 | 0.5% |
| Better use of antibiotics will not affect antimicrobial resistance? | Yes | 21 | 9.5% |
| | No | 179 | 81% |
| | Not sure | 21 | 9.5% |
| Is it always better to prescribe broad-spectrum antibiotics even if more narrow-spectrum antibiotics are effective? | Yes | 17 | 7.7% |
| | No | 179 | 81% |
| | Not sure | 25 | 11.3% |
| The mechanism of resistance to beta-lactams in <i>K. pneumoniae</i> is mainly enzymatic. | Yes | 64 | 29% |
| | No | 25 | 11.3% |
| | Not sure | 132 | 59.7% |
| The resistance mechanism of methicillin-resistant <i>S. aureus</i> is efflux pumps. | Yes | 66 | 29.9% |
| | No | 25 | 11.3% |
| | Not sure | 130 | 58.8% |
| The mechanism of resistance against vancomycin-resistant <i>E. faecalis</i> is by changing the region of binding. | Yes | 54 | 24.4% |
| | No | 13 | 5.9% |
| | Not sure | 154 | 69.7% |
| Antibiotic use shorter than the standard duration provokes resistance. | Yes | 180 | 81.4% |
| | No | 17 | 7.7% |
| | Not sure | 24 | 10.9% |
| Failure to debride the site of infection provokes resistance. | Yes | 176 | 79.6% |
| | No | 11 | 5% |
| | Not sure | 34 | 15.4% |
| Does the use of antibiotics for self-limiting bacterial infections provoke resistance? | Yes | 127 | 57.5% |
| | No | 24 | 10.9% |
| | Not sure | 70 | 31.7% |
| Overuse of antibiotics in livestock provokes resistance. | Yes | 156 | 70.6% |
| | No | 11 | 5% |
| | Not sure | 54 | 24.4% |

(*): Correct response

When antibiotic knowledge and resistance awareness and antibiotic knowledge and attitude scores of the intern doctors were evaluated separately, a significant but moderate positive correlation was found between antibiotic knowledge and resistance awareness ($rs=0.247$, $p=0.003$). Similarly, a significant but weakly positive correlation was found between antibiotic knowledge and attitude scores ($rs=0.610$, $p<0.001$), (**Figure 2**).

Table 2: Antimicrobial resistance awareness

| Question | Responses | N=221 | % |
|---|--|-------------|-------|
| How are antibiograms analyzed? | Do not know | 54 | 24.4% |
| | Know partially | 106 | 48% |
| | Know it well | 45 | 20.4% |
| | Know it very well | 16 | 7.2% |
| How to find authoritative data sources for treating infections? | Do not know | 17 | 7.7% |
| | Know partially | 130 | 58.8% |
| | Know it well | 65 | 29.4% |
| Know it very well | 9 | 4.1% | |
| | How to deal with a patient who wants antimicrobials? | Do not know | 27 |
| Know partially | | 97 | 43.9% |
| Know it well | | 79 | 35.7% |
| Know it very well | | 18 | 8.1% |
| Identify the correct spectrum of different antimicrobial therapies? | Do not know | 56 | 25.3% |
| | Know partially | 124 | 56.1% |
| | Know it well | 33 | 14.9% |
| | Know it very well | 8 | 3.6% |
| How to choose the best antimicrobials for a specific infection? | Do not know | 27 | 12.2% |
| | Know partially | 129 | 58.4% |
| | Know it well | 57 | 25.8% |
| | Know it very well | 8 | 3.6% |

4. Discussion

Physicians at the center of antibiotic stewardship have poor perceptions of antimicrobial therapy management and false perceptions about rational antibiotic usage [14, 15, 16]. The quality and adequacy of the education received by medical students directly impact their knowledge, perceptions, and attitudes toward the correct use of antibiotics. In one study, after infectious disease education, almost all the medical students who participated in the study thought that antimicrobial resistance is a public health problem today, and 98.4% of them thought that antimicrobial resistance should be prevented [17].

This study aimed to draw attention to the deficiencies, false attitudes, and perceptions of semester V students who will be interns for one month and intern doctors in antibiotic stewardship. We have once again identified the importance of general antibiotic knowledge and resistance awareness in rational antibiotic usage. These parameters directly relate to eliminating false perceptions and attitudes among intern doctors. There are many reasons for the irrational use of antibiotics. Antibiotic administration for nonbacterial infections, antibiotic administration for longer than necessary, treatment of colonization and contamination, lack of correct differentiation of other causes that increase acute phase reactants, and high fever are some of them [18, 19]. Unlike in the above study, most volunteer doctors who participated were still unaware of the importance of antimicrobial resistance. However, among European countries, Turkey has a high rate of antibiotic usage [20]. One-third of the participants still did not know or were unsure about the correct choice of antibiotic, and three-quarters did not know or were unsure about the appropriate dosage and the timing of antibiotic switching. A very small proportion had misconceptions, such as taking antibiotics for every fever and repeatedly taking too many antibiotics. Furthermore, about 90 percent of participants did not know or were not sure about the positive impact of antibiotics on resistance when used with better stewardship, and the fact that they believe that antibiotics can be discontinued

Table 3: Attitude and Perception

| Question | Responses | N=221 | % |
|--|-----------|-------|-------|
| Strong antimicrobial knowledge is important for my career. | Agree | 213 | 96.4% |
| | Disagree | 8 | 3.6% |
| Antimicrobials are overused in our country. | Agree | 218 | 98.6% |
| | Disagree | 3 | 1.4% |
| The antimicrobials I will prescribe/distribute will contribute to the problem of resistance. | Agree | 177 | 80.1% |
| | Disagree | 44 | 19.9% |
| I would like more training on the appropriate use of antimicrobials. | Agree | 197 | 89.1% |
| | Disagree | 24 | 10.9% |
| Efficacy is better if antimicrobials are newer and more expensive. | Agree | 23 | 10.4% |
| | Disagree | 198 | 89.6% |
| Antimicrobial resistance is not a major problem. | Agree | 14 | 6.3% |
| | Disagree | 207 | 93.7% |
| Antibiotics must be given when there is a fever. | Agree | 9 | 4.1% |
| | Disagree | 212 | 95.9% |
| Stop the antibiotics immediately when the patient feels better. | Agree | 15 | 6.8% |
| | Disagree | 206 | 93.2% |
| Leftover antibiotics should be saved for future use. | Agree | 49 | 22.2% |
| | Disagree | 172 | 77.8% |
| I should know the correct and relevant specimen to collect for an infection. | Agree | 209 | 94.6% |
| | Disagree | 12 | 5.4% |
| I can distinguish between normal flora and a true pathogen from a microbiology report. | Agree | 200 | 90.5% |
| | Disagree | 21 | 9.5% |
| I can understand the mechanisms of resistance based on a microbiology report. | Agree | 206 | 93.2% |
| | Disagree | 15 | 6.8% |

without waiting for adequate treatment time proves that the medical faculty education in our center should be reconsidered. Partial re-teaching of microbiology courses in semester V, making the infectious diseases compulsory, and extending their duration will seriously contribute to solving the problems we have identified in this study. The high number of students in academic institutions negatively affects the quality of education. In addition, the supply of adequate and effective equipment for the quality of education in hospitals and health institutions is another problem that needs to be addressed by politicians and government authorities. Seminars can be organized from time to time so that academicians can update their knowledge of effective teaching techniques. In addition, the potential integration of mobile learning applications, case-based discussions, or simulation-based training that will contribute to the development of students can contribute positively to the quality of education.

One of the main themes of antibiotic management is the problem of developing resistance. Knowing the resistance mechanisms of some gram-negative and gram-positive agents and choosing appropriate antibiotics accordingly will contribute to the prevention of resistance development [21]. In our study, it was shown that the general antibiotic knowledge of the intern doctors was good. They reported that they were aware of antibiotic resistance at a high rate. However, there is a serious lack of awareness of resistance methods and resistance awareness. Although there was no correlation between gender and resistance awareness, there was a poor correlation between age and resistance awareness.

There was no significant correlation between age and attitudes or perceptions toward antibiotics. This may be explained by the fact that the education received by the interns about infectious diseases was forgotten at that time. We think that the fact that the intern doctors, who were older than the Term V students, did not take any internship or course related to antibiotic knowledge in the last year was effective in this. Similar studies have found results that support this thesis [22, 23]. In addition, it may be thought that they are unaware that they have serious deficiencies in resistance. To overcome this deficiency, up-to-date guidelines can be prepared according to the resistance frequency of each center. Antibiotic resistance rates and the type and frequency of resistant pathogens may vary according to country, center, and region [24]. Alternatively, practical telephone applications adapted to international guidelines can be created. In addition, banning the usage of prescriptions without antibiotics as a policy in our country has been a wise decision that will contribute to the reduction of unconscious antibiotic usage and resistance development. Studies have shown that factors such as having more clinical experience and experience and seniority affect the correct attitude about antibiotics, whereas gender was shown to be an effective factor in our study [25]. In addition, it was determined that antibiotic stewardship program training led to significant improvements in knowledge and attitudes after the deficiencies of healthcare professionals on this subject were identified [26].

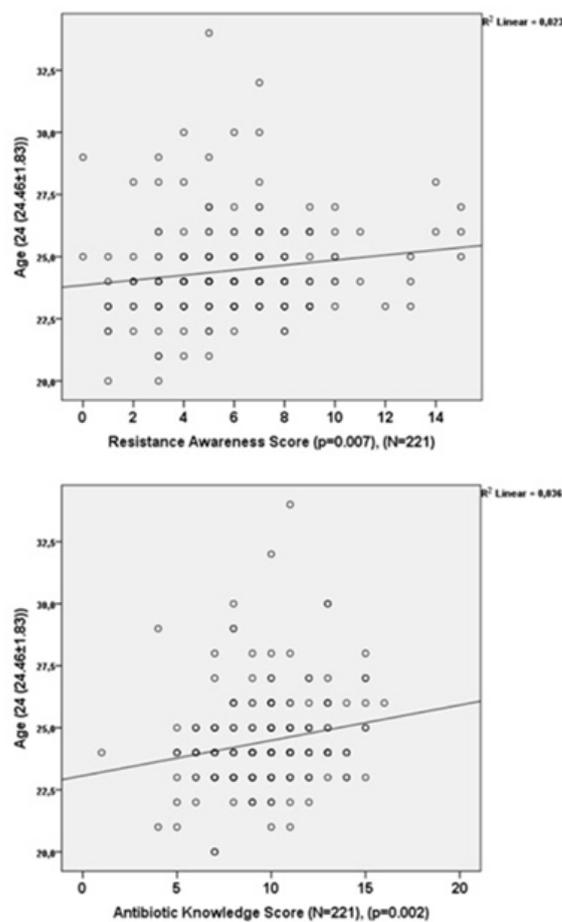


Figure 1: (A) Relationship between Resistance Awareness ($rs=0.152$) by Age, (B) Relationship between Antibiotic Knowledge ($rs=0.190$) by Age. rs: Spearman's rank correlation coefficient.

Table 4: Analyzing the Scoring According to Gender

| Scores | Gender | Mean | SD | p-values | 95% CI Lower | 95% CI Upper |
|----------------------------|--------|-------|-------|----------|--------------|--------------|
| Resistance Awareness Score | Male | 5.91 | 2.612 | 0.686 | -0.889 | 0.586 |
| | Female | 6.06 | 2.950 | | | |
| Antibiotic Knowledge Score | Male | 9.55 | 2.574 | 0.175 | -1.099 | 0.201 |
| | Female | 10.00 | 2.292 | | | |
| Attitude Score | Male | 10.69 | 1.495 | 0.004 | -0.872 | -0.163 |
| | Female | 11.20 | 1.123 | | | |

CI, Confidence Interval of the Difference; SD, Standard deviation

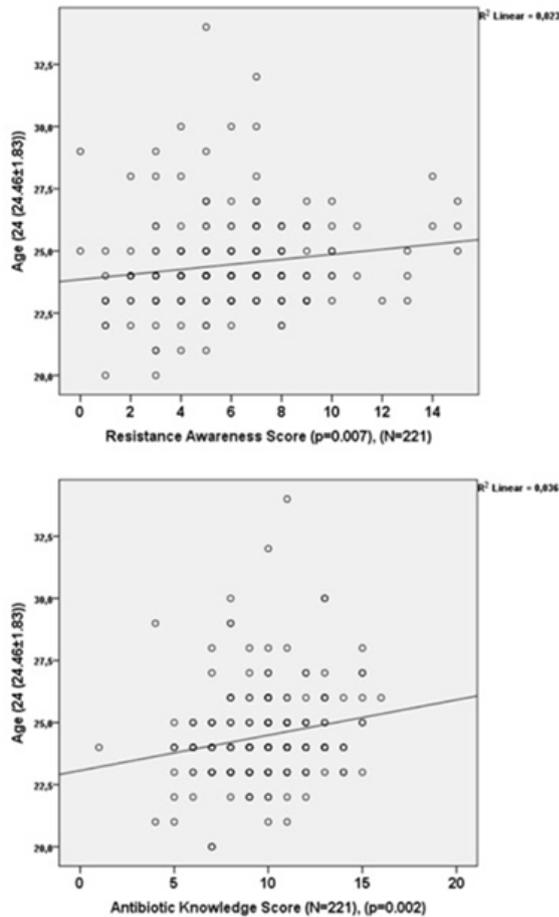


Figure 2: (A) Relationships between Antibiotic Knowledge ($r_s=0.247$) and Attitudes, (B) Resistance Awareness ($r_s=0.610$) and Attitudes. r_s : Spearman's rank correlation coefficient.

This study has several limitations. This study was conducted in a single center. The sample size was determined by calculating the minimum required number of participants based on the total number of semester V students and intern doctors in our center. Because of this, it cannot be generalized to the whole of our country. Factors such as the quality of training in other centers and differences in training programs may change the statistical significance and comprehensiveness. In addition, the accuracy of the results is related to the honesty of the participants in answering. Subjective responses were minimized as much as possible by not asking for any identity information that would reveal the participants. It may be possible to reach more reliable responses

in large-scale surveys where participants can easily give objective responses. In addition, the inclusion of semester five students with a very short internship period may have partially affected the homogeneity. Other limitations include the fact that a generally accepted validity scale could not be used for the study, and the questions were prepared only for this study by using similar studies in the literature.

5. Conclusions

As a result, despite serious resistance problems due to the mismanagement of antimicrobials, intern doctors still have serious knowledge deficiencies and perception-attitude inaccuracies, especially regarding antimicrobial resistance. The age of the intern doctor is partially associated with antibiotic knowledge and resistance awareness. General antibiotic knowledge was directly associated with correct perceptions and attitudes toward antibiotic treatment. Gender was also directly associated with attitude and perception, but not with antibiotic knowledge or resistance awareness. In conclusion, our education system should be revised or facilitated to train medical doctors governed by knowledge rather than obsession, and awareness practices should be implemented

Conflicts of Interest

None

Funding Source

None

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Institutional Review Board (IRB)

The study was approved by the Abant İzzet Baysal University Non-interventional Clinical Research Ethics Committee Unit. Ethical permission was received at the meeting on February 20, 2024, numbered 2024/28 (Approval no: BAIBU-28).

Large Language Model

None

Authors Contribution

Conceptualization was equally contributed by, AD, AS, BD and HŞÇ; methodology, AD, CR, EBN, ZA; software, LM; validation,

AD, AS, BD, HŞÇ, CR, EBN, ZA, MTA, RÖ; formal analysis, AD; investigation, AD, AS, BD, HŞÇ, CR, EBN, ZA, MTA, RÖ; resources, AD, AS, BD; writing—original draft preparation, AD; writing—review and editing, AD; visualization, AD; supervision, AD; project administration, AD. All authors have read and agreed to the published version of the manuscript.

Data Availability

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request. The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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Original Article

Efficacy and Safety of Optic Nerve Sheath Fenestration for Idiopathic Intracranial Hypertension. A Subgroup-Focused Systematic Review and Meta-Analysis.

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ABSTRACT

Introduction: Optic nerve sheath fenestration (ONSF) is an important surgical management option for patients with idiopathic intracranial hypertension (IIH) who have failed medical treatment. We conducted a systematic review and meta-analysis to evaluate the outcomes of ONSF and identify factors affecting treatment success.

Methods: A literature search was conducted up to December 2024. Primary outcomes included improvement in visual acuity, visual fields, and optic disc swelling resolution. We performed a detailed subgroup analysis based on geographic location, study design, surgical approach, and technical variations.

Results: Nineteen studies with a total of 1,159 patients were included in our study. ONSF significantly improved visual acuity in 34.5% (95% CI: 31.8-37.3%) and visual fields in 69.4% (95% CI: 65.9-72.7%) of cases. A 90.9% improvement rate was observed in reducing optic disc swelling. Significant heterogeneity was noted in visual acuity ($I^2=92.1%$) and visual field improvements ($I^2=73.8%$). The overall complication rate was 9% (95% CI: 5-16%). Centers that included 30 or more patients in their study demonstrated significantly lower postoperative complications.

Conclusions: ONSF demonstrates favorable efficacy in improving visual outcomes with an acceptable safety profile, lower postoperative complications were observed when the procedure was performed in high-volume centers using appropriate surgical techniques. Geographic variations and surgical approaches significantly affected outcomes, highlighting the importance of standardized protocols and adequate surgical experience. Future prospective studies with standardized outcome measures are needed to optimize patient selection and surgical techniques.

1. Introduction

Idiopathic intracranial hypertension (IIH), previously known as pseudotumor cerebri or benign intracranial hypertension, is a neurological condition characterized by elevated intracranial pressure (ICP) without identifiable structural or vascular causes [1]. This

disorder mainly affects women of reproductive age and demonstrates a strong association with obesity; despite the current research about IIH, the etiopathogenesis remains not fully understood yet [1]. The hallmark clinical manifestations of the disease include headache, papilledema, and visual disturbances that may progress to blindness if left untreated with proper management [1].

The management of IIH follows a systemic approach, beginning with conservative measures such as weight loss and medical therapy, with acetazolamide, topiramate, and diuretics [2, 3, 4]. However, around 25% of patients are developing refractory IIH in which they have limited or poor response to the initial medical interventions, necessitating surgical intervention [5]. Among the available surgical options, optic nerve sheath fenestration (ONSF) is considered to be among the surgical interventions for IIH patients to preserve vision in cases of progressive visual deterioration [5, 6].

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ONSF involves creating an opening in the optic nerve sheath to reduce localized cerebrospinal fluid (CSF) pressure, which, by role, decreases mechanical compression on the optic nerve [7]. While ONSF for IIH has been reported as a successful intervention for IIH in patients with threatened visual loss, previous studies did not have sufficient conclusive evidence about the optimal ONSF approaches and settings regarding its safety and efficacy for IIH patients [5, 8, 9].

Previous studies have highlighted important considerations in surgical procedures for IIH, but these studies either lacked complete evaluation of visual fields or have become outdated as new surgical techniques and further updated studies have been published [1, 5, 7, 8, 9, 10, 11, 12]. The timing of surgical intervention appears critical, with mounting evidence suggesting that delayed intervention may result in irreversible vision loss due to progressive optic nerve damage [13]. Also, technical aspects of the procedure, such as the size and location of the fenestration, muscle disinsertion requirements, and the use of minimally invasive approaches, may affect its efficacy and complication rates.

Recent advances in surgical techniques, especially the development of endoscopic and minimally invasive approaches, have renewed interest in evaluating the safety and efficacy of ONSF from different perspectives, even in the presence of other minimally invasive interventions such as venous sinus stenting where they may not be suitable for some patients due to several factors and considerations [14]. Additionally, the emergence of large-scale studies with detailed visual outcome data has created an opportunity for a more detailed analysis of factors influencing surgical success with the option of conducting subgroup analysis to explore further more factors affecting ONSF success [15]. Therefore, we aim to evaluate the safety and efficacy of ONSF in preserving vision in patients with IIH based on the most updated evidence in the most detailed manner, given the currently available data. Our study specifically focuses on three key outcomes: improvement in visual acuity, enhancement of visual fields, and resolution of optic disc swelling, in addition to investigating the reported postoperative complications from ONSF. Our study aims to perform detailed subgroup analyses based on geographical location, study design, surgical approach, and technical variations to identify factors that might influence surgical outcomes. Understanding these variables and factors related to ONSF in IIH patients has important considerations for optimizing patient selection and surgical technique, ultimately improving visual outcomes in this challenging patient population.

2. Methods:

Our systematic review and meta-analysis were conducted with adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. We conducted a literature search across multiple electronic databases, including PubMed/MEDLINE, Embase, Web of Science, Scopus, Google Scholar, and Cochrane Library, from inception through the 22nd of December 2024. The search strategy incorporated Medical Subject Headings (MeSH) terms and keywords related to "optic nerve sheath fenestration", "ONSF" "idiopathic intracranial hypertension", "IIH", "benign intracranial hypertension", and "pseudotumor cerebri". For methodological clarity, we classified all included studies into two categories: observational and interventional. It is important to note that all studies in both categories involved patients who underwent ONSF; our classification refers to study design rather than treatment allocation. Observational studies (n=16) included retrospective chart reviews, case series, and cohort

studies where the studies analyzed and reported the outcomes after ONSF without a predefined intervention protocol. Interventional studies (three studies) were those with prospective enrollment following a standardized surgical protocol and predefined outcome measures, representing a higher level of methodological confidence and validity.

2.1. Literature Review and Data Extraction:

Two independent reviewers screened titles and abstracts for eligibility, followed by a full-text review of the possible relevant articles. We included both observational and interventional studies reporting outcomes of ONSF in patients with IIH. Studies were eligible if they reported at least one of our primary outcomes: visual acuity improvement, visual field improvement, or optic disc swelling resolution. We excluded non-English articles, case reports, or case series, which included less than five patients, review articles, systematic reviews and meta-analyses, editorials, and letters. Data extraction was performed independently by two investigators using a standardized form. We collected information on study characteristics (publication year, country, study design), patient demographics, surgical techniques, and clinical outcomes. Complications were categorized into overall complications, diplopia, transient visual loss, worsening of visual functions, and anisocoria.

2.2. Risk of Bias Assessment

We assessed the risk of bias using the Risk Of Bias In Non-Randomized Studies—of Interventions (ROBINS-I) tool, which evaluates seven domains: confounding, selection bias, classification of interventions, deviations from intended interventions, missing data, outcome measurement, and selective reporting. The quality of evidence for each outcome was evaluated using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) framework, considering the risk of bias, inconsistency, indirectness, imprecision, and publication bias.

2.3. Statistical Analysis

For statistical analysis, we performed a single-arm proportion-based meta-analysis using RStudio software with the 'meta' and 'metafor' packages built on the R language. We calculated pooled proportions with 95% confidence intervals for each outcome using random-effects models. Heterogeneity was assessed using I^2 statistics and Cochran's Q test. We conducted pre-specified subgroup analyses based on country of study, either United States (US) vs. non-US based study, study type (observational vs. interventional), study design (retrospective vs. prospective), sample size (>30 vs. <30 vs. =30), surgical approach (medial transconjunctival vs. other), and surgical technique (with vs. without muscle disinsertion). Publication bias was evaluated using funnel plots, Egger's test, and the trim-and-fill method was used when appropriate. Statistical significance was set at $P < 0.05$, and all tests were two-sided.

The rationale for our geographic subgroup analysis (US vs. non-US) was based on the differences in practice patterns, patient selection criteria, reporting standards, and healthcare systems between the regions. Previous studies on IIH have demonstrated geographic variations in disease prevalence, management approaches, and outcomes reporting [16, 17]. We aim to identify any differences in ONSF outcomes that might inform international standardization efforts and highlight region-specific considerations for optimizing patient selection and surgical technique.

3. Results

Our systematic search yielded 597 records, with 19 studies meeting the final inclusion criteria after thorough screening (**Figure 1**) [18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36]. The included studies spanned from 1988 to 2021, comprising 16 observational and three interventional studies, with 14 retrospective and five prospective designs (**Supplementary Table 1**).

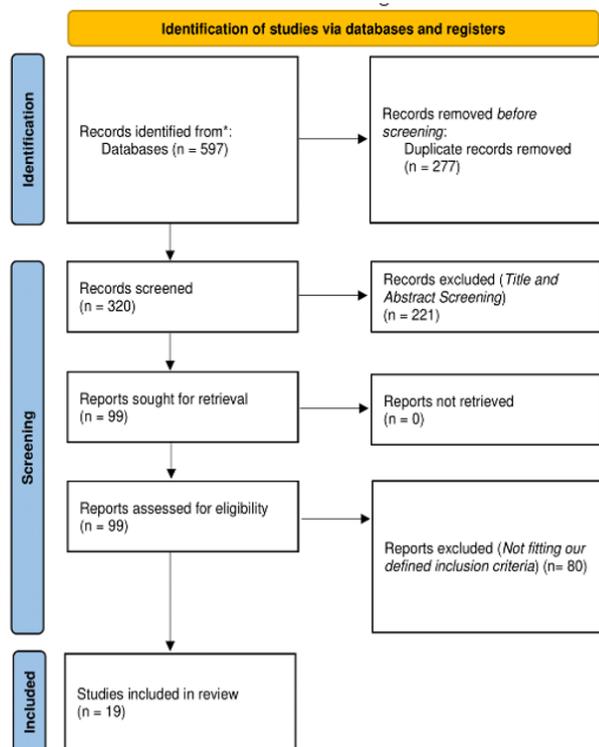


Figure 1: PRISMA flow chart diagram for our literature review results.

3.1. Risk of Bias Assessment:

The ROBINS-I risk of bias assessment highlighted varied methodological quality (**Supplementary Figure 1**). Three studies (Melson et al., Wadikhaye et al., and Nithyanandam et al.) demonstrated a consistently low risk of bias across all domains (+). Nine studies showed serious risk of bias (X) in their overall assessment, primarily due to confounding (D1) and missing data (D5). Domain D3 (bias in classification of interventions) uniquely showed low risk (+) across all studies. Domain D4 (bias due to deviations from intended interventions) showed mixed results, with eight studies having low risk and 11 showing moderate risk. Seven studies showed consistently poor performance across multiple domains, receiving serious risk ratings in D5, D6, and D7.

3.2. GRADE Framework Assessment

Our GRADE framework assessment (**Supplementary Table 2**) revealed heterogeneous quality across outcomes. Visual acuity improvement evidence (19 studies, n=1,160) received a low-quality rating ($\oplus \oplus \circ$) due to a serious risk of bias (-1) from lack of standardized visual acuity measurements and high heterogeneity (-1) with $I^2 > 50\%$. Visual field improvement (16 studies, n=719) achieved moderate quality ($\oplus \oplus \oplus \circ$), downgraded only for serious risk bias (-1) due to varied testing methods, but showed consistent

improvement across studies. Optic disc swelling resolution (11 studies, n=351) also received a moderate quality rating ($\oplus \oplus \oplus \circ$), with consistent resolution rates and low heterogeneity.

3.3. Efficacy Outcomes:

Visual acuity improvement results have demonstrated statistically significant differences between non-US and US studies (48.3% vs. 29.8%, $p < 0.001$), prospective versus retrospective designs (80.8% vs. 32.7%, $p < 0.001$), and surgical approaches (medial transconjunctival 30.6% vs. other 48.4%, $p\text{-value} < 0.001$). Visual field improvement demonstrated higher rates in US versus non-US studies (72.7% vs. 68.1%, $p\text{-value} = 0.221$) and interventional versus observational studies (83.9% vs. 70.5%, $p\text{-value} = 0.154$). Optic disc swelling resolution showed significantly better outcomes in US studies (97.3% vs. 76.5%, $p\text{-value} < 0.001$), interventional studies (98.7% vs 83.6%, $p < 0.001$), and medial transconjunctival approach (98.8% vs 82.8%, $p\text{-value} < 0.001$), as listed in (**Table 1**). We have used the single-arm proportion-based meta-analysis as our primary analytical approach due to the nature of available data extracted from included studies. The absence of randomized controlled trials and the limited number of comparative studies precluded traditional two-arm meta-analyses using direct comparison groups and direct comparison metrics, which were unavailable across most included studies.

3.4. Safety Outcomes

We listed the overall reported complications from our included studies in (**Table 2**). The overall rate was 9% (95% CI: 5-16%, $I^2 = 48\%$) (**Figure 2**). Significant subgroup differences were observed in the country of study (non-US 13.9% vs. US 7.4%, $p\text{-value} = 0.007$), surgical approach (medial transconjunctival 7.7% vs. other 13.2%, $p\text{-value} = 0.023$), and sample size (>30 : 6.6% vs ≤ 30 : 15.2% vs ≤ 30 : 16.7%, $p\text{-value} < 0.001$). Specific complications showed varying rates: worsening of visual functions (8%, $I^2 = 51\%$), diplopia (3%, $I^2 = 24\%$), anisocoria (4%, $I^2 = 0\%$), and transient visual loss (10%, $I^2 = 69\%$). In addition to that, bilateral versus unilateral approaches showed significant differences in transient visual loss (6.9% vs. 15.5%, $p\text{-value} < 0.001$) and worsening of visual functions (5.7% vs. 15.5%, $p\text{-value} = 0.018$); the forest plots for the efficacy outcomes are shown in (**Supplementary Figure 2 – 5**), while the subgroup analyses for safety outcomes are listed in (**Supplementary Table 3**).

3.5. Publication Bias

Publication bias assessment (**Supplementary Table 4**) indicated a moderate risk for visual acuity improvement (Egger's test $p\text{-value} = 0.034$), with right-skewed funnel plot asymmetry and four potentially missing studies identified through trim-and-fill analysis. Visual field improvement and optic disc resolution showed low publication bias risk (Egger's test $p\text{-value} = 0.245$ and $p\text{-value} = 0.789$, respectively).

4. Discussion

In our study, we evaluated the efficacy and safety outcomes of ONSF in IIH patients, focusing on detailed subgroup analyses based on multiple factors. Our findings provide important insights into the factors that may have significant considerations on ONSF outcomes and help identify optimal patient selection criteria.

Our analysis demonstrates that ONSF shows considerable efficacy in improving visual outcomes, with an overall visual acuity improvement rate of 34.5% (95% CI: 31.8-37.3%) and visual field improvement rate of 69.4% (95% CI: 65.9-72.7%). The subgroup

analyses revealed several groups for efficacy and treatment success and highlighted several important points that warrant discussion and further investigation. Studies from non-US centers showed significantly higher rates of visual acuity improvement (48.3% vs. 29.8%, p -value<0.001), suggesting potential variations in patient selection criteria or surgical techniques across different geographic regions [3, 16, 37, 38, 39, 40]. Prospective studies demonstrated markedly better outcomes in visual acuity improvement compared to retrospective designs (80.8% vs 32.7%, p -value<0.001), highlighting the importance of standardized protocols and careful patient monitoring in achieving optimal outcomes, which was previously discussed that we need more optimization and standardization for IHH studies to promote better quality studies and enhance our evidence about the disease [41]. The surgical approach emerged as a crucial factor, with non-medial transconjunctival approaches showing higher success rates (48.4%) compared to medial transconjunctival approaches (30.6%, p -value<0.001). This finding suggests that surgical technique selection may significantly influence visual outcomes. Sample size analysis revealed interesting patterns, with centers performing more than 30 procedures showing more consistent results compared to those with smaller case volumes. Regarding papilledema resolution, US studies demonstrated significantly better outcomes (97.3% vs. 76.5%, p -value<0.001), as did interventional studies compared to observational ones (98.7% vs. 83.6%, p -value<0.001). Also, the medial transconjunctival approach showed superior results in papilledema resolution (98.8% vs 82.8%, p -value<0.001), which is a complex and contradictory finding, especially since the overall success rates were higher in non-medial transconjunctival approach as we mentioned earlier; and based on that further studies with more focused controls and approach-focused outcomes and complications should be conducted to ensure the results about it.

It is important to mention that we had statistically significant heterogeneity in visual acuity ($I^2=92.1\%$) and visual field improvements ($I^2=73.8\%$), which warrants careful interpretation. This heterogeneity likely originates from multiple sources identified through additional analyses. First, patient-specific factors varied considerably across studies, with mean age ranging from 26.5 to 40.8 years, mean BMI from 26.8 to 39.6 kg/m², and disease duration before ONSF from 1.3 to 36 weeks. Second, follow-up protocols differed significantly, with some studies reporting outcomes at three months and others at up to two years post-procedure, introducing temporal bias in outcome assessment. Third, there was an inconsistency in measurement techniques, varying from Snellen charts to log MAR for visual acuity and from Goldmann to automated perimetry for visual fields, which created methodological variability that contributed to heterogeneous results. Also, the threshold for defining improvement was inconsistently applied across studies, with some requiring one-line improvement in visual acuity while others demanded two or more lines for positive classification.

Our safety analysis revealed an overall complication rate of 9% (95% CI: 5-16%, $I^2=48\%$), which is lower than previously reported in some studies from previous literature. The subgroup analyses of complications provided important significant considerations and factors to highlight risks and possible preventive strategies.

Geographic variation was significant, with non-US centers reporting higher complication rates (13.9% vs 7.4%, $p=0.007$). This difference might reflect variations in surgical expertise, patient selection, guidelines, or reporting practices between the US and other countries [17, 38]. The surgical approach significantly affected complication rates, with the medial transconjunctival technique

showing lower complications (7.7% vs 13.2%, $p=0.023$), suggesting it might be the safer approach, although the surgical technique findings warrant further verification as they are contradictory within our analysis findings between different variables. Sample size-based subgroup analysis demonstrated that centers in which they performed more than 30 procedures reported in their research paper had significantly lower complication rates (6.6%) compared to those with fewer cases (15.2% for <30 cases, $p<0.001$), highlighting the importance of surgical experience and center volume, and may also be considered that there is a possible effect from the influence of sample size power on overall results. Specific complications showed varying patterns, with diplopia being the most common (3%, $I^2=24\%$), followed by anisocoria (4%, $I^2=0\%$).

Our findings both support and extend the conclusions of the previous meta-analyses. Unlike Kalyvas et al.'s study [8], which focused broadly on various surgical interventions for IHH; our analysis provides a detailed focus on ONSF outcomes only. Compared to Friso et al.'s [42] pediatric-focused review, our study offers a comprehensive analysis across all age groups. When compared to Santos et al. study [43], they included only ten studies, with limited outcomes assessment compared to our defined methodology and results. Also, in comparison with the recent Prokop et al. meta-analysis [44], they had several limitations in their study, which we worked to overcome in our analysis, including more comprehensive subgroup analysis, analysis of postoperative complications in which they did not perform, handling of publication bias using multiple statistical techniques, correction of bias through trim-and-fill technique, performing more detailed risk of bias assessment, in addition to the introduction of a GRADE framework approach to our analysis in which they did not perform.

Despite the strengths and novel points of our analysis compared to previous studies, our study has several limitations that warrant acknowledgment. First, the retrospective nature of most included studies introduces selection and reporting biases. Second, the heterogeneity in outcome reporting and surgical techniques across studies may affect the generalizability of our findings. Third, the lack of standardized visual outcome measurements across studies made some comparisons challenging. Future studies should focus on prospective data collection with standardized outcome measures and longer follow-up periods. Multicenter randomized controlled trials comparing different surgical approaches would be valuable in definitively establishing the optimal technique. Additionally, studies investigating the role of modern surgical adjuncts and their impact on outcomes would be beneficial.

5. Conclusions

ONSF demonstrated significant efficacy in improving visual outcomes, with promising results in visual field improvement (69.4%) and papilledema resolution (90.9%). The procedure's effectiveness varied between different settings and approaches, with prospective studies and non-medial transconjunctival approaches showing superior visual acuity improvement rates. Centers performing more than 30 procedures demonstrated better outcomes and lower complication rates, suggesting a volume-outcome relationship in ONSF procedures. The overall safety profile was favorable, with a 9% complication rate, mostly including manageable complications such as diplopia (3%) and anisocoria (4%). The medial transconjunctival approach emerged as the safer technique with significantly lower complication rates (7.7% vs 13.2%), despite the fact that non-medial transconjunctival approaches demonstrated better efficacy outcomes earlier. Geographic variations in both

Table 1: Meta-Analysis of ONSF Outcomes and Subgroup Analyses

| Outcome/Subgroup Category | Subgroup | Events/Total | Proportion (95% CI) | P-value |
|---------------------------|--------------------------|--------------|---------------------|---------|
| Visual Acuity Improvement | Overall | 400/1160 | 0.345 (0.318-0.373) | <0.001* |
| | Country | | | |
| | Non-US | 153/317 | 0.483 (0.428-0.538) | <0.001* |
| | US | 243/816 | 0.298 (0.267-0.330) | |
| Study Type | Observational | 312/931 | 0.335 (0.306-0.366) | 0.034* |
| | Interventional | 84/202 | 0.416 (0.350-0.485) | |
| Study Design | Retrospective | 354/1081 | 0.327 (0.300-0.356) | <0.001* |
| | Prospective | 42/52 | 0.808 (0.681-0.892) | |
| Surgical Approach | Medial Transconjunctival | 261/854 | 0.306 (0.276-0.337) | <0.001* |
| | Other | 135/279 | 0.484 (0.426-0.542) | |
| Sample Size | >30 | 242/800 | 0.302 (0.272-0.335) | <0.001* |
| | <30 | 128/277 | 0.462 (0.404-0.521) | |
| | =30 | 26/56 | 0.464 (0.340-0.593) | |
| Visual Field Improvement | Overall | 499/719 | 0.694 (0.659-0.727) | <0.001* |
| | Country | | | |
| | Non-US | 169/248 | 0.681 (0.621-0.736) | 0.221 |
| | US | 323/444 | 0.727 (0.684-0.767) | |
| Study Type | Observational | 466/661 | 0.705 (0.669-0.738) | 0.154 |
| | Interventional | 26/31 | 0.839 (0.674-0.929) | |
| Study Design | Retrospective | 466/661 | 0.705 (0.669-0.738) | 0.154 |
| | Prospective | 26/31 | 0.839 (0.674-0.929) | |
| Surgical Approach | Medial Transconjunctival | 353/496 | 0.712 (0.670-0.750) | 0.999 |
| | Other | 139/196 | 0.709 (0.642-0.768) | |
| Sample Size | >30 | 312/436 | 0.716 (0.672-0.756) | 0.930 |
| | <30 | 143/204 | 0.701 (0.635-0.760) | |
| | =30 | 37/52 | 0.712 (0.577-0.817) | |
| Optic Disc Resolution | Overall | 319/351 | 0.909 (0.874-0.935) | <0.001* |
| | Country | | | |
| | US | 220/226 | 0.973 (0.943-0.988) | <0.001* |
| | Non-US | 75/98 | 0.765 (0.672-0.838) | |
| Study Type | Interventional | 157/159 | 0.987 (0.955-0.997) | <0.001* |

ONSF, Optic Nerve Sheath Fenestration; CI, Confidence Interval; US, United States; * Denotes Statistical Significance; P-values represent a comparison between subgroups within each category; Overall results for each outcome represent the pooled analysis across all studies

Table 2: Postoperative Complications Rate

| Study | Diplopia | Transient visual loss | Worsening of visual functions | Anisocoria | Overall complications |
|--------------------------|----------|-----------------------|-------------------------------|------------|-----------------------|
| Söylev Bajin et al. [18] | NR | 21/81 | 11/112 | NR | 7/56 |
| Göksu et al. [19] | NR | 0/9 | 0/9 | NR | 0/9 |
| Jefferis et al. [20] | 0/30 | 2/30 | 2/30 | NR | 5/30 |
| Melson et al. [21] | 0/66 | 4/66 | 4/66 | NR | 0/66 |
| Hagen et al. [22] | NR | NR | NR | NR | 5/10 |
| Wadikhaye et al. [23] | NR | 0/21 | 0/21 | 2/21 | 2/21 |
| Obi et al. [24] | 4/14 | 4/14 | 4/14 | NR | 3/14 |
| Moreau et al. [25] | 20/331 | 32/568 | 32/568 | NR | 23/331 |
| Pineles et al. [26] | 2/37 | 9/37 | 9/37 | 2/37 | 2/37 |
| Nithyanandam et al. [27] | NR | 2/21 | 2/41 | NR | 4/21 |
| Knapp et al. [28] | NR | 4/27 | 4/27 | NR | 0/13 |
| Goh et al. [29] | 0/19 | 0/19 | 0/19 | 0/19 | 0/19 |
| Acheson et al. [30] | NR | 3/14 | 3/14 | NR | NR |
| Kelman et al. [31] | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 |
| Spoor et al. [32] | NR | NR | NR | NR | 4/53 |
| Herzau et al. [33] | NR | 3/15 | 3/27 | NR | 3/15 |
| Corbett et al. [34] | NR | 5/40 | 5/NR | NR | 8/28 |
| Brouman et al. [35] | 1/6 | 1/6 | 1/6 | NR | 2/6 |
| Sergott et al. [36] | NR | NR | NR | NR | 2/23 |

NR, Not Reported; ONSF, Optic Nerve Sheath Fenestration

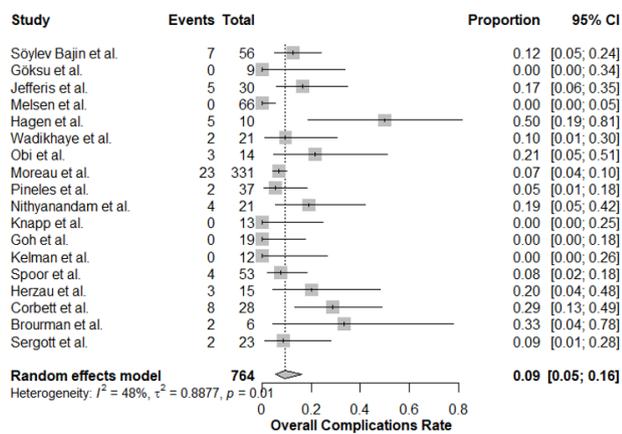


Figure 2: Overall rate of complications following ONSF Forest Plot.

efficacy and safety outcomes address the importance of standardizing surgical techniques and patient selection criteria. US centers showed better papilledema resolution rates and better safety profiles compared to non-US centers, suggesting possible differences in practice patterns that warrant further investigation. These findings support ONSF as a viable surgical option for IIH patients, especially when performed in experienced centers using appropriate surgical techniques. Future studies should focus on prospective studies with standardized outcome measures and surgical protocols to further optimize patient outcomes. Also, developing formal training programs and surgical guidelines could help reduce the observed outcome variations across different centers and regions.

Conflicts of Interest

The authors declare no competing interests that could have influenced the objectivity or outcome of this research.

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Authors Contribution

Conceptualization: FA, AA, and AYA; Methodology: FA, AA, AO, and AYA; Software: MAE and AYA; Validation: AH, YA, and AS; Formal analysis: YM, MA, and AH2; Investigation: FA, AA, and AO; Resources: DJA and AYA; Data curation: FA, AA, and MAE; Writing—original draft preparation: FA, AA, AO, AH, YA, and AS; Writing—review and editing: YM, MA, AH2, MAE, DJA, and AYA; Visualization: MAE and AYA; Supervision: DJA and AYA; Project administration: AYA. All authors have read and agreed to the published version of the manuscript.

Data Availability

This review article does not contain any new primary data. All information discussed is derived from previously published sources and publicly available databases, as cited in the manuscript.

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Original Article

Efficacy and Safety of Penehyclidine Hydrochloride in Postoperative Nausea and Vomiting Prevention: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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ABSTRACT

Introduction: Postoperative nausea and vomiting (PONV) is a common complication following anesthesia. Penehyclidine hydrochloride (PHC), an anticholinergic medication, selectively inhibits the M1 Muscarinic and M3 Muscarinic receptors involved in the nausea and vomiting pathways. This study aims to evaluate the efficacy of PHC in preventing PONV and its potential advantages over existing treatments.

Methods: This study investigated the efficacy and safety of PHC in preventing PONV by analyzing randomized controlled trials (RCTs) identified through a comprehensive search of the PubMed, Scopus, Web of Science, and Cochrane Library databases up to December 2024.

Results: Five RCTs involving 979 patients were included. Compared to the control group, PHC reduced the incidence of PONV in the first 24-72 hours after surgery (RR: 0.64, 95% CI [0.50, 0.82], $p = 0.0004$) and the requirement of rescue antiemetics (RR: 0.46, 95% CI [0.22, 0.96], $p = 0.04$). However, PHC significantly increased the incidence of dry mouth (RR: 2.64, 95% CI [1.98, 3.5], $p < 0.00001$). No significant differences were observed between the two groups regarding other secondary outcomes. Risk of bias assessment was done using RoB2.

Conclusions: PHC shows promising efficacy in reducing PONV and the need for antiemetic medications. Further large-scale RCTs are necessary to verify these results and determine the optimal dose.

1. Introduction

Postoperative nausea and vomiting (PONV) commonly complicates recovery, affecting about 30% of surgical patients [1, 2]. It involves nausea, retching, or vomiting within 24–72 hours after surgery in hospitalized patients [3]. PONV can cause severe health problems, including suture dehiscence in patients who cannot tolerate increased abdominal pressure or strain on suture lines, esophageal tears, postoperative bleeding, hematoma formation, dehydration, and aspiration pneumonia [4, 5]. Patients with PONV

also face a higher risk of hospital readmission compared to those without these symptoms [6]. Clinicians use various medications to prevent PONV, including serotonergic (5-HT₃) receptor antagonists, NK-1 receptor antagonists, corticosteroids, and anticholinergics. Gan et al. recommend using 1–2 prophylactic interventions for moderate-risk patients and at least two interventions for high-risk patients [7]. However, despite the availability of multiple antiemetic drug classes, no single agent is universally effective or free from adverse effects. This highlights the need for new antiemetic agents that effectively prevent PONV and offer patients a better safety and tolerability profile. Penehyclidine hydrochloride (PHC), chemically known as (2-hydroxyl-2-cyclopentyl-2-phenyl-ethoxy) quinuclidine, is an anticholinergic agent with antimuscarinic and antinicotinic effects. By crossing the blood-brain barrier, PHC influences both the central and peripheral nervous systems, providing strong anticholinergic effects throughout the body [8]. In China, clinicians use PHC to treat soman and organophosphorus compound toxicity. Its bronchodilatory properties also suggest potential for treating chronic obstructive pulmonary disease (COPD) [9]. Previous studies demonstrated that transdermal scopolamine,

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another anti-cholinergic agent, is effective in reducing the incidence of PONV [10, 11]. However, these reviews also highlighted several adverse effects associated with its use, including visual disturbances, dry mouth, agitation, and sedation [10, 11]. Several studies across various surgical settings have investigated the effectiveness and safety of PHC in preventing postoperative nausea and vomiting [12, 13, 14, 15, 16]. Consequently, we performed a systematic review and meta-analysis of all randomized controlled trials (RCTs) that assessed the efficacy and safety of PHC in reducing the incidence of postoperative nausea and vomiting.

2. Methods

2.1. Data collection and extraction

We searched the Medline/PubMed, Web of Science, Scopus, and Cochrane Library databases from inception up to December 2024 using the following search terms: (“Penehyclidine” OR “Penehyclidine hydrochloride raceme” OR “Penehyclidine hydrochloride”) AND (“Nausea” OR “Vomiting” OR “PONV” OR “Emesis” OR “Emeses”))

We removed duplicates with EndNote 20.5 software (Clarivate Analytics, PA, USA). Reference screening followed two phases: first, three authors independently reviewed titles and abstracts to assess relevance, and then they examined the full-text articles to confirm eligibility for quantitative analysis. A fourth author helped resolve any disagreements through discussion. We used the Rayyan website to facilitate the screening process [17]. This systematic review and meta-analysis protocol was registered on PROSPERO (CRD42025605004) on 02 January 2025.

We included RCTs that assessed the efficacy and safety of PHC in preventing PONV in patients undergoing any type of surgical procedure and receiving PHC. Included studies reported at least one of the following outcomes: incidence of PONV, time to first vomit, or incidence of adverse events. The control group in all the studies included received 0.9% normal saline as a placebo. We excluded non-RCT studies and studies with insufficient reporting of relevant outcomes. In these studies, PHC was not the primary intervention for PONV prevention, animal studies, or any study not published in English. For overlapping study populations, the most recent publication was chosen for inclusion. Four co-authors independently extracted the data to an MS Excel sheet, with any conflicts regarding study inclusion resolved by E.A. Extracted data were organized into two domains: (1) Baseline characteristics of the study population and (2) Study outcomes.

In the included studies, the dosage of PHC varied but remained within a similar range. Lu et al., Wang et al., and Ding et al. administered a fixed intravenous dose of 0.5 mg, while Sun et al. and Zhao et al. used a weight-based approach, with a dose of 10 $\mu\text{g}/\text{kg}$, capped at a maximum of 0.5 mg. Additionally, Zhao et al. employed a continuous infusion of PHC at 10 $\mu\text{g}/\text{kg}$ at a fixed rate of 2.0 mL/h over 48 hours in a postoperative analgesia pump.

2.2. Outcomes

The primary endpoint is the Incidence of PONV, defined as the development of nausea, retching, or vomiting at any time within the 72-hour postoperative period and the requirement of rescue antiemetics. Secondary outcomes included the incidence of dry mouth, dizziness, the requirement of rescue analgesics, and headache. We analyzed the overall rate of incidence of PONV regardless of time.

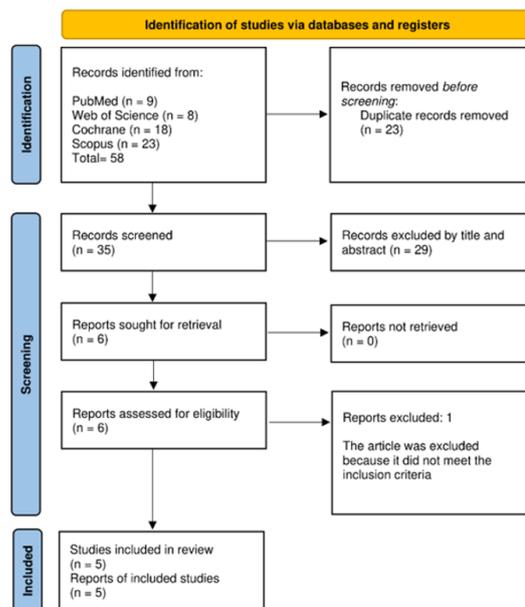


Figure 1: PRISMA flow diagram of the study

2.3. Risk of Bias Assessment

We used the revised Cochrane risk-of-bias tool (RoB2) for RCTs to evaluate the risk of bias in the included clinical trials [18]. This assessment included the randomization process, concealment of the allocation sequence, deviations from intended interventions, use of appropriate analysis to estimate the effect of the assigned intervention, outcome measurement, selection of reported results, and overall risk of bias. The methodological quality of the studies was categorized as either low risk, some concerns, or high risk of bias. Two independent co-authors (AM, IT) assessed the risk of bias, and disagreements were resolved through discussion with a third author (EA).

2.4. Statistical Analysis

We used RevMan (Version 5.3 for Windows) for statistical analysis [19]. Heterogeneity was assessed through visual inspection of forest plots and statistically using the I-squared and Chi-squared tests. When significant heterogeneity was detected (Chi-squared $p < 0.1$), we applied a random-effects model, which assigns relatively greater weight to smaller studies to account for heterogeneity. Otherwise, a fixed-effects model was employed. To address heterogeneity, we conducted sensitivity analyses systematically, excluding one study at a time. The pooled effect size (risk ratio) and its corresponding 95% confidence interval were calculated using the Mantel-Haenszel method. Extracted data were entered into a spreadsheet and carefully checked for accuracy.

3. Results

3.1. Literature search

The search strategy yielded 58 relevant articles. Of these, 23 duplicate articles were removed, and 35 were included in the title and abstract screening phase. Ultimately, six articles were selected for full-text review, resulting in the exclusion of one article. Finally, five eligible RCTs comprising 979 patients were included in the final meta-analysis [12, 13, 14, 15, 16] (Table 1) and (Table 2).

Table 1: Baseline Characteristics of Included Studies

| Study ID | Type of Study | Groups | Sample Size | Age (years), Mean (SD) | Females, n (%) | BMI, kg/m ² , Mean (SD) |
|----------------|---------------|----------------------|-------------|------------------------|----------------|------------------------------------|
| Zhao 2024 [16] | RCT | PHC | 46 | 44.1 (11) | 46 (100%) | 23.8 (4.1) |
| | | Placebo | 46 | 48.8 (12) | 46 (100%) | 24.9 (4.8) |
| Ding 2023 [12] | RCT | Placebo | 113 | 34 (9) | 88 (77.8%) | 38 (7) |
| | | PHC | 221 | 33 (8) | 153 (69.2%) | 38 (7) |
| Wang 2022 [15] | RCT | Placebo | 118 | 25 (4.50) | 81 (68.6%) | 20.5 (2.93) |
| | | PHC bolus | 117 | 24.33 (5.25) | 82 (70.1%) | 20.37 (2.40) |
| | | PHC bolus + infusion | 118 | 25.33 (5.25) | 81 (68.6%) | 21.2 (3.08) |
| Lu 2022 [13] | RCT | TIVA + PHC | 50 | 42.8 (9.6) | 37 (74%) | - |
| | | TIVA only | 50 | 43.6 (10.1) | 33 (66%) | - |
| Sun 2021 [14] | RCT | PHC | 114 | 11 (14) | 57 (50%) | - |
| | | Placebo | 104 | 10 (11) | 43 (41.3%) | - |

PHC, Penehyclidine Hydrochloride; RCT, Randomized Controlled Trial; BMI, Body Mass Index; SD, Standard Deviation

Table 2: Surgical and Anesthetic Characteristics of Included Studies

| Study ID | Groups | ASA | | Apfel Risk Score | | | Duration of Surgery, Mean (SD) | Duration of anesthesia, Mean (SD) | Length of stay in PACU, Mean (SD) |
|----------------|----------------------|---------|---------|------------------|------------|------------|--------------------------------|-----------------------------------|-----------------------------------|
| | | ASA 1/2 | ASA 2/3 | 2 | 3 | 4 | | | |
| Zhao 2024 [16] | PHC | - | 27/19 | 1 (2.2%) | 25 (54.3%) | 20 (43.5%) | 120.5 (60.6) | 147.1 (63.1) | - |
| | Placebo | - | 28/18 | 2 (4.3%) | 22 (47.8%) | 22 (47.8%) | 105.7 (55.3) | 132.2 (58.5) | - |
| Ding 2023 [12] | Placebo | - | 49/64 | 48 (42%) | 46 (41%) | 4 (4%) | 77 (22) | 93 (22) | 66 (23) |
| | PHC | - | 103/118 | 97 (44%) | 67 (30%) | 6 (3%) | 76 (22) | 92 (23) | 66 (27) |
| Wang 2022 [15] | Placebo | - | - | - | - | - | 201.33 (59.29) | 252 (69.05) | - |
| | PHC bolus | - | - | - | - | - | 209.67 (51.79) | 262.67 (56.30) | - |
| | PHC bolus + infusion | - | - | 30 (25.4%) | 71 (60.2%) | 11 (9.3%) | 204.33 (49.53) | 254.33 (52.54) | 83 (53.29) |
| Lu 2022 [13] | TIVA + PHC | 97/20 | - | 32 (27.4%) | 66 (56.4%) | 16 (13.7%) | 76.6 (13.9) | 95.9 (14.5) | 76 (58.55) |
| | TIVA only | 91/27 | - | 28 (23.7%) | 61 (51.7%) | 20 (16.9%) | 75.5 (15.5) | 95.9 (16.7) | 76.67 (60.04) |
| Sun 2021 [14] | PHC | - | - | - | - | - | 30 (16) | 63.5 (20) | 60 (30) |
| | Placebo | - | - | - | - | - | 28 (16) | 64 (17.3) | 59 (30) |

PHC, Penehyclidine Hydrochloride; RCT, Randomized Controlled Trial; TIVA, Total Intravenous Anesthesia; ASA, American Society of Anesthesiologists Physical Status Classification; SD, Standard Deviation; PACU, Post-Anesthesia Care Unit

The screening process is illustrated in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram (**Figure 1**). According to the Cochrane RoB 2 assessment, one study had an overall low risk of bias, whereas the other four studies had some concerns (**Supplementary Figure 1**).

3.2. Primary outcomes

PHC was associated with a significant decrease in the incidence of PONV (RR: 0.64, 95% CI [0.50, 0.82], $p = 0.0004$) compared to normal saline (**Figure 3**). However, the pooled studies were heterogeneous ($p = 0.04$, $I^2 = 61\%$). We conducted a sensitivity analysis in multiple scenarios. Heterogeneity was best resolved by excluding the study by Ding 2023 ($p = 0.46$, $I^2 = 0\%$). In the meta-analysis model, the overall risk ratio was still in favor of PHC (RR = 0.59, 95% CI [0.50 to 0.71], $p < 0.00001$) (**Figure 4**).

PHC significantly reduced the need for rescue anti-emetics compared to normal saline (RR: 0.46; 95% CI [0.22, 0.96]; $p = 0.04$), as shown in (**Figure 5**). However, the pooled studies showed considerable heterogeneity ($p = 0.002$, $I^2 = 76\%$). We conducted a sensitivity analysis. Excluding the study by Ding et al., 2023, most effectively resolved the heterogeneity ($p = 0.77$, $I^2 = 0\%$). After this adjustment, the meta-analysis still favored PHC, with an overall RR of 0.36 (95% CI [0.24, 0.55], $p < 0.00001$) (**Figure 6**).

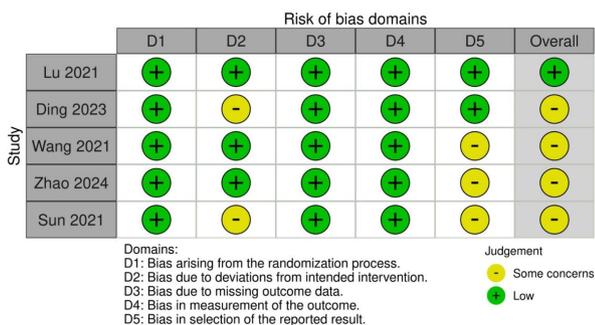


Figure 2: Risk of bias 2 diagram

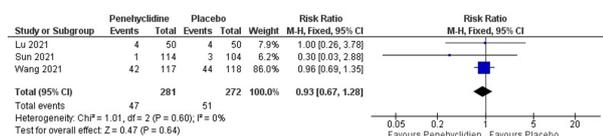


Figure 3: Forest plot of postoperative nausea and vomiting (PONV)

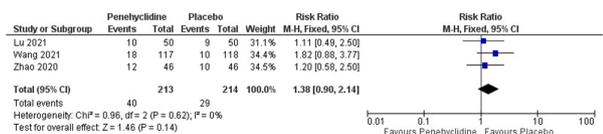


Figure 4: Forest plot of sensitivity analysis for PONV

3.3. Secondary Outcomes

PHC showed no significant difference from normal saline in the requirement for rescue analgesics (RR: 0.93; 95% CI [0.67, 1.28], $p = 0.64$). The pooled studies were homogeneous ($p = 0.60$, $I^2 = 0\%$), as illustrated in (**Supplementary Figure 2**). The use of PHC did not demonstrate a statistically significant difference in dizziness

occurrence compared to normal saline (RR: 1.38; 95% CI [0.90, 2.14], $p = 0.14$). The combined studies exhibited homogeneity ($p = 0.62$, $I^2 = 0\%$) (**Supplementary Figure 3**). The administration of PHC showed no significant effect on headache incidence compared to normal saline (RR: 1.00; 95% CI [0.53, 1.88], $p = 1.00$). The aggregated studies demonstrated homogeneity ($p = 0.70$, $I^2 = 0\%$), as shown in (**Supplementary Figure 4**). PHC was linked to a significantly higher occurrence of dry mouth when compared to normal saline (RR: 2.64; 95% CI [1.98, 3.50], $p < 0.00001$). The pooled studies were homogeneous ($p = 0.50$, $I^2 = 0\%$), as presented in (**Supplementary Figure 5**).

4. Discussion

This study aimed to investigate the effectiveness and safety of the novel anti-cholinergic drug PHC in preventing PONV. Our findings revealed that PHC significantly lowered the incidence of PONV while maintaining a commendable safety profile. Notably, PHC substantially reduced the need for rescue anti-emetics, although it markedly increased dry mouth incidence. In contrast, PHC had no meaningful impact on headache, dizziness, or the requirement for rescue analgesics.

PONV demonstrates a critical challenge for surgeons and anesthesiologists, significantly affecting patient outcomes. It can lead to severe complications such as aspiration of gastric contents, which may result in aspiration pneumonitis and wound dehiscence [20]. Moreover, PONV heightens the risk of postoperative bleeding and airway obstruction caused by hematoma formation, further worsening wound complications and intensifying postoperative pain. These complications collectively hinder recovery, extend hospital stays, and diminish patient satisfaction [4].

Vomiting is a complex neural reflex driven by five main afferent pathways: the chemoreceptor trigger zone (CTZ), the vagal mucosal pathway in the gastrointestinal tract, neuronal pathways from the vestibular system, reflex pathways from the cerebral cortex, and midbrain afferents [21]. Activation of any of these pathways can trigger the vomiting response, mediated by various receptors, including cholinergic, dopaminergic, histaminergic, and serotonergic (5-HT₃) receptors [22].

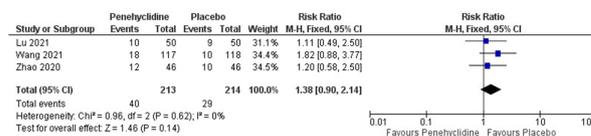


Figure 5: Forest plot of the requirement of rescue anti-emetics

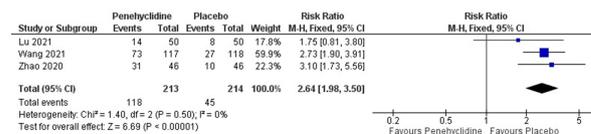


Figure 6: Forest plot of sensitivity analysis of the requirement of rescue anti-emetics

Type 1 muscarinic acetylcholine receptors, predominantly expressed in the vestibular system, play a key role in cholinergic transmission. Anticholinergic drugs block this transmission from the vestibular nuclei to the higher CNS and from the medullary reticular formation to the vomiting center [10]. Nonselective

muscarinic receptor antagonists like scopolamine and atropine are widely used to prevent nausea and vomiting linked to motion sickness [23].

PHC, an anticholinergic drug, selectively targets muscarinic 1 (M1) and muscarinic 3 (M3) acetylcholine receptor subtypes. This mechanism of action aligns with its observed effectiveness in reducing the incidence of PONV. Beyond its antiemetic properties, PHC provides organ protection, benefiting the heart and lungs through its antioxidant, antiapoptotic, and anti-inflammatory effects. Administering PHC prior to surgery enhances the depth of anesthetic sedation and prolongs the inhibition of respiratory secretions, making it particularly advantageous in surgical settings [24, 25, 26]. Additionally, Liang et al. found that PHC administration at a dose of 0.012mg/kg could reduce propofol dosage for anesthesia induction without affecting Bispectral index (BIS) values [27].

PHC demonstrates a longer half-life (10.35 hours) compared to scopolamine (1.35 hours), another anticholinergic drug commonly used for PONV prophylaxis [28]. While scopolamine significantly influences autonomic cardiovascular regulation by increasing vagal cardiac inhibition and lowering blood pressure in healthy young individuals, it can also cause postoperative tachycardia when administered transdermally [29, 30]. In contrast, Penehyclidine's selective antagonism of M1 and M3 receptors allows it to inhibit vagal reflexes without affecting heart rate [26]. Wang et al., who found that PHC did not increase cardiovascular side effects compared to placebo, confirmed these cardiovascular safety benefits [15]. Though not based on direct comparisons, these findings suggest that PHC may be an equally effective alternative to scopolamine for PONV prevention but with fewer unwanted cardiovascular side effects. Future head-to-head trials comparing Penehyclidine and scopolamine are warranted to validate these observations.

Additionally, PHC boasts a more favorable side-effect profile than other antiemetics commonly used for PONV prevention. While dry mouth remains its most frequent adverse effect, it avoids the complications associated with drugs like dexamethasone, such as delayed wound healing, hyperglycemia, and heightened infection risks, particularly in vulnerable patients like those with diabetes [31, 32]. Ondansetron, another widely used 5-HT₃ antagonist, has well-established efficacy and safety in preventing nausea and vomiting. However, it may cause headaches and a slight prolongation of the QT interval, warranting cautious use in at-risk patients [33].

Our analysis included studies with different patient populations, surgical procedures, and anesthesia techniques, leading to some variability. Some studies used a combination of intravenous and inhalational anesthesia, while others used total intravenous anesthesia (TIVA), which is generally associated with a lower risk of PONV [34]. This difference in anesthesia methods is important because inhalational agents can increase PONV risk, while TIVA has a protective effect [35, 36]. Additionally, the included studies assessed PHC across a range of surgical procedures, including gynecological laparoscopy, thyroidectomy, orthognathic surgery, strabismus surgery, and bariatric surgery, each carrying a different baseline risk for PONV. Notably, PHC did not significantly decrease the incidence of PONV in bariatric surgery, suggesting that its efficacy may depend on specific surgical and patient-related factors. However, the overall trend across studies demonstrated a reduction in PONV incidence with PHC, supporting its potential as an effective antiemetic in most surgical settings.

Our study constitutes the first comprehensive systematic review and meta-analysis assessing the efficacy and safety profile of the anti-cholinergic agent PHC in alleviating the incidence of PONV.

However, this study exhibits certain limitations. The patient cohort was relatively small and derived from a single center. Moreover, all of the studies included in our meta-analysis enrolled participants of Chinese descent, which may influence the external validity and potentially introduce selection bias. Furthermore, the types of surgical procedures across the analyzed studies displayed varied heterogeneity. Additionally, the included studies varied in anesthetic protocols, with some using inhalational anesthesia and others employing total intravenous anesthesia (TIVA), which has a lower baseline risk of PONV.

5. Conclusions

Our meta-analysis indicated that PHC significantly reduced the incidence of PONV compared to placebo. The most commonly reported adverse effect was dry mouth, while other side effects, such as dizziness and headache, were less frequent. The overall safety profile suggests that PHC-related adverse effects are generally mild and tolerable. However, further large-scale randomized controlled trials are needed to confirm these findings, explore optimal dosing strategies, and compare PHC with other antiemetic agents.

Conflicts of Interest

The authors declare no competing interests that could have influenced the objectivity or outcome of this research.

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Large Language Model Statement

The manuscript was language-edited using a LLM strictly to refine clarity, grammar, and readability. No new content was created or collected during this process, ensuring the original scientific content remained unchanged.

Authors Contribution

AMH and EA contributed equally to this work and were responsible for study conceptualization, data curation, formal analysis, and visualization. MW, KO, ATS, IT, MA, and AA assisted with methodology development, data validation, and critical review. MS, SE, and AH contributed to manuscript review and editing. AH supervised the project. All authors reviewed and approved the final version of the manuscript. AMH serves as the corresponding author and is responsible for all communication regarding this work.

Data Availability

This review article contains no new primary data. All information discussed is derived from previously published sources and publicly available databases, as cited in the manuscript.

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Review Article

Challenges and Infectious Complications in Living Donor Liver Transplantation in Egypt: A Comprehensive Review

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ABSTRACT

Background: Living donor liver transplantation (LDLT) is a crucial therapeutic option for patients with end-stage liver disease in Egypt, where deceased donor grafts are scarce. This study aims to investigate the challenges and infectious complications associated with LDLT in Egypt.

Methods: A comprehensive review of relevant literature was conducted, focusing on factors affecting donor selection, the prevalence of infections in recipients, and the impact of healthcare providers' knowledge on organ donation. The study included data on complications affecting donors and recipients in the context of LDLT.

Results: The high prevalence of the hepatitis C virus and poverty in Egypt negatively impact the live donor pool. Lack of knowledge about liver donation, inadequate media coverage, and family pressure contribute to the low number of liver donors. Infectious complications play a significant role in the outcomes of LDLT, with bacterial infections being the most common. Donors also experience complications, with intraabdominal collections and pneumonia being the most frequent. Healthcare providers' knowledge and attitudes toward organ donation need improvement, and educational efforts should be tailored to the cultural and religious context.

Conclusion: Addressing the challenges in donor selection, raising public awareness about organ donation, and improving healthcare providers' knowledge are essential steps toward optimizing LDLT outcomes in Egypt. Moreover, it is crucial to monitor and manage infectious complications in both donors and recipients to ensure the success of the transplantation process.

1. Introduction

End-stage liver disease (ESLD) refers to patients with chronic liver failure who have irreversible damage and become decompensated with cirrhosis complicated with ascites, variceal hemorrhage, hepatic encephalopathy, or renal failure. ESLD is caused by various factors, including viral hepatitis, alcoholic hepatitis, metabolic disorders, and selected hepatic malignancies. In Egypt, HCV is

the leading cause of chronic liver disease (24.3% prevalence) and is linked to schistosomiasis [1, 2]. Living donor liver transplant (LDLT) is an established treatment option for patients with ESLD. There are three types of liver transplant (LT): Deceased donor liver transplant (DDLT), transplants from living donors, and split transplants.

The prevalence of HCV in Egypt is the highest in the world, and LT is the only curative option for these patients. The first LDLT was performed in 1991 at the National Liver Institute in Egypt, and it is now a mainstay of therapy for patients suffering from ESLD [3, 4]. Due to cultural and logistical obstacles, the DDLT program has not yet been implemented in Egypt. Despite the ongoing reliance on LDLT in Egypt, systemic changes are emerging to support the introduction of deceased donor programs [5]. A large study found that age, pre-transplant diabetes, overweight status, and use of mTOR inhibitors significantly increase the risk of developing metabolic syndrome after LDLT in Egypt [5, 6]. This review aims

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to discuss the current status of Living Donor Liver Transplants in Egypt. It will also outline the challenges and complications associated with LT and the possible solutions.

2. Methods

A comprehensive literature search was done on relevant databases, including PubMed, Google Scholar, Scopus, Web of Science, and Cochrane. We used relevant keywords such as “Liver Cancers,” “Portal System Infections,” “Living Donor Transplants,” “Transplants in Egypt,” “Liver Transplants History,” “Hepatitis C in Egypt,” “Donor Selection,” “COVID-19” and “Organ Donation Awareness” and combined them with their synonyms using appropriate Boolean operators (AND, OR). Studies on living donor liver transplants in Egypt and those focusing on their infectious complication or history were included. Studies must be published in a peer-reviewed journal in English, and full-text articles must be available. The articles included were from inception to date and included systematic reviews, meta-analyses, original reviews, and narrative reviews.

Case reports, case series, and articles unrelated to living donor transplants in Egypt disorders, infectious complications, or their associations were excluded. Unpublished articles or ones published in a language other than English were also excluded.

3. Discussion

3.1. History and current status

In 1963, Starzl et al. [7] described the first three trials of deceased donor liver transplantation (DDLTL) that led to a 100% hospital mortality rate. Cyclosporine and advancements in graft preservation techniques have made DDLTL a more reliable curative treatment [8]. Although DDLTL has become a standard of care, the paucity of donors, technical difficulties, and cultural controversies have posed significant challenges to its use. As a result, LDLTL emerged as an alternative to DDLTL. In 1987, Strong et al. performed the first successful LDLTL between a mother and her son [9]. Historically, Egypt has had the highest prevalence of the Hepatitis C virus (HCV) in the world, contributing to the high burden of end-stage liver disease. Based on a systematic review published in 2013, Egypt has a prevalence of 14.6% of HCV [10].

As brain death and cadaveric organ transplantation are not yet widely accepted in Egypt due to cultural and ethnic controversies, LDLTL remains the only option for patients with ESLD. A surgical team from the National Liver Institute of Menofya University performed the first LDLTL in Egypt in 1991 with suboptimal results, as the longest recipient survival was 11 months. As a result, Egypt began to develop centers for liver transplantation with the assistance and supervision of international experts, resulting in a more ambitious and prestigious process. The LDLTL program at a private tertiary center was established in 2001. Egypt currently has thirteen comprehensive liver transplant centers [11].

A cross-sectional study in 2013 examined the current state of transplantation in the Arab world. According to the study, 3804 liver transplants were performed in 11 different Arab countries between 1990 and 2013, 2130 (56%) were performed in Egypt, and most were performed for HCV cirrhosis. Interestingly, all of them except two were LDLTLs [4]. The collective data from 2014 to the present is limited. The field of liver transplantation in Egypt continues to improve, but reporting of these improvements is lacking.

3.2. Pediatric liver transplantation

Pediatric liver transplantation has its own set of indications and challenges. The most common indications for liver transplantation are chronic liver disease and its complications, genetic disorders, hepatic tumors, and re-transplantation [12]. The number of liver transplants for pediatric patients in Egypt is limited. According to estimates, only 160 LDLTL procedures were performed by 2013 [11]. A study reviewed the current status of pediatric liver transplantation and its limitations at a university hospital in Egypt. The study followed 41 pediatric patients who were referred for liver transplantation. Within the study period of six months, only four patients received LDLTL, and eight patients, unfortunately, passed away while waiting for a transplant. There were several levels of limitations. For recipients, late presentations and existing comorbidities were the most common limitations. On the donor side, refusal to donate was the most common limitation. Regarding the transplant program, it was not possible to perform surgery on patients who were less than one year of age or weighed less than eight kilograms. This limited the chances of nearly half of the participants. There was also a limitation in the lack of re-transplantation resources in the institution, which was necessary for one patient [13]. Re-transplant in Egypt: The data for the status of liver re-transplantation in Egypt is lacking. More studies are needed to explore this important aspect of liver transplantation.

3.3. Liver Transplantation in the COVID-19 Era

During the COVID-19 pandemic, liver transplantation was disrupted, as were many other healthcare services. Several steps were taken to minimize infection transmission between transplant patients and healthcare workers (HCWs), including small team groups and better distribution of workloads, periodic training, and audits by infection control teams, as well as appropriate personal protective equipment. For example, the LDLTL program at El-Manial Specialized Hospital at Cairo University reopened on August 26, 2020, after a closure period when the national quarantine began in early March.

COVID-19 is considered a high-risk infection for patients who have undergone a liver transplant due to their immunosuppressive medications and concomitant morbidities. In order to safeguard the well-being of patients before and following transplantation procedures, a multitude of protocols have been meticulously instituted. These encompass comprehensive screening assessments for donors and recipients in conjunction with rigorous infection prevention and control measures. Despite all precautions, one of the three liver transplant recipients mentioned in the study contracted COVID-19 on his eleventh post-transplant day and was re-admitted to the intensive care unit. Later on, his respiratory symptoms resolved, and he was discharged safely from the hospital [14].

A retrospective analysis of 41 living donor liver transplant recipients at a tertiary center assessed the outcomes of COVID-19 infection. Viral PCR and CT chest criteria were used to detect COVID-19 infection from April 2020 to April 2021. The patients were categorized into mild, moderate, severe, and critical, according to the National Health Commission of China. Approximately 30% of patients showed mild symptoms, 46.5% showed moderate symptoms, 14% were severe, and 9% were considered critical. Two patients died, resulting in a mortality rate of 5%. The severity of the disease was associated with female gender, obesity, and hypertension. The limited number of participants presented a challenge to the study [15].

Although the effectiveness of the COVID-19 vaccine in solid organ transplant recipients is lower than in the general population, a

recent study conducted in Canada found a significant improvement in vaccination effectiveness against hospitalization and mortality after the third dose of the vaccine [16]. Therefore, national medical societies and authorities should strive to improve vaccine delivery, especially for vulnerable patients following liver transplantation. The World Health Organization (WHO) reported in December 2022 that less than 40% of the Egyptian population had been fully vaccinated. There are no details on the delivery of the booster vaccinations.

3.4. Quality of life after transplantation

Understanding and anticipating the quality of life after treatment are crucial components of an informed decision-making process, which is essential to patient autonomy. A significant operation, such as hepatic transplantation, necessitates implementing a predictive model that is, to some extent, anticipated and acknowledged by both the medical professionals and the patient involved. Additionally, it may predict survival for both patients and grafts. Researchers at a university hospital used the validated health-related quality of life (HRQOL) questionnaire in its Arabic version to assess the quality of life of 35 liver transplant recipients before and after transplantation at one and six months. All dimensions of HRQOL improved significantly after transplantation. However, 17 highly educated patients who repeated the test one year after transplantation reported no improvement in mental health other than a limitation in their role [17].

Another study combined HRQOL with the liver disease quality of life 1.0 (LDQOL 1.0) to evaluate the quality of life in the pre-transplantation and post-transplantation phases for 103 patients and 50 patients on a waiting list. As a result of both questionnaire components, all recipients had significantly higher HRQOL scores than those on the waiting list [18]. Since LDLT has a significant effect on the donors as well as the recipients, a cohort study evaluated the quality of life of 30 normal volunteers and 30 donors between six months and four years after surgery using the short form 36 (SF-36 V2) at a private hospital. The quality of life after full recovery was not compromised. They resumed their regular activities within two to four months [19]. Another study used the Physical, Cognitive, Affective, Social, Economic, and Ego Functioning (PCASSE) quality of life questionnaire to measure 33 living liver donors' quality of life, which included emotional and physical aspects. At the second follow-up visit, three months after surgery, their scores were significantly lower than at baseline. Patients were able to return to their normal activities and occupations, which significantly affected the social domain of the questionnaire. Again, the overall quality of life was not reduced after complete resolution [20].

3.5. Challenges and opportunities

3.5. Challenges and opportunities The transplantation of livers in Egypt is faced with many challenges. The shortage of organs in the face of increased demand for liver transplantation is one of the most pressing issues [4]. The lack of legislation in Egypt that permits deceased liver transplantation is one of the reasons for this shortage [21]. Although deceased liver transplants have been legalized in other Arab countries, their implementation remains limited due to cultural and logistical barriers [21]. The living donor liver transplant is the only one performed in Egypt and is associated with its challenges and risks [22]. In addition to these risks, the donor faces a risk of morbidity of 52.17% and mortality of 0.29% [23, 22]. After the donation, the donor's quality of life declines in the month following the donation but returns to its pre-donation level after three months [24].

Aside from the strict laws governing donation, LDLT is also hampered by the requirement that donors must be related to recipients, and if a donor cannot be found, the legal team must document the failure before finding a non-related donor who must be evaluated twice by an independent psychiatrist [25]. Additionally, the cost of the medical evaluation process that the donor must undergo ranges from 1050 to 1455 USD [26, 27]. Around 51.72% of patients awaiting liver transplantation are delisted due to the absence of a related donor [28].

Egypt's high HCV prevalence and poverty negatively impact the live donor pool [4]. About 56.6% of donors are rejected for donation [26], and about 96.2% of recipients are in contact with an excluded donor, with a median of three donors per recipient [29]. Anatomical variations are the most common cause of exclusion, followed by viral hepatitis [30]. Several factors contribute to the low number of liver donors in Egypt, including a lack of knowledge about liver donation, inadequate media coverage, and family pressure [21, 29]. According to a survey, 47% of Egyptians are willing to donate their organs after death. As soon as the participants were provided with information regarding the process, regulations concerning organ donation, and consenting options, this percentage increased to 78%. Furthermore, the participants did not understand the Egyptian transplant law articles. Many community-based interventions have successfully changed public behavior, especially in rural areas. Therefore, raising public awareness about organ donation through mass media campaigns and involving religious leaders and scholars is paramount [31]. One survey found that only 34% of healthcare providers would be willing to donate a liver. In Egypt, 53% of healthcare providers are unaware of the opinion of their religion regarding transplants, and 83% are dissatisfied with how the media covers organ donation [21]. A survey revealed that Egyptian medical students lacked an understanding of the legal aspects of organ donation (OD) and the OD process, negatively affecting their attitude towards OD. The undergraduate medical curriculum should be revised to emphasize the importance of organ transplantation and to define the concept of brain death to assist our prospective doctors in educating the public about this procedure and its advantages. Religious and cultural backgrounds should be taken into account in these approaches, as they play a significant role in influencing the decisions of Egyptians [32]. Continuing medical education for HCPs regarding liver transplantation and a better understanding of their religion's position on organ donation will enable them to recruit more donors [21]. A lack of suitable living donors and the lack of deceased donor grafts in Egypt has led to many Egyptian patients seeking transplants abroad in what is known as transplant tourism, where there are ample deceased donors [33, 29].

3.6. Complications associated with LDLT recipients

There is no doubt that infectious complications are among the most significant factors influencing the outcome of living donor transplantation for both the donor and the recipient. Infectious complications can be categorized into early or late complications.

3.7. An overview of early and late infections

A study of 128 liver transplant recipients found that bacterial infections were the most common early complications. The most prevalent pathogens among the study's survivors were *Klebsiella* and *Pseudomonas*. *Acinetobacter* dominated the non-survivors, followed by Methicillin-resistant *Staphylococcus aureus* (MRSA). In the same study, 29 patients experienced early mortality following LDLT, with sepsis accounting for 58% of the deaths. Within the initial year of the investigation, 23 participants experienced

mortality, among whom five succumbed to sepsis, accounting for approximately 22% of the deaths. Four of them had CMV infection, one isolated from CMV, and three had concomitant bacterial infections (*Pseudomonas*, enterococci, and *Acinetobacter*), as well as disseminated candida in two of them. The fifth patient who died of sepsis without contracting CMV had a single *Staphylococcus cohnii* infection [34].

Infections that develop during the early, intermediate, or postoperative periods are more likely to result in death. A separate study revealed that out of 128 patients, 53.1% acquired infections during the early postoperative period and 27.3% during the intermediate postoperative period. The mean survival of recipients with early infections (approximately 30.7%) and intermediate infections (about 25.4%) was significantly lower than that of recipients without pretransplant infections. MSSA, MRSA, and *Acinetobacter* infections were associated with a higher mortality rate following transplantation. Similarly, recipients with CMV and *Klebsiella* infections were more likely to die during the intermediate period [35].

A multicenter study found that 416 infections occurred in 127 (52%) of the 246 patients who underwent LDLT and participated in the study. Gram-negative bacteria caused 310 infections (74%), while Gram-positive bacteria caused 87 infections (21%). *Pseudomonas aeruginosa* accounted for the majority of infections (110 episodes, or 26%), followed by *Klebsiella* species (79 episodes, or 19%), *Escherichia coli* (69 episodes, or 16%), *Acinetobacter baumannii* (33 episodes, or 8%), and MRSA (32 episodes, or 7.7%) [36].

3.8. Site of infection

Almost all patients, including a few with cholangitis, had an intra-abdominal bacterial infection. Other common infection sites include the lungs, urinary tract, and wounds [34]. In another study, 73.3% of the 45 patients had bacterial infections. Infections most frequently occur in the bile. Additionally, isolated Gram-negative bacteria were the most prevalent. Some individuals experienced only a single episode, while others experienced multiple episodes. *Acinetobacter baumannii* was the most frequently isolated organism in both single and repeated infection episodes (19% and 33.3%, respectively), followed by *Escherichia coli* for repeated infections (11.1%) and *Pseudomonas aeruginosa* for single infections (19%) [37]. The most frequent site in 246 individuals, the biliary tract, affected 169 patients (or 40.6%), followed by the abdominal area (129 patients, or 31.0%), pneumonia, 44 patients, or 10.6%, bloodstream patients, 39 patients, or 9.4%, and urinary tract infections, 35 patients, or 8.2% [37].

3.9. Hospital-associated infections

In a scholarly investigation involving 337 ESLD patients admitted to the intensive care unit (ICU), it was observed that approximately 36.5% (n=123) were suspected of having healthcare-associated infections (HAIs), with 57 of these cases subsequently receiving confirmation. The most reported hospital-associated infections were bloodstream infections (49.1%), urinary tract infections (31.6%), pneumonia (12.3%), and spontaneous bacterial peritonitis (7%). Several Gram-positive bacteria were responsible for HAIs, with *Staphylococcus aureus* accounting for the majority (12/20, 60%). Gram-negative bacteria most commonly found were *Escherichia coli* (12/57, 21.1%). Gram-negative bacteria's prevalence is higher than Gram-positive bacteria's (43.9% versus 40.4%). Fungal infections were reported in 15.8% (9/57) of the patients. *Candida* species were the most prevalent (12.3%). Anaerobic infection was not detected. The discovery of *Sphingomonas paucimobilis* and

Achromobacter denitrificans as pathogens for UTI and BSI, respectively, in the ICU was a first [38]. A study on *Klebsiella pneumoniae* isolates in liver transplant recipients found full resistance to several antibiotics, with Amikacin being the most effective (50% efficacy), highlighting the need for targeted antibiotic strategies [39].

3.10. Impact of pre-transplant infection

The results of a study involving 50 patients with chronic liver disease who underwent liver transplantation revealed that those with high scores on the Model for End-Stage Liver Disease were more prone to infection, both before and after surgery. Chest infection was the most prevalent infection (n=10), followed by nasal mucosal infection (n=8), UTI (n=6), SBP (n=4), and gastroenteritis (n=1). The mortality rate was elevated at 40%, compared to a 23.3% mortality rate observed in 30 patients who did not present with infections prior to transplantation. The impacted group's causes of death were primarily medical (infections and sepsis), approximately 75%, compared to 28.6% in the other group [40].

3.11. Hepatitis C virus (HCV)

Today, chronic HCV infection, predominantly genotype 4, is the leading cause of ESLD and the primary reason for liver transplantation, according to a study conducted at the Gastrointestinal Surgery Center at Mansoura University. A total of 453, or 90.6%, of the 500 participants were infected with HCV. A total of 450 individuals (about 90%) had HCV recurrences, which required administering antiviral medications following surgery [41]. While following 38 patients in different settings, recurrence was observed in 10 individuals (26.3%), with the smaller the graft, the higher the recurrence rate [42]. In the following study of 74 patients with HCV infection who were undergoing LDLT for end-stage cirrhosis or HCC, the latter finding was refuted. Among the 74 individuals, 23 (31.1%) had recurrences of HCV. Researchers found that despite the absence of serum hepatitis B virus deoxyribonucleic acid in recipients, pre-transplant positive antibody to hepatitis B core antigen (total) was significantly associated with the recurrence of HCV [43]. This high rate of HCV recurrence led to the conclusion that Sofosbuvir-based regimens were effective with high sustained virological response rates 12 and relatively safe in a difficult-to-treat population, recurrent HCV post-LDLT [44].

3.12. COVID-19

COVID-19 infection is more likely to occur in the context of LDLT due to the risk of chronic immunosuppression; however, the consequences in terms of morbidity and the need for hospitalization or intensive care are often matched to the population [45?].

3.13. Complications associated with the donor of LDLT

It is important to note that complications do not only affect the recipient but also the donor. Multiple studies have reported infectious complications that vary according to the setting. The most commonly observed complication in a handful of donors was intraabdominal collections (21.1% of 145 patients) [22]. Among the significant early infections, pneumonia has been reported in two patients out of fifty, as well as wound infections [46, 23].

The strength of this article lies in its comprehensive coverage of the infectious complications associated with living donor liver transplantation in Egypt, addressing both the donor and recipient perspectives. It also highlights the social, cultural, and legal factors that influence the availability of liver donors in the country. By providing an extensive analysis of the different types of infections, their prevalence, and their outcomes, this article offers valuable insights for healthcare professionals, policymakers, and researchers

to understand better the challenges and opportunities in the field of liver transplantation in Egypt. The study complements recent localized data on post-transplant complications and educational interventions, though broader, multicentric studies are still needed [47]. However, the article has some limitations. Firstly, it relies heavily on existing studies, and given the dynamic nature of healthcare and the prevalence of infectious diseases, the data may become outdated over time. Secondly, the article does not directly compare the findings in Egypt to those from other countries or regions, which could have offered a better understanding of the global context.

4. Conclusions

Addressing the challenges and limitations in organ donation and transplantation can lead to better patient outcomes and a more robust healthcare system. This article presents a detailed overview of the infectious complications related to living donor liver transplantation in Egypt, emphasizing the need for improved awareness, education, and resources. Future research should focus on updating the findings presented in this article, comparing them to other regions, and exploring the potential for new strategies and interventions to improve the safety and success of living donor liver transplantation in Egypt.

Conflicts of Interest

The authors declare no competing interests that could have influenced the objectivity or outcome of this research.

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Large Language Model

The manuscript was language-edited using a LLM strictly to refine clarity, grammar, and readability. No new content was created or collected during this process, ensuring the original scientific content remained unchanged.

Authors Contribution

MA and AA conceptualized the idea; AA, AN, ME, MM, NM, EA, FA, MK, MY, ON, and MA equally contributed by reviewing, editing, performing data analysis, and refining the manuscript.

Data Availability

This review article does not contain any new primary data. All information discussed is derived from previously published sources and publicly available databases, as cited in the manuscript.

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Case Report

Acute Myeloid Leukemia Presenting as Bilateral Proptosis: A Case Report with Literature Review

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ABSTRACT

Introduction: Acute myeloid leukemia (AML), constituting 30% of pediatric malignancies, is the most common childhood cancer. This paper explores the rare presentation of AML with extramedullary involvement, specifically bilateral proptosis, in a 15-year-old boy.

Case report: The patient initially presented with worsening shortness of breath, palpitations, extreme fatigue, and bruising. Examination revealed bilateral proptosis, watery discharge from the right eye, and petechial rash. Blood investigations revealed low hemoglobin, severe thrombocytopenia, and high WBC count. Computed tomography (CT) revealed bilateral orbital infiltrative soft tissue lesions. Leukemia fusion gene screening identified RUNX1-RUNX1T1 later. The patient was admitted, received transfusions, and started on antibiotics. Despite initial improvement, he later developed sepsis, septic shock, and severe pancytopenia, necessitating intensive care and specific AML M2 targeting therapy.

Conclusion: Bilateral proptosis in AML, termed myeloid sarcoma (MS), is rare but responsive to chemotherapy. Orbital MS has higher responsiveness and survival rates in pediatric cases. The case highlights the importance of identifying AML subtypes, like RUNX1-RUNX1T1-positive AML, for tailored treatment strategies. This case underscores the challenges in diagnosing and treating pediatric AML with extramedullary involvement. Early recognition of AML subtypes is crucial for prognosis prediction and treatment tailoring.

1. Introduction

Acute leukemia, constituting approximately 30% of pediatric malignancies, stands as the most prevalent cancer in children [1]. Specifically, Acute myeloid leukemia (AML), which is the second most common form of leukemia, manifests in up to 15% of the pediatric leukemic population [2]. Leukemia, defined as a hematopoietic system malignancy, results in the infiltration of the bone marrow by myeloblasts in AML. These myeloblasts disrupt the development of normal blood cells in the bone marrow and are subsequently released into the bloodstream, reaching distant extramedullary sites such as the orbit, soft tissues, and bones, forming a solid tumor known as myeloid sarcoma (MS) [3]. While extramedullary involvement is rare in AML, it is exceptionally uncommon in bone structures [4]. Myeloid Sarcomas are most prevalent in specific AML subtypes, notably M6 (Di Guglielmo syndrome), M5a (monoblastic), M5b (monocytic), M4 (myelomonocytic), and M2 (myeloblastic with maturation) [5]. The incidence of extramedullary disease is low, accounting for 2.5–9% of AML, with 60% of Myeloid sarcomas occurring in children

under 15 years old [6]. Notably, the incidence appears slightly higher in Asia, the region of origin for our patient [7].

While extramedullary involvement in AML has been previously documented, the presentation of bilateral proptosis as the initial manifestation of AML with the RUNX1-RUNX1T1 fusion gene is exceptionally rare, with limited cases in the literature. This case contributes to understanding orbital involvement in AML and highlights the importance of early molecular characterization in guiding treatment decisions. In this report, we describe a case of AML in a 15-year-old boy who presented primarily to the Emergency Department with the chief complaint of fatigue, dyspnea, and bilateral proptosis.

2. Case Presentation

2.1. History

A 15-year-old male patient from South Asia presented with a chief complaint of worsening shortness of breath and palpitations on minimal exertion and extreme fatigue that was associated with back pain for the past 15 days. The patient has been feeling progressively weak for the past week, with no recent fever. Additionally, he reported associated bruising without any history of trauma or family history of similar conditions. The surgical history and medical history are unremarkable. There's no recent travel history for three years and no known allergies. The patient had been attending the gym for the past few months, intentionally reducing weight from 98

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Table 1: Leukemia Fusion Gene (Q30) Screening

| Translocation | Gene Fusion | Result |
|----------------------|---------------|---------------------------------------|
| t(9;11) (p22;q23) | KMT2A-MLLT3 | Fusion mRNA Not Detected |
| t(15;17) (q24;q21) | PML-RARA | Fusion mRNA Not Detected |
| t(8;21) (q22;q22) | RUNX1-RUNX1T1 | Fusion mRNA of RUNX1-RUNX1T1 Detected |
| t(4;11) (q21;q23) | KMT2A-AFF1 | Fusion mRNA Not Detected |
| t(12;21) (p13;q22) | ETV6-RUNX1 | Fusion mRNA Not Detected |
| t(1;19) (q23;p13) | TCF3-PBX1 | Fusion mRNA Not Detected |
| t(11;19) (q23;p13.3) | KMT2A-MLLT1 | Fusion mRNA Not Detected |
| t(9;22) (q34;q11) | BCR-ABL1 | Fusion mRNA Not Detected |

to 92 kg. No chest pain, abdominal pain, nausea, vomiting, changes in urine or bowel habits, melena, or blood in stool were reported.

2.2. Examination

On examination, the patient was vitally stable with a temperature of 37.1 °C, heart rate of 110, respiratory rate of 20, blood pressure of 106/60, and maintaining SpO₂ at 99% on room air. The patient has a patent airway, bilaterally equal, and clear entry with no added sounds. The patient is tachycardic, with the Glasgow Coma Scale at 15; however, he appears extremely pale. As shown in (Figure 1), bilateral proptosis of the eyes (right more than left) led to a change in facial appearance that has worsened over the past 15 days. There is a watery discharge from the right eye with lower lid retraction and reduced hearing bilaterally without pain and normal eye movements. No visual disturbances or ocular pain were reported. He exhibited a petechial rash, mainly noted on the lower lip.

2.3. Investigations

The patient's blood workup revealed critical values: low hemoglobin of 2.9 g/dL (Normal range: 13.5–17.5 g/dL), severe thrombocytopenia of 5,000/mm³ (Normal range: 150,000–400,000/mm³). High WBC count of 33,500/mm³ (Normal range: 4,500–11,000/mm³). Further investigations showed CRP: 13, MCV: 97, retic count: 0.97, LDH: 213, Haptoglobin: 2.46 g/L (Normal range: 0.3–2.0 g/L), INR: 1, and creatinine: 86. Liver function tests were within normal limits.

Blood film results indicated predominantly normocytic normochromic RBCs and leukocytosis with the following differential: Neutrophils 3%, Lymphocytes 9%, Monocytes 2%, Blasts + promyelocytes 86%. Blasts displayed characteristics such as Auer rods, Buttock cells, large size, scant granular cytoplasm, high N: C ratio, irregular nuclear contours, immature chromatin, and prominent 1–2 nucleoli.

The leukemia fusion gene report (Table 1) detected positive gene fusion mRNA of RUNX1-RUNX1T1 that correlates with the translocation in t(8;21) (q22;q22), which has been associated with both de novo and therapy-related AML and has a favorable prognosis.

FLT-3: negative, Flow cytometry post-Induction I: 3% CD34 positive, CD117 positive blasts. The Computed tomography (CT) Orbit Sella with Contrast (Figure 2) and (Figure 3) displayed bilateral, almost symmetrical enhancing extra-conchal soft tissue lesions observed at both orbits' superior and lateral aspects. A biopsy was not obtained to confirm the diagnosis of myeloid sarcoma.



Figure 1: Ophthalmology findings at the initial visit showed bilateral ocular proptosis, more prominently on the right eye, with lid retraction (Left). The side view displays ocular proptosis (Right).

2.4. Treatment

The patient is admitted to the High Dependency Unit (HDU). Anemia workup, TFT, occult blood, and blood film were sent. Autoimmune and viral screens were sent. An urgent type of cross for four units of PRBC/4 FFP/6 platelets was requested. Two units of PRBCs and six units of platelets were transfused, after which his HB improved to 6.5 and platelets improved to 30,000. Pan cultures were sent, and empirical ceftriaxone was started. Ophthalmology advised tobramycin-dexamethasone eye drops and a pan CT of the orbital region with contrast once the patient is stable vitally. Blood pressure is monitored, and MAP is kept above 65.

The patient was started on Intravenous hydration along with an Intravenous antibiotic given the blood workup, and the blood film showed the possibility of acute myeloid Leukemia for further workup. The next day, the patient's right eye showed more protrusion and redness with dryness compared to yesterday. The left eye was showing a new sub-scleral hemorrhage but no ophthalmoplegia. Eye movements were preserved. The patient was accepted to be transferred to a specialized hospital where an Oncology service is available for Acute Myeloid Leukemia chemotherapy.

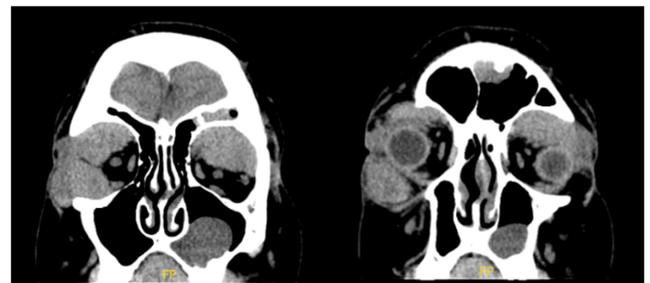


Figure 2: Sagittal view displaying poor definition of the superior and lateral recti muscles of both orbits, particularly prominent on the right orbit secondary to leukemic cell infiltration in a child with acute myeloid leukemia.

2.5. Outcomes and Follow-up

After 1 month after admission, the patient was brought by ambulance as a case of altered level of consciousness, lethargy, and loss of appetite and presented with chief complaints of fever, SOB, vomiting, and generalized weakness for one day. He vomited twice, but no coffee ground vomitus, no blood vomiting, no cough, no chest pain, and no bleeding from any site. On examination, the

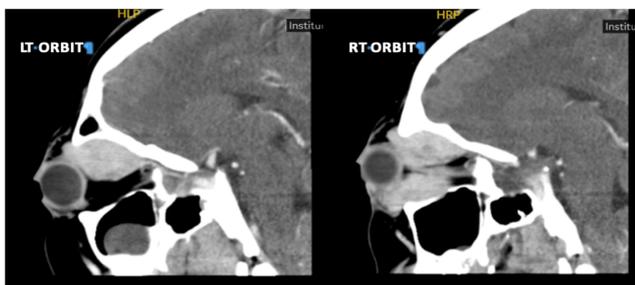


Figure 3: CT Left (LT) and Right (RT) Orbit Sella showing bilateral orbital enhancing infiltrative soft tissue lesions with subsequent bilateral proptosis of eye globes, particularly the right globe.

patient is vitally stable with HR: 78 bpm, BP 88/22 mm Hg, RR: 16 bpm. SpO₂: 96%. He was alert, conscious, oriented, chest clear, and his abdomen was soft, not tender. The patient developed sepsis and septic shock, acute kidney injury, and severe pancytopenia. Blood culture was positive for gram-negative rods identified as *Klebsiella pneumoniae* pan-sensitive. The patient required inotropic support and Intensive Care Unit admission, as well as being managed accordingly with cefepime, teicoplanin, and voriconazole.

WBC 0.03 x10³/mcL, HB 5.80 g/dL, platelet 9.00 x10³/mcL, he was started on filgrastim 300 mcg SC OD till absolute neutrophile 0.5 and managed with platelets and packed RBCs transfusion. Abdominal US showed mild hepatomegaly.

One month later, the patient was treated according to the Tawam AML protocol, which consists of standard induction with cytarabine (100 mg/m² continuous infusion for 7 days) and daunorubicin (60 mg/m² for 3 days), followed by four cycles of high-dose cytarabine consolidation therapy, tailored explicitly for RUNX1-RUNX1T1-positive AML M2 subtype. His chemotherapy was complicated by septic shock with gram-negative rods, which he recovered from successfully after prolonged admission and PICU stay. Fungal infection of the lungs, with Chest CT suggestive of fungal infection, was managed with Voriconazole. He had bilateral Retinal detachment and is currently followed by ophthalmology.

3. Discussion

Bilateral proptosis, being the main presentation in an AML patient, has been previously reported in some reports across the globe. Albeit far less common than their counterparts' presentations, unilaterally, Leukemic cellular infiltration of the retro-orbital space is the main pathophysiologic phenomenon reported behind proptosis in AML cases [8, 9, 10, 11, 12, 13]. In our case, bilateral proptosis was observed as the initial presentation of the disease. This aligns with several reports in the literature that describe orbital myeloid sarcoma as an initial manifestation of AML, where orbital involvement precedes the diagnosis of the underlying hematologic malignancy [14, 15].

Other contributory reasons include retrobulbar hemorrhages, obstructed venous drainage, and extraocular muscle infiltrates within the orbital space [16]. This specific extramedullary manifestation of AML was recognized by Allen Burns in 1811 as the green tumor and subsequently termed granulocytic sarcoma (GS) [17]. The green coloration due to myeloperoxidase concentration is variable, however, which leads to the broader nomenclature of orbital leukemic infiltrates by the term myeloid sarcoma (MS), or more commonly, chloroma [18].

Our patient, a 15-year-old male, presented with bilateral proptosis, which, although consistent with orbital involvement, falls slightly outside the most affected age group reported in the literature. Orbital MS is most frequently seen in children, with a mean age of presentation around 7 years [19]. Moreover, studies highlight a predilection for the 3–10-year-old age range, making it important to recognize that such presentations can also occur in older adolescents. More importantly, orbital MS was more responsive to Children's Cancer Group (CCG) chemotherapy protocols, 96% of which achieved complete remission at the end of the second treatment course compared to other non-CNS MS (78%) and non-MS (78%) AML patients undergoing similar protocols. Event-free survival (76%) and overall survival (92%) were also markedly higher in orbital MS compared to other extramedullary variants [20]. Independent survival rates, orbital MS was proven to be more likely associated with the M2 morphology of AML and t(8;21), which were noncontributory to the significance of survival difference compared to other AML morphologies. These characteristics of orbital MS were in consensus with another study conducted in Soweto, South Africa, but prognostic data remain conflicted with another study in Turkey on a similar population and is still a topic for further investigation [21, 22].

The significance of identifying the type of AML lies in the varying clinical picture it presents. The M2 subtype has the lowest mean hemoglobin levels among all other subtypes, reaching as low as 3g/dl, while having the highest platelet counts, reaching as much as 1000x10⁹ platelets/L [23]. Immunophenotyping variation was also significant in AML M2, as CD7 positivity was most predominant, guiding toward the use of promising targeted chemotherapeutic agents like the recent autologous CD7 CAR T-cell therapy [24].

The CT of the orbits shows poor definition of the superior and lateral recti muscles in both orbits, more prominently on the right side. This contrasts with previous studies that demonstrated diffuse infiltration and enlargement of all extraocular muscles without an associated mass [11, 25].

AML is a heterogeneous disease with various subtypes, each characterized by distinct genetic abnormalities [26]. Two of these subtypes are RUNX1-RUNX1T1 (previously known as AML1-ETO) and CBFβ-MYH11-positive AML [27]. RUNX1-RUNX1T1 is one of the most common genetic abnormalities found in the AML M2 subtype and is among the initial fusion genes employed for the surveillance of minimal residual disease [28]. It results from a translocation and fusion between chromosomes 8 and 21. Patients with RUNX1-RUNX1T1-positive AML typically have a more favorable prognosis than many other AML subtypes. This subtype is often associated with younger age, a higher likelihood of achieving complete remission (CR) with treatment, and special morphological features such as lower white blood cell counts, sizable blasts characterized by ample basophilic cytoplasm filled with numerous azurophilic granules, and Auer rods. There have also been instances of blasts with exceptionally large granules, possibly suggesting a fusion of these cells [29]. Treatment response in this specific subtype is primarily reliant on anthracyclines and cytarabine, coupled with subsequent 2-4 rounds of cytarabine; treatment can be enhanced through the incorporation of gemtuzumab-ozogamicin (GO), an antibody targeting CD33 [30]. However, long-term survival can vary, and additional factors, such as the presence of other mutations, are taken into consideration [31].

Another AML variant belonging to the favorable risk subtypes is CBFβ-MYH11-positive AML, which is associated with the AML-M4Eo subtype and results from the inv (16) (p13q22) translocation.

This subtype has a higher likelihood of achieving CR and prolonged disease-free survival [32]. Patients with CFBF-MYH11-positive AML tend to be younger and have other distinctive morphologic features, including an abundance of monocytes and a distinctive, atypical eosinophil element that defines this particular AML subgroup, which is why it is often referred to as M4Eo AML [33]. However, like RUNX1-RUNX1T1-positive AML, the presence of additional genetic mutations can influence prognosis. Response of this specific subtype was specifically proven to be sensitive to high-dose cytarabine-based consolidation regimens, thereby guiding treatment modalities and options towards better and more specific regimens [34, 35]. However, it is worth noting that relapses affect nearly 50% of adult patients, and the survival rate beyond five years is merely around 50% [36, 37, 38].

AML characterized by t(8;21) or inv(16) is typically grouped under the term "core binding factor AML (CBF-AML) [39]." CBF-AML comprises about 25% of pediatric and 15% of adult patients with newly diagnosed AML, making it the most prevalent cytogenetic subtype of AML [40]. Survival outcomes for pediatric CBF-AML patients, when compared to AML with typical cytogenetics, show a slight improvement. However, a subset with a less favorable prognosis exists within this patient population. This suggests that there is diversity among these patients, and it is likely that additional mutational changes can impact the development of the disease [41].

Given the rarity of extramedullary AML involvement, especially in the context of bone structures, additional diagnostic workup may be necessary to identify the subtype accurately. This may involve cytogenetic and molecular genetic testing to detect specific translocations, mutations, and fusion genes associated with AML subtypes. Management of AML in pediatric patients typically involves intensive chemotherapy regimens aimed at achieving CR. For patients with RUNX1-RUNX1T1 and CFBF-MYH11-positive AML, standard induction chemotherapy, often including anthracycline-based regimens, is the first-line treatment. Hematopoietic stem cell transplantation (HSCT) may be considered for eligible patients, particularly in cases of high-risk AML or relapsed disease. HSCT can offer a chance for long-term remission and potential cure, but it comes with its own set of risks and complications.

The patient developed bilateral retinal detachment, a rare but serious complication in leukemic patients, often linked to leukemic infiltration or hemorrhage. According to the updated Retina Society Classification for proliferative vitreoretinopathy (PVR), retinal changes are graded from A to CA/CP based on severity and location. Grade A includes mild findings like vitreous haze, while more advanced PVR is classified as posterior (CP) or anterior (CA), depending on whether the proliferative changes and retinal folds are located behind or in front of the equator [42]. Given the risk of relapses and the potential for long-term ophthalmologic complications such as retinal detachment, close and coordinated follow-up is essential. The patient will require regular hematological monitoring of visual outcomes and management of any late sequelae of orbital involvement or treatment-related complications.

Although 15-year-olds may fall at the intersection of pediatric and adult care, emerging evidence supports the use of pediatric protocols for adolescents with AML. Studies have shown that adolescents benefit more from pediatric AML protocols than adult ones, with studies showing improved remission and survival rates compared to those treated with adult protocols [27, 43]. The use of the pediatric-based Tawam AML protocol, in this case, aligns with current recommendations, especially given the favorable RUNX1-RUNX1T1 cytogenetic profile. In this case, the patient's clinical condition and response to initial treatment would be critical in

determining the appropriate course of action. The development of sepsis and septic shock, along with severe pancytopenia, indicates a complex clinical scenario that may require intensive supportive care in addition to disease-specific AML M2 targeting therapy. Regular monitoring, including minimal residual disease assessment, is crucial for evaluating treatment response and guiding further therapeutic decisions.

4. Conclusions

This case report sheds light on the intricacies of diagnosing and treating Acute Myeloid Leukemia (AML) in a pediatric patient presenting with extramedullary involvement and bilateral proptosis. Recognizing the specific AML subtype, such as RUNX1-RUNX1T1 and CFBF-MYH11-positive AML, is pivotal in predicting prognosis and tailoring the treatment strategy. Early and precise diagnosis, coupled with a comprehensive multidisciplinary approach to care, can significantly enhance the outcomes for pediatric AML patients, positively impacting their overall well-being and recovery.

Conflicts of Interest

The authors declare no competing interests that could have influenced the objectivity or outcome of this research.

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Informed consent

Informed consent was obtained from the patient, and verbal witness informed consent was obtained from parents, anonymizing identifiable information.

Large Language Model

None

Authors Contribution

AMY conceived and designed the study. AMY and MMA provided research materials. and collected and organized data. AMY, MMA, and FA wrote the initial and final drafts of the article. OH and MS have critically reviewed and approved the final draft. MS supervised the conduction of the research.

Data Availability

This case report is based on a single patient's clinical presentation, diagnostic findings, and treatment course. All relevant data are included within the article. No new datasets were generated or analyzed beyond the information documented in the patient's medical records, which are not publicly available due to privacy and confidentiality considerations.

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