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# TABLE OF CONTENTS

**Editorial Board Bali Medical Journal** .................................................................................................................................................................................................................................................... ii

**Table of Contents** ............................................................................................................................................................................................................................................................ v

1. **Neglected tropical disease-chromoblastomycosis: a simple KOH staining for definitive diagnosis** .............................................................. 1  
   Suharyadi Sasmanto, Pepy Dwi Endraswari, Deby Kusumaningrum

2. **Description of SARS-CoV-2 IgG titers in COVID-19 survivor who get three doses vaccine in Mataram** ............................... 4  
   Metta Octora

3. **Drug-resistant tuberculosis pattern in Indonesia: a systematic review** ................................................................................................................................. 8  
   Syandrez Prima Putra, SM Rezvi, Gestina Aliska, Andani Eka Putra

4. **Laboratory spectrum and antibiotic resistance profile of melioidosis association with patient outcomes** ......................... 11  
   Dewi Anggraini, Fajri Marindra Siregar, Dani Rosdiana, Rahmat Azhari Kemal, Indra Yovi, Zhana Daisya Triani, Novira Jasmin, Norsila Jelita

5. **Sea urchins as a source of the active substance linalool: a drug candidate for Alzheimer’s disease** ............................... 14  
   Herpan Syafii Harahap, Dini Suryani, Arina Windri Rivarti, Nurhidayati Nurhidayati, Legis Ocktaviana Saputri, Fitriannisa Faradina Zubaidi

6. **The differences between gene expression of tryptophan-aspartate containing coat protein at the infection period of tuberculosis patients** ......................................................................................................................... 17  
   Rebekah Juniati Setiabudi, Ni Made Mertaniasih, Muhammad Amin, Wayan Tunas Artama

7. **Permanent cardiac pacemaker expulsion due to methicillin-resistant Staphylococcus aureus: a case report** ......................... 20  
   Yusra Pintaningrum, Ketut Angga Aditya Putra Pramana

8. **Pregnancy complicated by thyroid heart disease: a case report** ................................................................................................................................. 23  
   Yusra Pintaningrum, Lalu Shalya Kusuma Putra

9. **Challenge of histopathological method to diagnose double cutaneous invasive fungal infection in Indonesia: a rare pediatric malignancy case report** .......................................................................................................................................................................................... 26  
   Metta Octora, Arthur Pohan Kawilarang, Nurmi Hasbi

10. **Consumption of marine fish and the clinical course of Alzheimer’s dementia** ................................................................. 29  
    Arina Windri Rivarti, Herpan Syafii Harahap, Dini Suryani, Nurhidayati Nurhidayati, Legis Ocktaviana Saputri, Fitriannisa Faradina Zubaidi

11. **The antimicrobial activity of bacteriocin producing Lactobacillus from growol isolate** ................................................................. 31  
    Lilis Suryani

12. **Prevalence, risk factors, and treatment of preoperative hypertension at a top referral hospital in Lombok, Indonesia** ... 34  
    I Gede Yasa Asmara, Catarina Budyono, I Gusti Ngurah Ommy Agustriadi

13. **The effect of the type of COVID-19 vaccines on the neutralization response** ................................................................. 37  
    Mutia Lailani, Linosefa, Andani Eka Putra

14. **The relationship between haze and increased pneumonia at Mandau District Hospital in Sumatra 2015-2016** ............... 40  
    Rayhana, Hanifah Amalia
<table>
<thead>
<tr>
<th>No.</th>
<th>Title</th>
<th>Authors</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>Role of nutritional status in multidrug-resistant tuberculosis in Indonesia: a systematic review</td>
<td>Desmawati Desmawati, Gestina Aliska, Linosefa, SM Rezvi, Andani Eka Putra</td>
<td>43</td>
</tr>
<tr>
<td>16</td>
<td>A five-year retrospective study of ESBL-producing <em>Escherichia coli</em>: prevalence and antibiotic susceptibility pattern</td>
<td>Gajah Nauli Dalimunthe, Dimas Seto Prasetyo, Rika Febriana Pinem, Suratno Lulut Ratnoglik, Delly Chipta Lestari</td>
<td>46</td>
</tr>
<tr>
<td>17</td>
<td>COVID-19 antigen is not identified in the purulent discharge of patient with acute and chronic suppurative otitis media</td>
<td>Hamsu Kadriyan, Lalu Hizrian Rizkika Abtartu, Didit Yudhanto, Bayu Tirta Dirja</td>
<td>49</td>
</tr>
<tr>
<td>18</td>
<td>Leadership competency of hospital managerial: a literature review</td>
<td>Metta Octora, Ratri Wahyuningtyas</td>
<td>52</td>
</tr>
<tr>
<td>19</td>
<td>Mupirocin sensitivity and biofilm producer of methicillin resistant <em>Staphylococcus aureus</em> at Dr. Moewardi General Hospital Surakarta</td>
<td>Dessy Kurnia Sari, Leli Saptawati, Abu Tholib Aman, Titik Nuryastuti</td>
<td>56</td>
</tr>
<tr>
<td>20</td>
<td>Characteristic and risk factors of ventilator associated-pneumonia in ICU of tertiary referral hospital, West Nusa Tenggara, Indonesia</td>
<td>Putu Diwyananda, Priyahita, Metta Octora, Bayu Tirta Dirja, Mould Hidayat</td>
<td>60</td>
</tr>
<tr>
<td>21</td>
<td>The potential of <em>Allium sativum</em> Linn as an inhibitor of <em>Salmonella Typhi</em> bacterial growth</td>
<td>Hasta Handayani Idrus, Yusriani Mangarengi, Wa Ode Sri Ariani Taufan, Nesyana Nurmadili, Yani Sodiqah, Amrizal Muchtar, Sarwo Handayani, C. S. Whinie Lestari, Hermiaty Nasrudin</td>
<td>63</td>
</tr>
<tr>
<td>22</td>
<td>Prevalence and antimicrobial susceptibility patterns of ESBL-producing <em>Klebsiella pneumoniae</em>: A five-year retrospective cross-sectional study</td>
<td>Aiman Idrus Alatas, Dimas Seto Prasetyo, Conny Riana Tjampakasari, Tjahjani Mirawati Sudiro, Delly Chipta Lestari</td>
<td>67</td>
</tr>
<tr>
<td>23</td>
<td>Comparison of DNA extraction modification using QIAamp DNA mini kit vs boiling methods for <em>M. Tuberculosis</em> isolate</td>
<td>Deby Kusumaningrum, Ni Made Mertaniasih, Soedarsono Soedarsono</td>
<td>70</td>
</tr>
<tr>
<td>24</td>
<td>Methicillin-resistant coagulase-negative <em>Staphylococci</em> in breastfeeding mothers and their babies</td>
<td>Rieke Syahniar, Adinta Anandani, Aning Subiyatin, Firyal Alifa Andavyta, Ghina Nafisah</td>
<td>72</td>
</tr>
<tr>
<td>25</td>
<td>Correlations between Ki-67 biomarkers and grading meningioma</td>
<td>Irasyidina Hasana Bharata, Rohadi Muhammad Rosyidi, Lale Maulin Prihatina, Fathul Djannah</td>
<td>75</td>
</tr>
<tr>
<td>26</td>
<td>Association between asphyxia neonatorum and neurodevelopmental delay in children aged 1-3 years</td>
<td>Rizqi Al Kasiron, Titik Pamudbo Karuniawatu, Herpan Syafii Harahap</td>
<td>77</td>
</tr>
<tr>
<td>27</td>
<td>Interferon γ – (QIAREACH®) assay compatibility to Genexpert® MTB/Rif for lung tuberculosis diagnosis in children</td>
<td>Ardiana Kusumaningrum, Tri Angelia Syam, Yulia Rosa Saharan, Nastiti Kaswandani, Fahrira Aditya Neldy</td>
<td>81</td>
</tr>
<tr>
<td>28</td>
<td>Knowledge of nasopharynx and nasopharyngeal carcinoma during the COVID-19 pandemic among the Indonesian community and the lesson learnt for the future management</td>
<td>Hamsu Kadriyan, Camelia Herdini, Sukri Rahman, Nova Audrey L. Pieter, Didit Yudhanto, Cuti Warnaini, Decky Aditya Zulkarnaen, Fahriz Ramadhan Andiwijaya</td>
<td>84</td>
</tr>
<tr>
<td>29</td>
<td>Views of school managers about incidence of scabies in Islamic boarding school, Mataram, Indonesia</td>
<td>Muhammad Mahfuzzahrahi, Yunita Hapsari, Metta Octora</td>
<td>88</td>
</tr>
<tr>
<td>30</td>
<td>The antibacterial effect of Sumbawa honey (<em>Apis dorsata</em>) against <em>Staphylococcus aureus</em> (ATCC 25923)</td>
<td>Much Rivandha Islami Yoga Pratama, Metta Octora, Nurmi Hasbi</td>
<td>91</td>
</tr>
<tr>
<td>31</td>
<td>Examining referral communication in maternal healthcare: Perceptions, gaps, and opportunities for improvement</td>
<td>Dian Puspita Sari, Yoga Pamungkas Susani, Rizkinov Jumsa, Mohammad Rizki</td>
<td>94</td>
</tr>
</tbody>
</table>
32. **Analysis of referral characteristics of obstetric cases and maternal outcomes at the University of Mataram Hospital, Indonesia**
   Theophany Margareta Kurniawan, Meilisva Audila Anggraini, Muhammad Rizkinov Jumsa, Dian Puspita Sari

33. **Opportunistic fungi that caused fungaemia among HIV patients in Adam Malik General Hospital Medan**
   Cherry Siregar, Tambar S Kembaren, Arthur P Kawilarang, Eddy B Wasito

34. **Modulating effect of Heat Shock Protein-70 (HSP 70) in acute ischemic stroke: A review to the recent knowledge**
   Ilsa Hunaifi, Andi Kurnia Bintang, Jumranini Tammassse, Isra’Wahid

35. **Hypertension in mortality and morbidity of COVID-19: A systematic review and meta-analysis of prospective cohort study**
   Lalu Hizrian Rizkika Abtartu, Hamsu Kadriyan, Yusra Pintaningrum

36. **Dominant gut microbiota profile in pediatric and adult patients with diarrhea**
   Resti Hardianti Lestari1, Yeva Rosana, Fera Ibrahim, Conny Riana Tjampakasari, Dimas Seto Prasetyo
Neglected tropical disease-chromoblastomycosis: a simple KOH staining for definitive diagnosis

Suharyadi Sasmanto1*, Pepy Dwi Endraswari2,3, Deby Kusumaningrum2,3

ABSTRACT

Background: A neglected tropical disease (NTD)-chromoblastomycosis (CBM) is a chronic progressive cutaneous fungal infection caused by several naturally melanized or brown-pigmented fungi. Diagnosis is quite easy with KOH staining, and treatment success is higher if diagnosed early.

Case presentation: A 19-year male with multiple plaques and verrucous nodules on the right upper arm, accompanied by pain and itching. The lesions occur in childhood and are slow progressive. The patient was previously diagnosed as lymphangioma, and had undergone excision surgery 4 years ago, but a year later, new lesions appeared and multiplied. On physical examination, there were multiple plaques and nodules in the region of the brachialis, axilla, and scapula dextra. The size of the verrucous plaque varies from erythematous to hyperpigmented, with exudate and no grain visible. Later it was diagnosed as chromoblastomycosis based on the identification of muriform-sclerotic bodies. The patient was treated with an antifungal combination and heat therapy. After 6 months of treatment, the lesions persisted. Chromoblastomycosis often presents diagnostic challenges due to its polymorphic clinical manifestations. Confirmation through direct mycological examination and/or histopathology is essential for accurate diagnosis. The presence of muriform cells in clinical specimens is crucial for establishing CBM as the causative agent.

Conclusion: In cases of persistent cutaneous infections, CBM should be considered as a potential differential diagnosis. Early and appropriate diagnosis, along with effective treatment, can significantly improve the patient’s quality of life.

Keywords: Neglected tropical disease, chromoblastomycosis.

INTRODUCTION

Chromoblastomycosis is characterized as a chronic, granulomatous, and suppurative mycosis affecting the skin and subcutaneous tissue. This condition arises due to the traumatic inoculation of dematiaceous fungi, belonging to the order Chaetothyriales and family Herpotrichiellaceae.1,2 Fonsecaea spp. is the most common pathogen, followed by Cladophialophora, Phialophora, and Rhinocladiella.3

In 2017, the World Health Organization (WHO) included CBM in category B of the NTD portfolio, which are described as endemic tropical and subtropical illnesses in low-income countries that affect thousands of people each year.1,5 This disease affects people worldwide, but the incidence remains unclear because CBM is not a mandatory notifiable disease, and another possibility is that the illness is misdiagnosed with another disease, making it a rare case. Here we present a 19-years-old male with chromoblastomycosis who had no resolution of skin lesions after 6 months of treatment. The purpose of this article is to describe the chromoblastomycosis case in a healthy young man and to emphasize the importance of simple microbiology examination with KOH staining for diagnosing suspected invasive fungal infection.

CASE PRESENTATION

A male, 19 years old, seeks treatment for the first time at Dr. Soetomo Hospital Dermatovenerology polyclinic in July 2022 with complaints of a lump on his upper arm and right armpit. The lump first appeared in childhood, the size of a red-black corn kernel, solitary, and getting bigger. In 2018, the patient was diagnosed with lymphangioma and underwent excision at the previous hospital because the lump was getting bigger and more painful. One year after surgery, new lumps appeared around the same location, increased in number and size, and discharge from skin lesions was accompanied by pain and itching.

On dermatological examination, the brachialis et axilla et scapula dextra regions were found to have multiple plaques et verrucous nodules. The size of the plaques varies, the color is erythematous to hyperpigmented, there is exudate in several areas of the lesion, and no grain is visible. Posterior thoracic dextra region: solitary, skin-colored nodule, 1 cm in diameter, immobile, slight tenderness. The fine needle aspiration biopsy (FNAB) results obtained recidive lymphangioma with inflammation. MRI examination found lymphangioma in the brachial region to the antebrachii 1/3 proximal with multiple KGB in the right axilla and brachii. Histology-anatomic pathology results showed skin biopsy tissue covered with epidermis with acanthosis of elongated rete ridges. In periodic acid-Schiff staining (PAS) staining, no fungal spores or hyphae were found.

The results of the culture of the lesional tissue with Sabouraud dextrose agar obtained are as follows: Macroscopic growth of gray colonies with wrinkled surfaces, microscopic conidiaospores (+), Cladosporium spore type (conidiaospores of...
different lengths and branching like trees) with conclusion *Fonsecaea pedrosoi*. KOH scrapings on verrucous plaques showed muriform bodies. Following anamnisis and examination results, the patient was diagnosed as Chromoblastomycosis and lymphangioma. Patients were given therapy with itraconazole tab 2x200mg, terbinafine tab 2x250mg, PZ compresses 2 times a day on wet lesions, natrium fusidate cream 2 u.e. on the erosion area, heating pad and control advice for 1 week. After 6 months of treatment, complaints of itching have decreased, there is still pain in the lesions, and there has been no significant resolution of hyperkeratotic and verrucous lesions. The patient underwent a reduction excision in the axilla dextra region with an LD flap and continued antifungal therapy.

**DISCUSSION**

The initial phase of chromoblastomycosis pathogenesis involves the inoculation of dematiaceous filamentous fungi into the skin and subcutaneous tissue through micro- or macro-traumatic injuries. Most patients do not remember the trauma process due to the long period from the start of the inoculation until the onset of clinical manifestations. Following inoculation, the fungus adheres to epithelial cells and transforms into specialized structures known as muriform, fumagoid, or sclerotic cells, commonly referred to as medlar bodies, which serve as a defense mechanism against the host’s immune response. Fungal implantation in CBM is mostly caused by plants and agricultural equipment, although it can also be caused by insect stings, cow stumps, buck rears, cockroach spines, caterpillar touch, and leech bites.

In principle, diagnosing CBM only requires simple laboratory equipment, but because it is considered a “neglected disease” by health workers, it takes a long time to diagnose this disease. A literature study conducted by Guevara et al, 2022 takes an average of about 9 years from initial onset to diagnosis as CBM. Late diagnosis affects morbidity, including disease progression, the risk of co-infection, and transformation into malignancy. Polymorphic lesions can be found in chronic cases of CBM. The presence of fibrotic changes and lymphatic vascular stasis causes lymphedema, which in some cases mimics elephantiasis. This polymorphic appearance can also resemble various disorders, both infectious and non-infectious.

Direct mycological examination and/or histopathology are necessary in establishing the diagnosis of CBM. The presence of muriform cells in clinical specimens is pathognomonic for CBM. Pigmented fungal elements in the superficial parts of the lesion can easily be seen as small black dots (cayenne pepper appearance). In cases of CBM, especially with moderate to severe clinical manifestations, healing of the lesions is almost impossible to achieve, and is often even refractory. Combination therapy can be in the form of physical therapy, topical or systemic antifungals, and surgery, especially for early lesions. Although data from the randomized control trial regarding treatment options for CBM do not exist, itraconazole is the first line treatment option in this case and terbinafine is the second line. Voriconazole, posaconazole, posaconazole, and isavuconazole are only used in refractory cases.

Cure criteria for discontinuing antifungal therapy were achieved through clinical, mycological, and histopathological evaluation. Clinically, this is seen as the resolution of previously active lesions, the formation of scar tissue, and the relief of pain and itching. Mycological evaluation is achieved when no fungal elements are found on direct microscopic examination and the culture of the tissue specimen shows no fungal growth. On histopathological evaluation, muriform cells and micro abscesses were not found.

**CONCLUSION**

Among other implantation fungal diseases, the incidence of CBM is unknown due to its varied clinical manifestations, which can lead to misdiagnosis. The classification of CBM as a NTD emphasizes the role of health promotion in developing programs and strategies for the prevention, detection, and management of patients. CBM should be considered in the differential diagnosis of persistent cutaneous infections. Early detection and treatment can improve a patient’s quality of life.

**CONFLICT OF INTEREST**

None to declare.

**FUNDING**

None to declare.

**ETHICAL STATEMENT**

Prior to publication in the Medical Journal, all patients provided signed, written informed consent for the publication of their respective medical data, ensuring compliance with ethical standards.

**AUTHOR CONTRIBUTION**

All authors actively contributed to the writing of the manuscript and have given their consent for the final version to be published.

**REFERENCES**


INTRODUCTION

The utilization of different COVID-19 vaccines has been sanctioned by the World Health Organization. These vaccines include mRNA vaccines like mRNA-1273 (Moderna) and BNT162b2 (Comirnaty BioNTech and Pfizer), viral vector vaccines such as ChAdOx1 nCoV-19 (University of Oxford/Astra-Zeneca) and Ad26.COV2.S (Janssen), as well as whole-cell inactivated vaccines like BBIBP-CorV (Sinopharm) and CoronaVac (Sinovac Biotech). In December 2021, the Indonesian government initiated a program prioritizing the administration of the CoronaVac (Sinovac Biotech) COVID-19 vaccination to healthcare professionals. Healthcare professionals will begin receiving the mRNA-1273 (Moderna) vaccination as a booster dose commencing in August 2021. The Centers for Disease Control and Prevention (CDC) advises the administration of booster immunizations to specific demographic groups, primarily individuals aged 65 years and older, as well as those employed in settings characterized by a heightened likelihood of transmission, such as healthcare professionals.2

The primary objective of most vaccines is to stimulate the production of neutralizing antibodies (nAb) that can effectively bind to the SARS-CoV-2 S protein, thereby impeding the virus’s ability to engage with target cells. After 28 days following the administration of the second dosage, the CoronaVac vaccine developed by Sinovac Biotech induced the production of neutralizing antibodies in a range of 94-100% of individuals.3,4 In contrast to the CoronaVac vaccine developed by Sinovac Biotech, the nAb mRNA-1273 vaccine developed by Moderna exhibits a distinct pattern of antibody formation. Specifically, the production of neutralizing antibodies commences following the administration of the initial dose and attains its highest level approximately 14 days after the administration of the second dose.5

The determination of antibodies is commonly performed in nAb examinations by the utilization of the plaque-reduction neutralization test (PRNT) or microneutralization assay, which are widely recognized as the established standards for this purpose. The nAb examination possesses various drawbacks, including its restricted accessibility to certain laboratory settings and its substantial financial requirements.1,5 The constraints associated with nAb assays can be addressed through the utilization of commercially accessible assays that prioritize the examination of the S protein, particularly its S1 and RBD domains.3 This study aims to analyze the description of SARS-CoV-2 IgG titers in individuals who have survived COVID-19 and have received three doses of the vaccination in Mataram, Indonesia.

METHODS

This study is retrospective cohort analysis in order to evaluate the SARS-CoV-2 IgG II quantitative titers between 100 subjects who have survived COVID-19 and those who have not survived, both of whom have received a combination of two doses of CoronaVac vaccine (Sinovac Biotech) and one dose of Moderna vaccine.

Results: Disparity levels of SARS-CoV-2 IgG antibodies is observed between groups with a confirmed history of COVID-19 and those without such a history. Additionally, a significant correlation can be observed between body mass index (BMI) and the levels of SARS-CoV-2 IgG antibodies (p<0.05).

Conclusion: There was no significant difference in the levels of SARS-CoV-2 IgG antibodies among COVID-19 survivors after vaccination.

Keywords: COVID-19, herd immunity, IgG SARS-CoV-2 titers, vaccines.
the CoronaVac vaccination developed by Sinovac Biotech, followed by a single dose of the Moderna vaccine. Additionally, these individuals must have undergone a SARS-CoV-2 IgG titer assessment at least 6 months after receiving the Moderna vaccine. The exclusion criteria encompass the presence of concomitant or comorbid conditions, the use of immunosuppressive medication, as well as the manifestation of symptoms and indications indicative of COVID-19 over the course of the study. The study was carried out in Mataram City Hospital during the period of January to December 2022.

**RESULTS**

Table 1 displays the attributes of the research participants. In both the case and control groups, a higher proportion of male participants were included in the study (55% versus 45%). In general, a significant proportion of the research participants exhibited a BMI within the normal range, specifically accounting for 51% of the total sample.

The titer of SARS-CoV-2 IgG is quantified in the standard binding antibody unit (BAU)/ml units set by WHO. The average number of cases was 823.00 (standard deviation ± 2393.15), whereas the average number of controls was 695.00 (standard deviation ± 1732.75). The T-test results indicated a statistically significant disparity in titers (p = 0.000) between the two groups, with a 95% confidence interval ranging from -6874.99 to -5993.72. The outcomes of the Pearson correlation test are presented in Table 2. The body mass index (BMI) exhibits a statistically significant association with the SARS-CoV-2 IgG titer, but with a relatively low correlation coefficient of 0.233.

**DISCUSSION**

There is no disparity in the likelihood of COVID-19 infection between men and women. However, they did find that male patients face a threefold higher risk of requiring intensive care treatment compared to female patients. The mean age of research subjects in the case group was 32.48 years with a standard deviation of 9.45 years, while in the control group, the mean age was 32.48 years with a standard deviation of 5.8 years. The mean age of individuals in the case group was seen to be greater than that of the control group; however, this difference did not reach statistical significance.

There is evidence to suggest that age plays a significant role in determining an individual’s vulnerability to SARS-CoV-2 infection. The susceptibility to infection is higher among those aged over 60 years in comparison to younger ones, even when both groups are exposed to the same level of risk. The BMI of individuals in the case group had a higher prevalence compared to those in the control group. A correlation exists between BMI and the susceptibility to COVID-19. There is an increased susceptibility to COVID-19 in individuals who are classified as overweight or obese. There was an observed increase in ACE2 and TMPRSS2 expression in the trachea and lung tissue of experimental animals with obesity, which serve as the entrance points for SARS-CoV-2. Moreover, individuals with comorbidities are susceptible to COVID-19 effect.

The antibody response to the SARS-CoV-2 spike protein after vaccination exhibits variability, which can be attributed to factors such as prior infection status, age, gender, vaccine type, and dosage regimen. Individuals who had previously been infected with SARS-CoV-2 exhibited higher levels of IgG and neutralizing antibodies (nAb) compared to those without a history of infection. However, it is important to note that despite these elevated antibody levels, those with a previous infection remained susceptible to reinfection.

The administration of a full inactivated vaccine has been found to confer a level of protection against hospital treatment at a rate of 87.5% and against intensive treatment at a rate of 90.3%. Individuals who received a combination of two doses of whole inactivated vaccine followed by a booster of one dose of mRNA vaccine and had a history of infection exhibited higher IgG titers compared to individuals who received two doses of mRNA vaccine alone and had no history of infection. In the case group, the average titer value of SARS-CoV-2 IgG in this investigation was determined to be 9953.81 BAU/ml. The observed value exhibits a greater

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**Table 1. Characteristics of subjects**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total (n =100)</th>
<th>Case (n =50)</th>
<th>Control (n =50)</th>
<th>p-value</th>
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<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>45 (45%)</td>
<td>24 (48%)</td>
<td>21 (42%)</td>
<td>0.315</td>
</tr>
<tr>
<td>Male</td>
<td>55 (55%)</td>
<td>26 (52%)</td>
<td>29 (58%)</td>
<td></td>
</tr>
<tr>
<td>IMT (kg/m²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Underweight</td>
<td>2 (2%)</td>
<td>0 (0%)</td>
<td>2 (4%)</td>
<td>0.021</td>
</tr>
<tr>
<td>Normal</td>
<td>51 (51%)</td>
<td>21 (42,1%)</td>
<td>30 (60%)</td>
<td></td>
</tr>
<tr>
<td>Overweight</td>
<td>47 (47%)</td>
<td>29 (57,8%)</td>
<td>18 (36%)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
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</tr>
</tbody>
</table>

**Table 2. Correlation test for SARS-CoV-2 IgG titers**

<table>
<thead>
<tr>
<th>Variable</th>
<th>IgG SARS-CoV-2 titer</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.583</td>
<td>0.062</td>
</tr>
<tr>
<td>Sex</td>
<td>0.383</td>
<td>0.280</td>
</tr>
<tr>
<td>BMI</td>
<td>0.032</td>
<td>0.233</td>
</tr>
<tr>
<td>Comorbid state</td>
<td>0.592</td>
<td>0.062</td>
</tr>
</tbody>
</table>

**Table 1. Characteristics of subjects**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total</th>
<th>Case</th>
<th>Control</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
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</tr>
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<td></td>
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<tr>
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<td></td>
<td></td>
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<td>18</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>Underweight</td>
<td>2</td>
<td>0</td>
<td>2</td>
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</tr>
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</tr>
</tbody>
</table>
magnitude in comparison to the findings reported in prior study.\textsuperscript{11-12}

Individuals having a previous exposure to SARS-CoV-2 exhibited elevated levels of antibodies against the virus. Moreover, these individuals displayed a broader range of protection compared to those who had not been previously infected, following administration of the BNT162b2 mRNA vaccine. Individuals who have previously contracted COVID-19 exhibit a greater degree of vaccine-induced immunological memory. Individuals who have successfully recovered from COVID-19 shown a notable increase in the presence of memory B cells that are specific to SARS-CoV-2 and are capable of secreting antibodies, as compared to individuals who are in good health. The levels of antibody and memory B cell responses exhibited a substantial rise following administration of the initial mRNA vaccination dosage in persons who had previously recovered from COVID-19. This suggests that individuals who have recovered from COVID-19 may potentially attain optimal memory B cell responses with just a single vaccine dose. Individuals who have successfully recovered with COVID-19 have been found to possess memory B cells specific to the SARS-CoV-2 S protein. Mild infection with COVID-19 results in the development of durable and specific humoral immunological memory. The binding activity of protein S was shown to be higher in the plasma cells of persons who tested positive for the presence of antibodies compared to those who tested negative.\textsuperscript{13}

Patients who were infected with SARS-CoV-2 experienced a steady decline in their levels of anti-S IgG, IgM, IgA, and nAb titers over a period of one year. The levels of SARS-CoV-2 IgG antibodies exhibit a decline after a period of 15 weeks. Notably, those without a prior history of SARS-CoV-2 infection tend to suffer a more pronounced fall in IgG titers compared to those who had previously been infected with the virus. Individuals who have previously been infected with SARS-CoV-2 would exhibit a higher IgG titer compared to those who have not been previously infected. The SARS-CoV-2 IgG titer is influenced by the specific type of vaccine administered. The participants in this research were administered a heterologous vaccination, consisting of two doses of whole inactivated vaccine followed by an mRNA vaccine booster.\textsuperscript{13,14}

The administration of homologous vaccines resulted in a notable increase in antibody titers, ranging from 4 to 20 times. In contrast, the use of heterologous vaccines led to a more substantial elevation in titers, ranging from 6 to 73 times. Individuals who received the heterologous vaccine had a more pronounced and enduring rise in specific T cell responses targeting protein S.\textsuperscript{15,16}

The levels of SARS-CoV-2 specific IgG antibodies in individuals who had experienced mild, moderate, and severe cases of COVID-19, one year after their first infection. Individuals with more severe symptoms of COVID-19 exhibited a more rapid increase in antibody titers, ultimately reaching higher peak levels. The antibody titers of persons who exhibit symptoms of SARS-CoV-2 infection are generally higher compared to those who are asymptomatic. There exists an inverse relationship between BM and the immunoglobulin G (IgG) titer of SARS-CoV-2, whereby an increase in BMI is associated with a decrease in IgG titer. The BMI did not exert a statistically significant influence on the levels of SARS-CoV-2 IgG antibodies following the delivery of mRNA-based vaccinations.\textsuperscript{17,18} 49% patient of kidney transplantation exhibited no discernible increase in antibody levels subsequent to the administration of two doses of the mRNA vaccine. The study excluded individuals with multiple comorbidities or a Charlson Comorbidity Index (CCI) score more than 3 in order to maintain comparability of comorbid characteristics among the research participants.\textsuperscript{17}

CONCLUSION

A disparity exists in the levels of SARS-CoV-2 IgG antibodies among individuals who have undergone a vaccination regimen consisting of two doses of whole inactivated vaccine followed by one dose of mRNA vaccine. This disparity is observed between groups with a confirmed history of COVID-19 and those without such a history. Additionally, a correlation can be observed between BMI and the levels of SARS-CoV-2 IgG antibodies.

CONFLICT OF INTEREST

The authors affirmed that there were no conflicts of interest in this study.

FUNDING

The authors were responsible for all research funding without obtaining financial support.

ETHICAL STATEMENT

Author has secured informed consent from the subjects in this study

AUTHOR CONTRIBUTION

All authors contributed equally in this research and publication of this manuscript.

REFERENCES

8. Wedari NLP, Sukrama IDM, Budayanti NNS, Sindhughosa DA, Prabawa IPY, Manabua IBAP. One Health concept and role of animal reservoir in avian influenza: a literature


Drug-resistant tuberculosis pattern in Indonesia: a systematic review

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1Department of Microbiology, Faculty of Medicine, Universitas Andalas, Padang, Indonesia; 2Center for Diagnostic and Research on Infectious Diseases, Faculty of Medicine, Universitas Andalas, Padang, Indonesia; 3Department of Pharmacology and Therapy, Faculty of Medicine, Universitas Andalas, Padang, Indonesia.

*Corresponding to: Syandrez Prima Putra Department of Microbiology, Faculty of Medicine, Universitas Andalas, Padang, Indonesia; syandrez@med.unand.ac.id

ABSTRACT

Background: One of the most pressing and challenging issues facing global tuberculosis (TB) control is the ongoing spread of drug-resistant tuberculosis. Patients with multidrug-resistant (MDR) TB, or forms of the disease resistant to isoniazid and rifampicin, are essentially incurable by first-line conventional therapy. This systematic review aims to address Indonesia’s specific patterns of drug-resistant tuberculosis.

Methods: We examined 178 articles and selected eight studies that met DR-TB criteria in Indonesia, analyzing 1,415 patients. Systematic review conducted using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol.

Results: We found mono-resistant (403, 28.5%), poly-resistant (362, 25.6%), multi-drug resistant (MDR) (571, 40.4%), pre-extensively drug-resistant (pre-XDR) (47, 3.3%), and XDR (32, 2.3%) cases. Among these, 758 DR-TB cases were analyzed, with the most common resistances being to rifampicin (706, 93.1%), isoniazid (325, 42.9%), ethambutol (95, 12.5%), streptomycin (79, 10.4%), kanamycin (7, 0.9%), amikacin (7, 0.9%), pyrazinamide (2, 0.3%), capreomycin (1, 0.1%), levofloxacin (1, 0.1%), and moxifloxacin (1, 0.1%). There was no data on bedaquiline or delamanid resistance.

Conclusion: These findings highlight the concerning prevalence of pre-XDR and XDR TB cases in Indonesia, even amidst the challenges posed by first-line drug resistance in DR-TB cases.

INTRODUCTION

Tuberculosis (TB) remains a global health threat, causing 1.6 million deaths in 2021, ranking second to COVID-19. Better access to treatment, especially for drug-resistant TB (DR-TB), is crucial, as only one-third received proper care in 2021.1 In 2019, MDR-TB rates reached 5.63 per 100,000 globally, with highest mortality in pre-extensive drug-resistant (pre-XDR) and XDR cases.2 While global TB rates are declining, Indonesia still faces challenges, with cases rising from 429,219 to 523,614 between 2017 and 2019. Treatment success improved to 86.51%, and mortality rates remained relatively stable at around 3%.3 However, effective management requires understanding drug resistance patterns.5

A study from 2009-2011 with 497 strains found 8% resistance to one drug, 5.2% poly-resistance (mostly isoniazid + ethambutol). Among 158 MDR strains (31.8%), over 60% were resistant to all first-line drugs, primarily streptomycin (86.1%) and ethambutol (67.7%).5 Second-line drug resistance included kanamycin (23.4%) and ofloxacin (8.2%).4 Bedaquiline is effective but less so in pre-XDR TB or prior bedaquiline/clofazimine exposure.7 Research on DR-TB patterns in Indonesia is lacking, and this systematic review aims to address this knowledge gap.

METHODS

The literature search was performed on May 19, 2023, using the databases PubMed, Science Direct, Scopus, and Google Scholar. The inclusion criteria for eligible studies were as follows: (1) providing information on the number of drug-resistant tuberculosis cases, (2) being original research articles, and (3) including case reports or case series.

RESULTS

After identifying 178 articles, we removed duplicates, leaving us with 81 articles. After screening the titles and abstracts, we selected 39 papers for full-text review. Ultimately, eight studies met the criteria for inclusion in our analysis of DR-TB cases in Indonesia.

DISCUSSION

Indonesia faces a significant challenge with highly drug-resistant TB, primarily in first-line drugs, especially rifampicin resistance. Similarly, in Pakistan, rifampicin resistance is common (10.2%), followed by isoniazid (9.9%), streptomycin (2.9%), ethambutol (2.7%), and pyrazinamide resistance (1.6%). Additionally, 9.3% had multi-drug resistant TB (MDR-TB), resistant to both isoniazid and rifampicin.7 In contrast, Iran showed different results with higher resistance in streptomycin.

Figure 1. Drug-resistant tuberculosis pattern search strategy using PRISMA flowchart.
### Table 1. Demography of references and pattern of drug-resistant tuberculosis cases included in the systematic review

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Study Population</th>
<th>Median age</th>
<th>Mean age ± SD</th>
<th>Male</th>
<th>DR</th>
<th>MR</th>
<th>PR</th>
<th>MDR</th>
<th>Pre-XDR</th>
<th>XDR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burhan et al.</td>
<td>2022</td>
<td>7 DR-TB referral hospitals (Dr. Soetomo, Surabaya; Sanglah, Denpasar; Dr. Sardjito, Yogyakarta; Dr. Kariadi, Semarang; Persahabatan, Jakarta; H. Adam Malik, Medan; and Dr. Wahidin Sudirohusodo, Makassar)</td>
<td>n/a</td>
<td>41.3 ± 14.1</td>
<td>274 (61%)</td>
<td>154</td>
<td>33</td>
<td>22</td>
<td>87</td>
<td>12</td>
<td>n/a</td>
</tr>
<tr>
<td>Choerunisa et al.</td>
<td>2021</td>
<td>Dr. Hasan Sadikin Hospital, Bandung, West Java</td>
<td>38</td>
<td>n/a</td>
<td>274 (61%)</td>
<td>122</td>
<td>n/a</td>
<td>121</td>
<td>n/a</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Kusmiati et al.</td>
<td>2020</td>
<td>Dr. Soetomo General Academic Hospital, Surabaya, Indonesia.</td>
<td>n/a</td>
<td>44.38 ± 12.28</td>
<td>253 (58.4%)</td>
<td>434</td>
<td>11</td>
<td>335</td>
<td>41</td>
<td>16</td>
<td>31</td>
</tr>
<tr>
<td>Maladan et al.</td>
<td>2021</td>
<td>Papua Province referral laboratory</td>
<td>n/a</td>
<td>n/a</td>
<td>153 (68.6%)</td>
<td>223</td>
<td>5</td>
<td>5</td>
<td>168</td>
<td>19</td>
<td>n/a</td>
</tr>
<tr>
<td>Manurung et al.</td>
<td>2018</td>
<td>H. Adam Malik Hospital, Medan</td>
<td>n/a</td>
<td>n/a</td>
<td>434 (64.3%)</td>
<td>43</td>
<td>n/a</td>
<td>n/a</td>
<td>43</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>Nurhajati et al.</td>
<td>2019</td>
<td>Indramayu District, West Java</td>
<td>n/a</td>
<td>n/a</td>
<td>59 (60.2%)</td>
<td>96</td>
<td>n/a</td>
<td>n/a</td>
<td>96</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>Paulus et al.</td>
<td>2021</td>
<td>Sanglah Public Hospital, Bali</td>
<td>40 (12-65)</td>
<td>n/a</td>
<td>328</td>
<td>328</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>van Kampen et al.</td>
<td>2015</td>
<td>West-, Central- and East-Java</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>1415</td>
<td>403</td>
<td>362</td>
<td>571</td>
<td>47</td>
<td>32</td>
</tr>
</tbody>
</table>

Total N (%) | 1415 (100%) | 403 (28.5%) | 362 (25.6%) | 571 (40.4%) | 47 (3.3%) | 32 (2.3%) |

Abbreviations: DR, drug resistant; MR, mono-resistant; PR, poly-resistant; MDR, multi-drug resistant; XDR, extensively drug resistant; n/a, data not available.

### Table 2. Resistance pattern of anti-tuberculosis drugs reported in the studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Total sample</th>
<th>Detection method</th>
<th>INH</th>
<th>RIF</th>
<th>PZA</th>
<th>EMB</th>
<th>SM</th>
<th>KM</th>
<th>AK</th>
<th>CM</th>
<th>OFX</th>
<th>LFX</th>
<th>MFX</th>
<th>PTM</th>
<th>DLM</th>
<th>BQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burhan et al.</td>
<td>447</td>
<td>DST</td>
<td>120</td>
<td>116</td>
<td>n/a</td>
<td>78</td>
<td>66</td>
<td>6</td>
<td>5</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Choerunisa et al.</td>
<td>121</td>
<td>MGIT</td>
<td>121</td>
<td>121</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Maladan et al.</td>
<td>19</td>
<td>WGS</td>
<td>15</td>
<td>16</td>
<td>1</td>
<td>5</td>
<td>4</td>
<td>n/a</td>
<td>1</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Nurhajati et al.</td>
<td>43</td>
<td>DST</td>
<td>43</td>
<td>43</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
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<td>n/a</td>
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<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Paulus et al.</td>
<td>98</td>
<td>DST</td>
<td>26</td>
<td>82</td>
<td>1</td>
<td>12</td>
<td>9</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>van Kampen et al.</td>
<td>328</td>
<td>DST</td>
<td>328</td>
<td>n/a</td>
<td>n/a</td>
<td>328</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
</tbody>
</table>

Total N (%) | 758 (100%) | 325 (42.9%) | 706 (93.1%) | 2   | 95  | 79  | 7  | 7  | 1   | 0    | 1    | 1    | 0    | 0    | 0    | 0    |

Abbreviations: INH, isoniazid; RIF, rifampicin; PZA, pyrazinamide; EMB, ethambutol; SM, streptomycin; KM, kanamycin; AK, amikacin; CM, capreomycin; OFX, ofloxacin; LFX, levofloxacin; MFX, moxifloxacin; PTM, proteomanid; DLM, delamanid; BQ, bedaquiline; n/a, data not available.
Rifampicin-resistant TB results from rpoB gene mutations, while isoniazid resistance relates to katG and inhA gene mutations. A common drug-resistant TB type is rifampicin-susceptible, isoniazid-resistant TB (Hr-TB).

In India, 19.76% were MDR, 8.63% had mono-resistance to isoniazid, and 6.14% to rifampicin. Indonesia faces concerns with Pre-XDR and XDR TB. Globally, XDR-TB is rising, notably in certain age groups. The Xpert MTB/XDR assay, known for sensitivity, should be used for detection. While this study has limitations, it sheds light on DR-TB patterns to guide future strategies.

**CONCLUSION**

The high prevalence of pre-XDR and XDR TB in Indonesia, alongside first-line drug resistance, calls for an urgent and proactive response. Preventing further XDR-TB emergence, amid limited effective drugs, is crucial.

**CONFLICT OF INTEREST**

The author reports no conflicts of interest in this study.

**FUNDING**

This research is funded by the Faculty of Medicine, Universitas Andalas.
Laboratory spectrum and antibiotic resistance profile of melioidosis association with patient outcomes

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ABSTRACT

Keywords: Antibiotic-resistant Burkholderia pseudomallei, laboratory investigation, melioidosis.

Background: Estimating cases of melioidosis caused by Burkholderia pseudomallei is challenging, especially in Asian countries. This infection can cause a mortality rate of up to 42%. Riau Province, Indonesia, is at high risk due to its proximity to affected countries. This study aims to investigate diagnostics, antibiotic resistance, and patient outcomes on melioidosis cases in Pekanbaru, Riau Province.

Methods: The data took from microbiology laboratories in two hospitals, i.e., Arifin Achmad General Hospital and Eka Hospital Pekanbaru in Riau Province, from 2009 to 2021. Culture and resistance tests were performed using the Vitek 2 system. The relationship between laboratory parameters and outcomes was assessed using the Chi-squared test.

Results: Among the 68 patients with positive B. pseudomallei culture results, various laboratory findings were observed, including leukocytosis (72.7%), elongated erythrocyte sedimentation rate (ESR) (89.5%), hypoalbuminemia (85.2%), elevated blood urea nitrogen (BUN) (76.9%), increased alanine transaminase (ALT) (57.5%) and aspartate aminotransferase (AST) (52.6%) levels, and hyponatremia (76.7%). The mortality rate was 46.6%. Selected antibiotics showed sensitivity rates of meropenem (85.5%), cotrimoxazole (87.0%), and ceftazidime (81.5%). High ALT levels were significantly associated with mortality (OR: 6; 95% CI: 1.274-28.254).

Conclusions: High ALT levels may be a sign of melioidosis patients with higher mortality risk; this marker could be used as a warning to improve outcomes. Meropenem, cotrimoxazole, and ceftazidime are antibiotics with high sensitivities for melioidosis.

INTRODUCTION

Globally, there have been more reports of melioidosis, with estimations of up to 165,000 cases and 89,000 fatalities annually.1-3 The cornerstone of laboratory diagnosis continues to be the culture of relevant clinical material. Although mass spectrometric methods have been described, phenotypic methods are the most effective for identification.3

Burkholderia pseudomallei causes melioidosis. Estimating cases is challenging, especially in Asia. The mortality rate can reach 42% around the world and 43% in Indonesia.2 Although some data about this infection exists, there is still a need for laboratory tests associated with patient outcomes. Riau Province, Indonesia, is at high risk due to its proximity to affected countries. This study aims to investigate diagnostics, antibiotic resistance, and patient outcomes in melioidosis cases in Pekanbaru, Riau Province.

METHODS

Data collection took place from 2009 to 2021 at microbiology laboratories in Arifin Achmad General Hospital and Eka Hospital Pekanbaru. Culture and resistance tests were performed using the Vitek 2 System.

RESULTS

Figure 1. Percentage of susceptibility to antibiotics.
Table 1. Laboratory result of melioidosis

<table>
<thead>
<tr>
<th>Laboratory Examination</th>
<th>Result</th>
<th>n/N</th>
<th>%</th>
<th>Laboratory Examination</th>
<th>Result</th>
<th>n/N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin (n=44)</td>
<td>Normal</td>
<td>18/44</td>
<td>40.9%</td>
<td>BUN (n=39)</td>
<td>Normal</td>
<td>9/39</td>
<td>23.1%</td>
</tr>
<tr>
<td></td>
<td>Anemia</td>
<td>24/44</td>
<td>54.6%</td>
<td>Increase</td>
<td>Creatinine Serum (n=41)</td>
<td>28/41</td>
<td>68.3%</td>
</tr>
<tr>
<td></td>
<td>Increase</td>
<td>2/44</td>
<td>4.6%</td>
<td></td>
<td>Normal</td>
<td>30/39</td>
<td>76.9%</td>
</tr>
<tr>
<td>Haematocrit (n=43)</td>
<td>Normal</td>
<td>15/43</td>
<td>34.9%</td>
<td>Decrease</td>
<td>High</td>
<td>13/41</td>
<td>31.7%</td>
</tr>
<tr>
<td></td>
<td>Increase</td>
<td>8/43</td>
<td>18.6%</td>
<td></td>
<td>Normal</td>
<td>4/27</td>
<td>14.8%</td>
</tr>
<tr>
<td>Leucocytes (n=44)</td>
<td>Leukocytosis</td>
<td>32/44</td>
<td>72.7%</td>
<td>ALT (n=40)</td>
<td>Normal</td>
<td>17/40</td>
<td>42.5%</td>
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<tr>
<td></td>
<td>Normal</td>
<td>12/44</td>
<td>27.3%</td>
<td></td>
<td>Increase</td>
<td>23/40</td>
<td>57.5%</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td>25/47</td>
<td>53.2%</td>
<td>AST (n=38)</td>
<td>Normal</td>
<td>18/38</td>
<td>47.4%</td>
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<tr>
<td>Platelets (n=47)</td>
<td>Thrombocytopenia</td>
<td>13/47</td>
<td>27.7%</td>
<td>Natrium (n=30)</td>
<td>Increase</td>
<td>20/38</td>
<td>52.6%</td>
</tr>
<tr>
<td></td>
<td>Thrombocytosis</td>
<td>9/47</td>
<td>19.2%</td>
<td>Normal</td>
<td>Normal</td>
<td>7/30</td>
<td>23.3%</td>
</tr>
<tr>
<td>ESR (n=19)</td>
<td>Normal</td>
<td>2/19</td>
<td>10.5%</td>
<td>Hyponatremia</td>
<td>23/30</td>
<td>76.7%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Elongated</td>
<td>17/19</td>
<td>89.5%</td>
<td></td>
<td>Normal</td>
<td>20/29</td>
<td>69.0%</td>
</tr>
<tr>
<td></td>
<td>Prediabetic</td>
<td>11/41</td>
<td>26.8%</td>
<td>Hipokalemia</td>
<td>6/29</td>
<td>20.7%</td>
<td></td>
</tr>
<tr>
<td>Blood glucose (n=41)</td>
<td>Hyperglycemia</td>
<td>25/41</td>
<td>61.0%</td>
<td></td>
<td>Hyperkalemia</td>
<td>3/29</td>
<td>10.3%</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td>3/41</td>
<td>7.3%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypoglycemia</td>
<td>2/41</td>
<td>4.9%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*ESR: erythrocyte sedimentation rate, BUN: blood urea nitrogen, ALT: alanine transaminase, AST: aspartate aminotransferase

DISCUSSION

High ALT levels were significantly associated with mortality in our analysis. Previous studies also linked markers of end organ dysfunction (e.g., uremia, hyperbilirubinemia) to poor outcomes in melioidosis. Leukopenia, hepatic dysfunction, renal dysfunction, and metabolic abnormalities predicted mortality. Liver disease was identified as the only comorbidity associated with increased risk of death.1,4

* B. pseudomallei, a tier 1 select agent and the endemic cause of melioidosis, is prevalent in northern Australia and Southeast Asia, where its prevalence is also higher. B. pseudomallei is inherently resistant to many antimicrobial agents. Ceftazidime resistance rate was 0.5% in a study from Thailand and Singapore, while cotrimoxazol resistance ranged from 0 to 13%.4,6

CONCLUSION

A high ALT level may be a useful marker of higher-risk mortality in melioidosis patients. Early recognition of illness severity based on this laboratory parameter leads to improved patient outcomes.

CONFLICT OF INTEREST

The authors declare no competing interests.

FUNDING

This study was funded by DIPA, Universitas Riau.
**ETHICAL CLEARANCE**

This study received approval from the Ethics Unit of the Faculty of Medicine, Universitas Riau (No. B/120/UN19.5.1.1.8/UEPKK/2021).

**AUTHOR CONTRIBUTIONS**

Conceptualization DA; methodology DA, FMS, DR, RAK, IY; software FMS, NJ, ND; validation DA, FMS, ZDT, DR, RAK, IY, NJ, ND; formal analysis DA, FMS, NJ, ND; investigation DA, ZDT, DR, NJ, NJD, IY; data curation DA, FMS, ZDT, DR, RAK, NJ, ND; and original draft preparation DA, review DA, FMS, ZDT, DR, RAK, IY, NJ, ND; and editing DA, FMS, ZDT, DR, RAK, NJ, ND.

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INTRODUCTION
Alzheimer’s disease (AD) is a chronic progressive neurodegenerative disease and is currently the most common cause of dementia in the population aged ≥65 years. The underlying pathophysiology includes neurotoxic deposition of extracellular amyloid-β (Aβ) fibrils, hyperphosphorylation of tau protein and deposition of neurofibrillary tangles (NFT) on the inner side of neurons, and neurodegeneration in brain tissue. This disease is characterized by a progressive decline in cognitive function, especially in the memory domain. At a severe degree of disease, the patients will experience a decrease in their quality of life which causes them to be an economic and social burden for their caregivers and also a health burden for the health service authorities. The currently available pharmacological treatments, including donepezil, rivastigmine, galantamine, and memantine, are very useful in inhibiting the progression of dementia in most people with AD. However, reports of side effects due to the use of these drugs are not uncommon in patients with AD who enter the dementia stage. The limitations of existing drugs continue to encourage researchers to investigate bioactive compounds available in nature which have the potential to be developed into new drugs with better drug efficacy profiles and minimal side effects for AD.

Various species of marine biota are currently receiving attention from researchers regarding their potential to be developed as drugs for various medical conditions, including AD. One of them that has begun to be widely studied for this purpose is sea urchins, an invertebrate commonly found in coastal areas. A bioactive compound contained in sea urchin that has the potential to be developed as a drug for AD is the monoterpene linalool. Previous studies have shown that this bioactive compound has properties needed to inhibit the progression of AD, including anti-inflammatory, antioxidant, and neurotropic properties. This literature review aims to discuss the potential of sea urchin and linalool they contain to be developed into drugs for AD in the future based on the results of recent studies.

Pathophysiology of AD
The pathological process in the brain that underlies AD is the deposition of Aβ plaques and NFT in brain tissue, especially in the hippocampus. Several risk factors that are thought to contribute to the deposition of Aβ plaques and NFT in the brain tissue of patients with AD include genetic abnormalities, errors in amyloid precursor protein (APP) processing, and disturbances in energy metabolism. Genetic mutations in the APP, Presenilin 1 (PSEN1), and PSEN 2 genes will cause errors in enzymatic APP processing which results in the formation of Aβ fibrils. Mutations in the apolipoprotein E (ApoE), clusterin (CLU), and Sortilin Related Receptor 1 (SORL1) genes impair the clearance and degradation of Aβ fibrils. Therefore, the pathological process of AD is a complex one that involves the combined effect of genetic and environmental factors.

Sea urchins as a source of the active substance linalool: a drug candidate for Alzheimer’s disease

Herpan Syafii Harahap1*, Dini Suryani2, Arina Windri Rivarti2, Nurhidayati Nurhidayati3, Legis Ocktaviana Saputri3, Fitriannisa Faradina Zubaidi4

ABSTRACT
Background: Alzheimer’s disease (AD) is a chronic progressive neurodegenerative disease which has implications for the progressive decline of the patient’s cognitive function. The currently available pharmacological treatment for AD is still not fully satisfactory since there are reports of side effects that are quite common. Sea urchins are a marine biota known to contain a bioactive compound with therapeutic effects for AD known as linalool. This literature review aims to discuss the potential of sea urchins-derived linalool to be developed into AD drugs in the future.

Methods: This literature review describes previous studies for future support development of a new drug from this compound to slow the progression of AD through experimental studies.

Results: Sea urchins-derived linalool has anti-inflammatory, antioxidant, and neurotrophic properties, properties needed to slow the progression of AD. Several potential therapeutic targets of sea urchins-derived linalool identified include inhibition of amyloid-beta fibril deposition, decreased activity of glycogen synthase kinase-3 beta (GSK-3 beta), inhibition of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) activation, and competitive antagonist for the neurotransmitter glutamate in binding to N-methyl-D-aspartate (NMDA) receptors.

Conclusion: There are few previous experimental studies supporting the use of linalool contained in sea urchin in the further development of new drugs to slow the progression of AD. Nevertheless, this literature review opens the horizon for researchers to further explore the potential of linalool to be developed as a drug for AD.

Keywords: Alzheimer’s disease, sea urchins, bioactive compounds, linalool, neurodegeneration.
of preformed Aβ and therefore increase the aggregation and deposition of Aβ fibrils in brain tissue. This excessive formation of Aβ fibril plaques is a trigger for hyperphosphorylation of tau protein and deposition of NFT. The abnormal presence of Aβ plaques and NFT deposition will further trigger a series of major pathological processes that form the basis of neurodegenerative processes and neuronal cell death, including oxidative stress, neuroinflammation, and glutamate excitotoxicity.

**Potential use of sea urchin extract as a treatment for AD**

Sea urchins are invertebrates belonging to the phylum Echinodermata which are commonly found in coastal areas. Several studies have shown that the distribution of various species of sea urchin in marine waters in Indonesia is quite wide. In vitro and in vivo studies show that sea urchin extract contains active compounds that have neuroprotective properties. Thus, its wide distribution on the coast in various regions in Indonesia is an advantage of this marine biota as an abundant source of raw materials, both for research and development of new drugs for various medical conditions.

The results of recent experimental studies have begun to show the potential for sea urchin to be developed as a new drug candidate for AD. This fact is supported by the results of several pharmacological studies which have proven the existence of neurotrophic, anti-inflammatory and antioxidant activities possessed by various active compounds contained in sea urchin. Since neuroinflammation and oxidative stress are pathological processes in brain tissue that underlie neurodegenerative processes in AD, it is not surprising that the properties possessed by sea urchin place this marine biota as a drug candidate for AD.

**Potential role of linalool as a natural treatment for AD**

Previous study has shown that linalool has anti-inflammatory and antioxidant properties. Its anti-inflammatory properties are demonstrated by its ability to suppress NF-kB activation and thereby also reduce the production of pro-inflammatory cytokines, including TNF-α, IL-1, and iNOS. Meanwhile, the antioxidant capacity of linalool is demonstrated by its ability to reduce ROS production and restore endogenous antioxidant enzyme superoxide dismutase (SOD) and glutathione peroxidase (GPx) to their normal levels. Second, linalool also has neurotrophic properties through its ability to inhibit Aβ fibril formation, tau phosphorylation, NFT formation, and glutamate excitotoxicity. Finally, linalool is highly lipophilic which makes it an ideal compound to be developed as a drug that acts on the central nervous system, such as in AD. The chart below summarized the potential mechanisms of linalool as a treatment for AD (Figure 1).

**CONCLUSION**

In conclusion, previous experimental studies supporting the use of sea urchin-derived linalool in further development of new drugs for AD are still limited. However, these studies generally support the neuroprotective effects of linalool. Nevertheless, this literature review opens the horizon for researchers to explore further the potential of linalool to be developed as a drug for AD.

**ETHICAL STATEMENT**

This review article has followed International Committee of Medical Journal Editors (ICMJE) guidelines regarding publication ethics.

**FUNDING**

This literature review did not receive any funding.

**AUTHORS CONTRIBUTION**

All authors have the same contribution in writing this article.

**REFERENCES**


INTRODUCTION

Tuberculosis (TB) is one of the major causes of morbidity and mortality in developing countries. It has remained one of the top 10 causes of death worldwide in 2022 and it kills more people every year than any other pathogenic bacteria. TB can take a minimum of 6 months treatment because of the pathogenesis slow-growing Mycobacterium tuberculosis (MTB) bacteria. Initially, treatment of TB disease used the combination of three kinds of first-line oral anti-TB drugs. Monitoring an outcome of treatment is usually done for 2 months after the start of a treatment and 1 month before an end of treatment, i.e., in the 5th month. Therefore, this research intends to highlight one of the cells in the natural immunity, i.e., macrophages. Inside the phagocyte cells, MTB is trapped in a room formed by a phagocyte cell membrane called a phagosome. The process of host parasite interaction occurs within the phagosome. Furthermore, phagocyte cells excrete pro-inflammatory cytokines as intercellular communication signals that will work with other immunocompetent cells to eliminate incoming MTB. The pathogenic MTB bacteria have various strategies to avoid this elimination process.5,7

One of the strategies applied by pathogenic Mycobacteria is by the recruitment of TACO that originally exist in the cortex area of phagocyte cells to the surface of the phagosome membrane; then, TACO will cause Ca^{2+} influx and activation of Ca^{2+} dependent phosphatase Calcineurin to which will inhibit the fusion of phagosomes and lysosomes. Ca^{2+} influx also inhibits the work of the phosphatidylinositol-3-kinase (PI3K) enzyme that promotes an increase in phosphatidylinositol-3-phosphate (PI3P), which would play a vital role in the phagolysosome fusion. This study would like to prove explicitly in patients whether only active and multiplying active MTB could recruit and retain TACO on the surface of the phagosome membrane and what role of TACO is in the pathogenesis and treatment period of TB infection.

METHODS

Twenty-seven samples were peripheral blood monocyte cells (PBMCs) from TB patients in a Directly Observed Treatment Short course (DOTS) polyclinic at Dr. Soetomo General Hospital Surabaya, Indonesia, and Pegirian Primary Health Care, from aged between 21 to 65 years, who were not suffering from diabetes mellitus, cancer, HIV infection, and not smoking. Whole blood was examined at the TB Laboratory, Department of Clinical Microbiology, Dr. Soetomo General Hospital. Examination was done at the Electron Microscopy Unit and Integrated Laboratory of Universitas Airlangga with monoclonal antibodies bought from MYBIOSOURCE, Inc., USA and the Real Time PCR using Light Cycler machine 2.0 (ROCHE) in Universitas Airlangga Hospital. Peripheral blood monocyte cells isolation from “whole blood” specimens used Ficoll-Histopaque 1077 solution, a suitable reference procedure to obtain pure mononuclear cells.3 The RNA extraction was done using GENEaid for
Blood and Tissue Kit, then was measured for the number of RNAs eligible for real time polymerase chain reaction (rtPCR) using NanoDrop. The TACO gene was amplified using the primers 5’-CCAGTGCTATGAGGATGTGCGG and 5’-GACACGACTCGCTTGTCCAGG-3’. These genes were amplified using PCR programs: 94 °C for 45 cycles; 60 °C for 45 cycles; 72 °C for 90 cycles (22 cycles).

RESULTS

From the statistical analysis using one-way ANOVA, there was a significant difference in TACO expression between new TB patients and TB patients after 2 months of treatment, there was a significant difference in TACO expression between new TB patients and TB patients after 5 months of treatment, and there were no significantly difference in TACO expression between TB patients after 2 months of treatment and after 5 months of treatment. The immunocytochemistry (ICC) examination of 3 different groups shown in Figure 1.

DISCUSSION

TACO expression was lower when compared with that of TB patients who had been treated for 2 months and 5 months. Various enzymes and proteins are released by the MTB in order to inhibit the phagosome maturation, inhibit the fusion of phagolysosomes, and inhibit the cytokines produced by macrophages. Comprehensive proteomic analysis of the MTB H37Rv bacteria found at least 3 growth phases of “mid-log phase” (14-day culture), “early stationary” (28-day culture), and “late stationary” (50-day culture) changes in the expression of certain proteins following the growth of MTB bacteria from the “mid-log phase” to the “late-stationary phase”. Biomolecular research on proteins produced by MTB, host-produced proteins to combat intracellular microorganisms and host-parasite interaction processes, is still required.

The exact mechanism of the mycobacterial phagosome TACO retention remains to be investigated, which may involve lipoamide dehydrogenase secreted by the Mycobacteria, which are also known to be involved in the fight against the toxic effects of nitrogen intermediates issued by the host cells. In line with the important role of calcineurin in improving the viability of Mycobacteria, it is shown that calcineurin inhibitors such as cyclosporin A and FK506 can induce the fusion of the phagosome containing Mycobacteria to lysosomes and destruction. TACO is an important molecule involved in the homeostasis of T lymphocyte cell phagosomes containing Mycobacteria, which are known to continuously inhibit PI3P, which is the key to phosphoinositide that is known to regulate phagosome acceptance of the underlying elements of lysosomes. The process of dephosphorylation of vacuolar proteins especially protein 33B prevents membrane fusion events that are essential for phagosome maturation.

CONCLUSION

mRNA examination of TACO levels varies because MTB has a very complex self-defense mechanism against the host’s natural immunity therefore living MTB in the phagosome only uses TACO expression to avoid phagolysosomes fusion in the macrophages.

CONFLICT OF INTEREST

None declared.

FUNDING

None declared.

ETHICAL CLEARANCE

This study was approved by the Ethical Committee in Health Research of Dr. Soetomo General Hospital, Surabaya, Indonesia (no. 404/Panke.KKE/VIII/2015).

AUTHOR CONTRIBUTION

All authors contributed equally in collecting the data and wrote the paper.

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INTRODUCTION

The use of cardiac implantable electronic devices (CIED), such as cardiac pacemakers, implantable cardioverter defibrillators, and cardiac resynchronization therapy (CRT) devices, is crucial in the management of bradyarrhythmias, the prevention of sudden cardiac death, and the treatment of heart failure.1 The most frequent reason for lead removal and a serious CIED consequence, infection has increased more rapidly over the past several decades.2-4

The current recommendations for treating CIED infections call for the removal of the device, regardless of whether the infection is localized to the pocket (abscess or skin erosion) or systemically into the bloodstream (septicaemia, with or without detectable lead related endocarditis).3-4 According to reports, the main microbiological organisms responsible for CIED infections include Staphylococcus spp.4 Optimizing diagnostic and therapeutic strategies are important that can be used to detect the infections early and treat them effectively. We herein report the case of cardiac pacemaker expulsion due to methicillin-resistant Staphylococcus aureus infection.

CASE PRESENTATION

A 70-year-old male presented with left chest pain due to PPM pocket infection 1 week ago. He also complained of redness of the surrounding skin at the PPM insertion site and pulse generator expulsion from PPM pocket. He has a history of complete heart block and a left-sided pacemaker was placed in May 2022. Physical examination documented there is no abnormality in the patient’s vital signs, cardiovascular examination on presentation was unremarkable, and evidence of pocket infection at sites on left sides of the chest. From laboratory examination we found leukocytosis. Blood cultures revealed methicillin-resistant Staphylococcus aureus. The patient was taken to the operating room for total device system removal and replaced with a temporary pacemaker. The patient was given vancomycin injection, mefenamic acid and after 6 days in the ward, the patient planned for PPM insertion again.

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Conclusion: Untreated PPM pocket infection can cause high mortality. System-wide infection control measures and team-based multidisciplinary management of patients are essential for optimal outcomes.

Background: Cardiovascular implantable electronic devices (CIED) including permanent pacemaker (PPM) play an important role in the treatment of arrhythmias. The major complication in CIED is infection and becomes the most common cause for lead removal. Infection is a serious complication, with an in-hospital mortality rate of 5-15%. Optimizing diagnostic and therapeutic strategies are important that can be used to detect such infections early and treat them effectively.

ABSTRACT

INTRODUCTION

The use of cardiac implantable electronic devices (CIED), such as cardiac pacemakers, implantable cardioverter defibrillators, and cardiac resynchronization therapy (CRT) devices, is crucial in the management of bradyarrhythmias, the prevention of sudden cardiac death, and the treatment of heart failure.1 The most frequent reason for lead removal and a serious CIED consequence, infection has increased more rapidly over the past several decades.2-4

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On the PPM site insertion, there was evidence of swelling, redness, discharge, wound dehiscence, and pulse generator expulsion at the pacemaker pocket in left hemithorax (Figure 1A). From laboratory examination we found leukocytosis with a predominance of neutrophils. Blood cultures revealed methicillin-resistant Staphylococcus aureus. A transthoracic echocardiogram performed and showed left ventricular (LV) dilatation, concentric LV hypertrophy, normal LV systolic function (ejection fraction 53%), and there is no vegetation or sign of infective endocarditis.

The patient diagnosed with pacemaker pocket infection with generator expulsion et causa methicillin resistant staphylococcus aureus. Patient was admitted to cardiovascular care unit (CVCU) and planned for debridement of infected pocket tissue and total device system removal. A temporary pacing wire was placed in the right ventricular apex via a subclavian approach. The patient also given intravenous vancomycin 1 g every 12 hours for 14 days and per-oral mefenamic acid 500mg every 8 hours. The patient remained hospitalized for 1 week for management of his infected pacemaker sites, the complaints of swelling, redness, discharge, and pain have decreased (Figure 1B) and the patient planned to repeat the...
blood culture. If the result of blood culture is negative, the patient planned for re-implantation of PPM on the contralateral side (right side). The intravenous vancomycin will be given continuously 1 g every 12 hours to the patient until 14 days.

**CONCLUSION**

A lack of effective treatment for CIED infections, which are occurring more often than ever, is linked to a high fatality rate. Due to the variety of clinical symptoms associated with infections, diagnosis can be difficult, and involvement of other cardiac structures must always be ruled out. Complete system elimination constitutes definitive therapy. For the best results, a system-wide approach to infection prevention and team-based multidisciplinary patient treatment are crucial.

**DISCUSSION**

The risk of CIED infection has sharply increased and surpassed the rise in implantation rate as therapeutic indications have extended. When a CIED has been colonized by pathogens, complete device removal (including lead extraction) is the standard procedure. Based on this instance, methicillin-resistant *Staphylococcus aureus* was found in the patient’s blood cultures. Most pocket and intravascular infections are caused by skin flora (Gram-positive, coagulase-positive *S. aureus* and coagulase-negative *S. epidermidis*). The most frequent cause of CIED infection within two weeks post pocket manipulation is *S. aureus* infection and frequently linked to longer-lasting bacteremia and increased mortality.

Infections of the subcutaneous tissue and pockets can manifest as wound dehiscence, discomfort, swelling, redness, and discharge. After the pus is discharged, the discomfort subsides and a persistent fistula may emerge. With lead infection or bacteremia, systemic symptoms of infection, such as fever, chills, malaise, lethargy, and anorexia with weight loss, are present, although they are often absent in localized pocket infection. The most frequent laboratory abnormalities are elevated levels of erythrocyte sedimentation rate, C-reactive protein, leukocytosis, microscopic hematuria, and anemia. From this case, we found swelling, redness, discharge, wound dehiscence, and pulse generator expulsion at the pacemaker pocket in left hemithorax and leukocytosis with neutrophil dominant in laboratory examination.

Before beginning any antimicrobial medication, blood cultures should be collected when clinical signs and symptoms point to CIED infection. Since it can measure vegetation size, detect electrode or heart valve involvement, and estimate tricuspid valve insufficiency, echocardiography is a critical component of diagnosis. When it comes to identifying lead or valvular endocarditis and its attendant problems, transesophageal echocardiography is more effective than transthoracic echocardiography. Because we lack a modality for transesophageal echocardiography, we employ transthoracic echocardiography in this instance. Complete device removal is advised if the findings of the echocardiogram revealed valve vegetation, lead vegetation, or normal with a condition. In this patient, we performed complete device removal because in echocardiography result was normal and accompanied with pocket infection with abscess formation, superficial erosion, and occult Gram-positive bacteremia.

If an echocardiogram reveals a heart valve vegetation, a lead vegetation, or a normal echocardiogram with a problem, antibiotic medication is maintained for 4-6 weeks, 2-4 weeks, and 2 weeks, respectively. Patients with CIED infections typically choose contralateral reimplantation. Following CIED removal, blood cultures are performed, and several studies advise clearing the bacteremia (blood cultures negative for 72 hours) prior to reimplantation. In this patient, after the blood culture was negative, the patient was implanted with a new pacemaker at the right chest.

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Pregnancy complicated by thyroid heart disease: a case report

Yusra Pintaningrum1,2, Lalu Shalya Kusuma Putra*1

ABSTRACT

Background: Hyperthyroidism can give disturbance to the cardiovascular system and pregnancy. Uncontrolled thyrotoxicosis can increase the risk of feto-maternal complications such as preeclampsia, congestive heart failure, miscarriage, prematurity, low birth weight (LBW), stillbirth, and intrauterine growth restriction (IUGR). This case report aims to describe pregnancy complicated by thyroid disease.

Case Presentation: A 35-year-old pregnant woman presented with dyspnea a year ago and progressively worsened since her 3rd month of pregnancy. Other symptoms were swollen legs, palpitation, thyroid enlargement, and sweating. Blood pressure was 140/50 mmHg and heart rate was 97 bpm. On physical examination, thyroid mass, Means-Lerman scratch, and pitting edema was found. Chest X-ray showed pulmonary edema and cardiomegaly. Echocardiography revealed normal left ventricular systolic function abnormal diastolic function grade 3, and mild concentric left ventricular hypertrophy (LVH). Decrease in TSHs and increase in FT3 and FT4 was noted. The patient diagnosis was G3P2 GA at 22-23 weeks and thyroid heart disease with heart failure preserved ejection fraction (HFpEF). Furosemide, propranolol, and propylthiouracil were given with monitoring of fetal heart rate and an improvement was seen throughout the hospitalization.

Conclusion: Hyperthyroid is important to diagnose early during pregnancy or, if possible, before pregnancy. This was based on the risk of maternal and fetal disease that could happen if there is a delay in diagnosing hyperthyroid.

INTRODUCTION

Thyroid is an endocrine gland that can affect multiple organs in the human body. This function is achieved by secreting thyroxine (T4) and triiodothyronine (T3). Secretion of these hormones are controlled by anterior pituitary by thyroid stimulating hormone (TSH). Anterior pituitary is also controlled by hypothalamus via secretion of thyroid releasing hormone (TRH). One of the organs that is affected by thyroid hormones is heart. It could give a positive chronotropic and inotropic effect.

On hyperthyroid state, arrhythmias, vascular changes, and myocardial remodeling could happen. These changes will reduce the cardiac output and, eventually, increase the risk of heart failure. Among pregnant patients, hyperthyroid was found in 0.05% to 3% with 85% case of Graves’ disease. Uncontrolled thyrotoxicosis in pregnancy will increase cardiac burden, the risk of developing heart failure, pregnancy-induced hypertension, pregnancy loss, stillbirth, premature, low birth weight, and intrauterine growth restriction (IUGR).

This case report will discuss about pregnant women complicated by thyroid heart disease with heart failure preserved ejection fraction (HFpEF).

CASE PRESENTATION

A 35 year-old pregnant woman came to the emergency department with dyspnea. The patient had already felt this symptom since 1 year ago and worsened since her 3rd month of pregnancy. She also felt a fast heart beat without any trigger. Her palpitation also accompanied by neck mass enlargement, increasing appetite, excessive sweat, fatigue, and cold extremities. She had felt swollen legs for 3 days before admitted to hospital. Her blood pressure and heart rate were 140/50 mmHg and 95 beats per minute (bpm). On physical examination, there are palpable masses on the neck with 7 x 3 cm in size, soft surface, and well demarcated. Reduced vesicular pulmonary sound was heard on the basal part. A mid-systolic scratching sound was heard over the upper part of the sternum or second left intercostal space at the end of expiration (Means–Lerman scratch).

Her fundal height was two fingers under her umbilical. Pitting edema was positive on both lower extremities. Her Wayne's Index was 24.

Chest X-ray showed cardiomegaly and pulmonary edema. Ultrasound examination showed gestational age at 17 weeks 3 days, estimated fetal weight 198 grams, normal amniotic fluid volume, with estimated due date on November...
Figure 2. Echocardiogram showed: (a) normal LV systolic function (EF by teich 65%) with mild concentric left ventricular hypertrophy; (b) abnormal LV diastolic function grade 3; (c) normal RV systolic function; (d) normal left atrium and right ventricle.

Figure 3. Ultrasonography showed normal amniotic fluid volume with gestational age 17 weeks 3 days and estimated fetal weight 198 grams.

20th, 2022. On echocardiography, normal LV systolic function (EF by teich 65%), abnormal LV diastolic function (grade 3), and mild concentric LVH was found. Her thyroid function test decreased in TSHs (0.17 uIU/mL), increased in FT3 and FT4 (35.7 Pmol/L and >100,00 Pmol/L). She was diagnosed with G3P2A0L2 gestational age 22-23 weeks and thyroid heart disease with HFpEF. The patient was hospitalized for 4 days. She was administered furosemide using syringe pump injection, propranolol 40 mg t.i.d, and propylthiouracil 100 mg t.i.d. After an improvement of symptoms was seen, furosemide was stopped on the 3rd day of hospitalization. While giving treatment, fetal heart rate was also observed.

DISCUSSION

In pregnancy, cardiovascular changes are seen such as vasodilatation, increase in cardiac output (up to 45%), heart rate, and decrease in blood pressure. With hyperthyroidism, the heart workload will increase. This condition can affect the heart by increasing resting heart rate, stroke volume, myocardial contractility, fraction ejection, and an improvement in diastolic relaxation. In pregnancy, manifestations of hyperthyroidism are varied, thus delaying the diagnosis. In this case report, a wide pulse pressure was found. This happens due to an increase in resting LV systolic function and an increase in relaxation rate of LV chamber and LV filling. This contributes to an increase in systolic arterial pressure and a decrease in diastolic arterial pressure. Another finding was The Mean-Lerman Scratch which is usually found in patients with hyperthyroid. Midystolic murmur happens when there is a rubbing of pericardial and pleural that is heard on the left upper sternal border.

Wayne's Index is a clinical scoring system used to help in assessing whether there is a possibility of hyperthyroid state and its degree. A score less than 11 showed euthyroid meanwhile a score > 19 increased the possibility of toxic hyperthyroidism. This patient's Wayne's Index was 24 which leads to a suspicion towards uncontrolled thyrotoxicosis state. This condition was then confirmed with laboratory results. Abnormal LV diastolic function and mild concentric of LVH due to high-output heart failure which is caused by tachycardia-mediated cardiomyopathy.

The treatment of choice for hyperthyroidism during pregnancy is antithyroid agent. If the level of FT4 is at or slightly elevated from the normal value, therapy could be delayed with monitoring of the patient's thyroid status. Pregnant patient thyroid level should be kept in a subclinical state, this consideration was based on no maternal or fetal complication reported up until now. The goal of therapy is an euthyroid state using the lowest dose that can maintain FT4 level up to 10% of normal range. The drugs of choice are propylthiouracil (PTU) and methimazole. In this case, we use PTU because the
risk of congenital abnormalities was low compared to methimazole.8-11

Hyperthyroid is important to diagnose early during pregnancy or, if possible, before pregnancy. This is based on the risk of maternal and fetal disease that could happen if there is a delay in diagnosing hyperthyroid. These risks will be increased if the patient is in an uncontrolled thyrotoxicosis state. Maternal complications that could happen are preeclampsia, thyroid storm, and congestive heart failure. Congestive heart failure was found in 10% of pregnant women in uncontrolled thyrotoxicosis. The fetal complication that could happen are prematurity, miscarriage, stillbirth, low birth weight, and intrauterine thyroid dysfunction.6,9

CONCLUSION
Thyroid heart disease can bring harm both to feto-maternal health. Early diagnosis and prompt treatment of hyperthyroid is important with the goal to improve the condition for maternal and fetal health.

CONFLICT OF INTEREST
All authors declare there is no conflict of interest regarding publication of this report.

ETHICAL CONSIDERATION
Patients had received signed written informed consent regarding publication.

FUNDING
None.

AUTHOR CONTRIBUTION
All authors had contributed in manuscript writing and agreed for the final version of the manuscript for publication.

REFERENCES
Challenge of histopathological method to diagnose double cutaneous invasive fungal infection in Indonesia: a rare pediatric malignancy case report

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INTRODUCTION

Invasive fungal diseases were frequently observed as a prevalent form of infection in various clinical settings worldwide. Cutaneous mucormycosis and candidiasis are fungal infections that are increasingly prevalent among individuals with immunocompromised, such as hematologic malignancies (e.g., acute lymphoblastic leukemia, acute myeloid leukemia, among others).1,2 Double cutaneous invasive fungal infection is an infrequent occurrence typically acquired via direct inoculation resulting from traumatic injury.2

The primary cutaneous invasive fungal infection often arises from the introduction of spores into the skin and subcutaneous tissues due to various factors such as trauma, contaminated dressings, surgical procedures, burns, automobile accidents, vascular devices, and the use of nitroglycerine patches.3,6 The development of the condition can be attributed to the genera Mucor, Absidia, Rhizopus, and Rhizomucor. Various types of mucormycosis exist, such as gastrointestinal mucormycosis (2–11%), disseminated (6–11%), pulmonary (10–11%), cutaneous (10–19%), rhino orbital–cerebral (44–49%), and miscellaneous.3,4

The Gomori methenamine silver (GMS) stain possesses the capability to detect the presence of invasive fungal species within the context of granulomatous inflammation associated with tuberculosis. So that is crucial for the diagnosis and treatment of both infectious and malignant diseases. The examination of tissue is a fundamental aspect of the diagnostic microbiology laboratory, and various techniques have been devised to detect the causative microorganism through histological staining and culture.5,6 This case report aims to describe the challenge of histopathological method to diagnose double cutaneous invasive fungal infection.

CASE PRESENTATION

A male child, five years old, Javanese ethnicity, weighing 18.7 kg, who is currently undergoing immunosuppressive therapy and has been diagnosed with a concurrent infection involving both cutaneous mucormycosis and candidiasis. He was diagnosed with acute lymphocytic leukemia, accompanied by septicemia and febrile neutropenia. The observed clinical manifestations encompassed elevated body temperature, cognitive impairment, the presence of ulcers accompanied by necrotic tissue, and swelling in the right hand. The presence of *Acinetobacter baumannii* and *Candida tropicalis* was detected in the blood cultures. The initial findings of the biopsy and histopathological analysis using the PAS stain indicated the presence of candida infection (Figure 1).

The culture of Sabouraud Dextrose Agar (SDA) exhibited the presence of *Candida tropicalis* infection. The patient’s condition deteriorated following the administration of fluconazole at a dosage of 100 mg within a 24-hour period. The wound is demonstrating a gradual increase in size and actively releasing a discharge that is characterized by the presence of...
hematoxylin and eosin stain when it comes to observing thick, hyaline, non-septated, and bifurcated hyphae. The GMS stain employs chromic acid as an oxidizing agent during the initial stage, similar to the PAS stain. In comparison to the PAS stain, chromic acid exhibits greater oxidizing capabilities than periodic acid, leading to the additional oxidation of certain aldehyde groups. Consequently, this process yields a compound that is incompatible with silver ions. Hence, the collagenous matrix present in tissues lacks pigmentation. When a light green solution is applied as a counterstain, the fungal elements exhibit black staining with well-defined boundaries and a transparent middle, which stands out against the light green background of the tissue (Figure 2).

GMS stain offers the advantage of generating enhanced staining contrast in tissue sections, thereby enabling the detection of fungal elements that may be deceased or degraded, which could potentially be overlooked by the PAS stain. This feature renders GMS a more advantageous choice for the screening of general tissue fungal infections.

The utilization of GMS tissue staining, in combination with microbiologic culture, is commonly employed for the diagnosis of fungal infections, as the presence of fungal organisms in tissues indicates an invasive infection. Histopathological analysis of tissues plays a crucial role in determining the diagnostic implications of positive culture isolates, encompassing fungal infiltration of tissues and vessels, as well as the host’s immune response to the fungal presence. This method is and will continue to be an indispensable tool in this regard.

In the field of histopathology, it is recommended to employ a comprehensive approach by utilizing a minimum of two staining techniques, such as PAS and GMS to enhance the diagnostic accuracy and provide a more thorough evaluation of tissue samples. The GMS method employs distinct incubation durations for Candida and Mucor. Specifically, Candida is subjected to a 14-minute incubation period with methenamine silver, whereas suspected mucormycosis samples are incubated for 25-30 minutes. The modification techniques have proven
to be advantageous in enhancing the positive attributes of the specimen. The utilization of the GMS stain technique revealed the presence of diminutive yeast cells, measuring approximately 3-5µm in size, interspersed among pseudo hyphae.\(^{10}\) The characteristic symptom indicative of mucormycosis is the presence of nonseptate, broad hyphae measuring between 7 to 30 micrometers, which exhibit branching at 90-degree angles.\(^{11-13}\) The improvement of survival rates in cutaneous mucormycosis and candidiasis requires the implementation of a multidisciplinary approach, which is intricately linked to the diagnostic process. The holistic management of this condition should involve surgical debridement, administration of antifungal therapy, addressing the underlying metabolic or immunological condition, and implementing measures to prevent the occurrence of additional concurrent infections. The preferred initial treatment involves the use of Amphotericin as a single therapy.\(^{11}\)

**CONCLUSION**

Histological investigation is crucial in determining the diagnosis and demonstrating tissue invasion besides culture. GMS stain is more superior than PAS to diagnose tissue fungal infection.

**REFERENCES**

**INTRODUCTION**

Alzheimer’s Disease (AD), the most prevalent form of dementia, has emerged as a significant worldwide health concern. The global prevalence of AD was 43.8 million in 2016 and is expected to increase threefold by 2050. Environmental factors such as nutrition potentially treat and prevent dementia. Marine fish is rich in omega-3 polyunsaturated fatty acids (PUFAs), which have many health benefits, especially on cognitive function. Several studies have known that diets rich in omega-3 PUFAs or supplementation with omega-3 PUFAs have a neuroprotective impact and potentially inhibit the progression of AD. Inconsistent study results on the neuroprotective effect of omega-3 PUFAs in Alzheimer’s patients show that further research is required to deepen the neuroprotective mechanism of omega-3 PUFAs in AD. Thus, this review examines the molecular neuroprotective mechanism of omega-3 PUFAs and genetic variables that might inhibit the neuroprotective effect of omega-3 PUFAs.

**METHODS**

Peer-reviewed articles were searched using the search terms “Marine Fish,” “PUFA,” “Omega 3,” “Alzheimer’s Dementia,” “cognitive function,” “neurodegenerative,” “Amyloid,” and “genetic” on PubMed, Scopus, and Google Scholar. The reference list of the articles retrieved is rechecked and used to support discussion topics that are not covered by the articles retrieved in the initial search.

**RESULTS**

**Neuroprotective activity of PUFA in the brain**

The benefits of dietary PUFA as a neuroprotective have been studied in several animal models. The effect of PUFA is known to play a role in synapse formation, preventing Aβ accumulation, increasing neurotrophic factors expression, reducing inflammation, reducing oxidative stress, and increasing cell survival. High levels of ω-3 PUFA in the blood were associated with lower production of proinflammatory cytokines in individuals. Aged mice that were given a high eicosapentaenoic acid (EPA)/docosahexaenoic acid (DHA) diet for 2 months showed a decrease in the expression of proinflammatory cytokines (TNFs, IL-1β, IL-6). EPA inhibits excessive inflammatory processes through multiple direct mechanisms against microglia, including 1) EPA increases phagocytosis of Aβ by microglia, leading to a decrease in inflammatory markers, and 2) EPA reduces NF-κB activity, leading to a decrease in various proinflammatory cytokines. Moreover, a diet rich in n-3 PUFA is related with enhanced spatial memory.

EPA is a competitive inhibitor in the AA cascade pathway for the formation of inflammatory mediators. In addition, n-3 PUFAs contribute to the synthesis of lipid mediators, such as resolvins, protectins, and maresins, which are specialized pro-resolving mediators (SPMs). This group of mediators plays a role in limiting the inflammatory process through inhibition of polymorphonuclear (PMN) infiltration, increasing the clearance of apoptotic cells, and changing the type of macrophages to anti-inflammatory macrophage phenotype M2.

A meta-analysis found that omega-3 long chain (LC) PUFA plays a significant...
part in improving total antioxidant capacity (TAC), increasing glutathione peroxidase (GPx) activity, and decreasing malondialdehyde levels (MDA). Omega-3 LC PUFA can reduce MDA through multiple mechanisms, including: 1) DHA is known to inhibit the formation of inflammatory mediators prostaglandins from the arachidonic acid pathway; and 2) omega-3 LC PUFA has an inhibitory effect on COX2, which is involved in the production of various inflammatory mediators that cause lipid peroxidation.

The effect of omega-3 PUFA is also known to increase TAC by: 1) increasing Ω3 isoprostanes, which play a role in encouraging the expression of genes that regulate detoxification of reactive oxygen species (ROS), particularly nuclear factor, erythroid 2 (NFE2) related factor 2 (Nrf2); and 2) significantly increased superoxide dismutase (SOD) activity, NO levels and decreased the thiobarbituric acid reactive substances (TBARS) levels.

Omega-3 PUFA also has a role in enhancing Aβ elimination by boosting glymphatic system activity. Aquaporin 4 (AQP4) is a canal found in the astrocyte terminal foot that plays a role in the glymphatic system. A study using AQP4-knockout mice found that omega-3 PUFA supplementation has no effect on enhancing the amyloid beta-clearing. There are no effects of n3 PUFA supplementation on neuronal cell survival and memory function in AQP4-knockout mice.

Omega-3 LC PUFA play a part in improving the activity of Aβ-degrading enzymes, namely insulin degradation enzyme (IDE) is secreted by microglia and neurons into the extracellular space. It is known that EPA has a direct influence on enhancing the activity of the IDE enzyme and its expression. While DHA has a direct effect on boosting the activity of IDE and has an indirect effect on increasing the exosomal secretion of IDE.

Genetic factors that reduce the neuroprotective effect of PUFA

Studies in the community indicate that PUFA supplementation can reduce the risk of AD. Unfortunately, the majority of intervention studies did not demonstrate the similar effect. This disparity may be caused by a genetic predisposition to Alzheimer's disease. Epidemiology studies indicate that diet n3 PUFA can significantly increase DHA plasma levels in non-apolipoprotein E4 (APOE4) carriers compared to APOE4 carriers. In addition, only individual without the APOE polymorphism have the neuroprotective effect of PUFA.

DHA-enriched LDL is the lipoprotein most easily able to traverse the BBB via the receptor mediator process. The primary ligand of the LDL receptor on BBB is ApoE. Hence, it is possible that the e4 allele affects the efficacy of APOE binding with the LDL receptor, thereby influencing DHA and EPA transport into the brain. However, this hypothesis has not been investigated further and needs further research.

CONCLUSION

Marine fish are the primary sources of omega-3 LC PUFA, a kind of fatty acid that effectively prevents inflammation and degenerative diseases, such as age-related cognitive decline and dementia.

CONFLICT OF INTEREST

The author reports no conflicts of interest in this work.

ETHICAL STATEMENT

This review article has followed International Committee of Medical Journal Editors (ICMJE) guidelines regarding publication ethics.

FUNDING

There was no funding provided for this literature review.

AUTHOR CONTRIBUTION

All authors have the same contribution, from preparing ideas and searching the literature to writing a literature review.

REFERENCES

INTRODUCTION

Lactic acid bacteria (LAB) create bacteriocins, which are antibacterial compounds. Bacteriocin can be formed in a liquid substrate, and MRS broth is frequently determined to be the most prominent for the development of LAB and bacteriocin synthesis. LAB produces antimicrobial compounds such as lactic acid, acetic acid, ethanol, formic acid, hydrogen peroxide, and bacteriocin. Bacteriocin is a protein that can kill other bacteria but is resistant to the bacteria that produce it. Lactic acid bacteria are often involved in fermentation processes, especially in food, milk, and dairy products, including traditional food growol in Kulonprogo, Yogyakarta.

Lactic acid bacteria are Gram-positive bacteria that ferment carbohydrates and produce lactic acid as their metabolite product. During the fermentation process, lactic acid bacteria will produce metabolites such as lactic acid, hydrogen peroxide, and bacteriocins, which function as antibacterial compounds. Bacteriocins are peptides or protein compounds that are released extracellularly by lactic acid bacteria and have a bactericidal effect against harmful bacteria that are phylogenetically close. The existence of this antibacterial activity can be utilized to prevent the development of pathogenic bacteria. Bacteria that produce extended-spectrum beta-lactamase are pathogens that contribute to multidrug-resistant organism (MDRO) infections. Currently, MDRO infections are increasing and becoming a public health problem. These bacteria have increased resistance to various types of antibiotics. Along with the increasing cases of antibiotic resistance, it is necessary to look for alternative sources of new and effective antibacterial compounds. Bacteriocins are peptides that have a bactericidal effect against pathogenic bacteria. It is important to study the utilization of bacteriocins produced by lactic acid bacteria from Growol as an antibacterial against several microorganisms. The purpose of this study was to examine the utilization of bacteriocin produced by Lactobacillus growol isolates against amoxicillin-resistant Escherichia coli and Candida. 

METHODS

Isolation of lactic acid bacteria growol isolate

The basic ingredients for growol are obtained from growol entrepreneurs in Kulonprogo, D.I. Yogyakarta Province. 10 grams of growol were weighed in a sterile Erlenmeyer and dissolved in 225 mL of 0.1% w/v peptone solution. The sample was homogenized using a Stomacher 400 lab blender for 1 minute, and then a 10^{-1} dilution was made. The solution was poured as much as 1 mL on de Man Rogosa Sharp Agar medium. Petridis was incubated at 37°C, 48 hours, anaerobic conditions. The growing bacterial colonies were identified based on morphology, Gram-staining, catalase testing, and gas production from glucose. Furthermore, the isolates were subcultured into MRS broth media and incubated at 37 °C for 2 x 24 hours.

Bacteriocin isolation

Bacterial colonies incubated in MRS broth were poured into six Eppendendorf tubes and then centrifuged at 15,000 rpm for 20 minutes. Transfer each supernatant...
from the bacteriocin sample that has been centrifuged into six different Eppendorf tubes.

**Bacteriocin antibacterial test using the Kirby-Bauer method**

Inoculation of the test bacteria amoxicillin-resistant *E. coli* in trypticase soy agar (TSA) media and Candida in SDA media, incubated at 37°C, for 24 hours. Preparation of the test bacterial inoculum into BHI media. The concentration of the test bacteria was 10⁶ CFU/ml using the McFarland standard. A sterile cotton swab was dipped into the test bacterial suspension, rubbed evenly on the surface of the MHA media, and left for 15 minutes. 20 µl of bacteriocin was added to the sterile antibiotic disc paper and placed on the media that already contained the test bacteria. Furthermore, the MHA media was incubated at 37°C for 24 hours. The diameter of the inhibition zone formed was measured to determine the antimicrobial activity of the bacteriocins against the test bacteria.

**RESULTS**

The results of lactic acid bacteria culture in anaerobic conditions showed white and mucoid colonies. The Gram-staining of growol isolate bacteria showed bacilli, rods, coccocalculus, and Gram-positive, catalase-negative, and producing gas. All of the four bacterial isolates showed the same characteristics. These characteristics are similar to the microscopic characteristics of Lactobacillus bacteria. Table 1 shows the results of measuring the diameter of the bacteriocin inhibition zone against amoxicillin-resistant *E. coli* and *Candida* sp. The mean bacteriocin inhibition zone of lactic acid bacteria isolated against amoxicillin-resistant *E. coli* was 10.2 mm, and that of *Candida* sp was 0 mm. The bacteriocin produced by the lactic acid bacteria isolate growol has strong antimicrobial activity against *E. coli* and no activity against *Candida* sp.

**DISCUSSION**

This study showed that the bacteriocin produced by Lactobacillus isolate growol had antibacterial activity against amoxicillin-resistant *E. coli* but was unable to inhibit Candida. The antibacterial activity of bacteriocins against pathogenic bacteria can be seen based on the diameter of the resulting inhibition zone. The bacteriocin inhibitory activity produced by *L. plantarum* against *E. coli* has an inhibition zone of 6.24 mm. *L. plantarum* has bacteriocin inhibitory activity against *E. coli*, with an average inhibition zone of 4 mm. Differences in antibacterial activity produced by bacteriocins can occur due to the use of different isolates of lactic acid bacteria, the indicator bacterial strains used, and differences in the structure of the cell wall between Gram-positive and negative bacteria. In addition, differences in the resulting inhibition zones can be caused by competition for nutrients and other metabolites produced, such as organic acids, diacetyl, and hydrogen peroxide. It is necessary to carry out further research on the active compounds making up the bacteriocins produced by Lactobacillus growol isolates.

**CONCLUSION**

Bacteriocin produced by Lactobacillus growol isolate is able to inhibit amoxicillin-resistant *Escherichia coli*. However, bacteriocin is not effective against the *Candida* sp.

**CONFLICT OF INTEREST**

The authors declare that there are no conflicts of interest.

**ETHICAL CLEARANCE**

This research is a laboratory experiment and has obtained permission from the Health Research Ethics Committee, School of Medicine, Universitas Muhammadiyah Yogyakarta, Yogyakarta, Indonesia no. 051/EC-EXEM-KEPK FKIK UMY/IV/2022.

**FUNDING**

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**AUTHOR CONTRIBUTION**

Lilis Suryani contributed to data collection and the owner of the idea of this research, research design, data collection, writing and submitting manuscript, editing and approval of final draft.

**REFERENCES**


Prevalence, risk factors, and treatment of preoperative hypertension at a top referral hospital in Lombok, Indonesia

I Gede Yasa Asmara1, Catarina Budyono1, I Gusti Ngurah Ommy Agustriadi1

ABSTRACT

Background: Hypertension is associated with other risk factors related to anesthesia and surgery. Limited studies have reported the incidence and treatment of preoperative hypertension. Therefore, this study aims to determine preoperative hypertension prevalence, risk factors, and treatment.

Methods: This cross-sectional study of patients aged >18 who consulted for elective surgery at the internal medicine clinic of the West Nusa Tenggara General Hospital from July to September 2021. Descriptive, bivariate, and multivariate analysis were performed on normotensive and hypertensive groups.

Results: Fourteen outpatient clinics, mainly urology, oncology, and general surgery, consulted 456 preoperative patients. The median age of the patients was 49 years; 52.7% were female, and 19.8% were elderly. The prevalence of preoperative hypertension was 33.7%, of which 23.9% was grade 1 hypertension and 9.8% was grade 2 hypertension. Age, body mass index, and neutrophil-to-lymphocyte ratio were associated with hypertension. The multivariate analysis showed that elderly patients had 2.8 times (p<0.001), and overweight patients had 3.3 times (p=0.003) higher risk of preoperative hypertension. Fifty-four of 138 hypertensive patients received treatment (27.5% single agent and 11.6% combination). Antihypertensive agents prescribed were calcium channel blockers (CCB) (60.7%), angiotensin receptor blockers (ARB) (30.9%), beta-blockers (4.8%), and angiotensin-converting enzyme inhibitors (ACEI) (3.6%).

Conclusion: Preoperative hypertension was common and related to old age and overweight. Less than half of hypertensive patients were given antihypertensive therapy, while CCB and ARB were much more prescribed than beta-blockers and ACEI.

Keywords: hypertension, preoperative, prevalence, risk factors, therapy.

INTRODUCTION

Blood pressure measurement in preoperative evaluation is essential because preoperative blood pressure is associated with postoperative mortality.1,2 Preoperative hypertension is associated with perioperative hemodynamic disturbances such as hypotension, tachycardia, and target organ damage.3,4 Mild-to-moderate preoperative hypertension does not appear to be a significant risk factor for complications, according to studies done over the previous 20 years.1,3 While several studies have found a univariate link between elevated blood pressure and perioperative cardiac problems, this link tends to vanish when significant cardiac risk factors such heart failure and prior myocardial infarction are taken into account.5-7

The majority of people having surgery are taking drugs for noncommunicable, chronic conditions. Cardiovascular pharmaceuticals make up 48% of all prescription drugs, the bulk of all medications. The most frequent comorbidity, accounting for up to 27% of delayed procedures, is hypertension. Hypertensive patients frequently develop intraoperative blood pressure (BP) lability, which, in the worst case, might result in myocardial ischemia. Not many studies have reported preoperative hypertension incidence and risk factors. The attitude of clinicians in the preoperative administration of antihypertensive drugs is still controversial. Therefore, this study aims to determine preoperative hypertension prevalence, risk factors, and treatment.

METHODS

This cross-sectional study was conducted at the West Nusa Tenggara General Hospital, from July to September 2021. All medical record data for patients >18 years old who underwent elective surgery were included in the study. Patients with incomplete baseline data were excluded from the study. The blood pressure level was categorized based on the World Health Organization (WHO) guidelines in 2020.8 The frequency distribution of hypertensive and normotensive groups is presented in the table. Bivariate analyses of different proportions were analyzed using the Chi-square or Fisher’s exact test. The difference in numerical variables between the two groups was analyzed using the independent t-test or the Mann-Whitney U test. A multivariate logistic regression analysis was performed to explore the leading risk factors by including all variables with a significance of at least <0.05 in the bivariate analysis. All statistical analysis was done using SPSS program version 25.

RESULTS

Four hundred fifty-six patients underwent surgery and were consulted by 14 different clinics. Forty-six patients with
Table 1. Comparison of preoperative hypertensive and normotensive patient characteristics.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Normotension (272), n (%)</th>
<th>Hypertension (138), n (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elderly (&gt;60 years)</td>
<td>39 (14.3)</td>
<td>42 (30.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male</td>
<td>129 (47.4)</td>
<td>65 (47.1)</td>
<td>1.000</td>
</tr>
<tr>
<td>Female</td>
<td>143 (52.6)</td>
<td>73 (52.9)</td>
<td></td>
</tr>
<tr>
<td><strong>Nutritional status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Underweight (&lt;18.5 kg/m^2)</td>
<td>48 (17.6)</td>
<td>10 (7.2)</td>
<td>0.007</td>
</tr>
<tr>
<td>Normal (18.5-22.9 kg/m^2)</td>
<td>123 (45.2)</td>
<td>61 (44.2)</td>
<td></td>
</tr>
<tr>
<td>Overweight (&gt;23 kg/m^2)</td>
<td>101 (37.1)</td>
<td>67 (48.6)</td>
<td></td>
</tr>
<tr>
<td><strong>Laboratory results</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia (&lt;10 mg/dL)</td>
<td>29 (10.7)</td>
<td>13 (9.4)</td>
<td>0.695</td>
</tr>
<tr>
<td>Leukocytosis (&gt;10,000 /uL)</td>
<td>86 (31.6)</td>
<td>51 (37.0)</td>
<td>0.279</td>
</tr>
<tr>
<td>Thrombocytopenia (&lt;100,000 /uL)</td>
<td>8 (2.9)</td>
<td>2 (1.4)</td>
<td>0.506</td>
</tr>
<tr>
<td>NLR &gt; 6</td>
<td>29 (10.7)</td>
<td>5 (3.6)</td>
<td>0.015</td>
</tr>
<tr>
<td>eGFR (&lt;60 ml/min/1.73 m^2)</td>
<td>34 (13.2)</td>
<td>25 (20.2)</td>
<td>0.077</td>
</tr>
<tr>
<td>Hyperglycemia (&gt;200 mg/dL)</td>
<td>17 (6.5)</td>
<td>9 (6.8)</td>
<td>0.901</td>
</tr>
<tr>
<td>Elevated AST (&gt;100 mg/dL)</td>
<td>5 (1.9)</td>
<td>0 (0.0)</td>
<td>0.178</td>
</tr>
<tr>
<td>Elevated ALT (&gt;100 mg/dL)</td>
<td>6 (2.3)</td>
<td>1 (0.8)</td>
<td>0.435</td>
</tr>
<tr>
<td>Hypernatremia (&gt;145 mmol/L)</td>
<td>6 (2.4)</td>
<td>8 (6.8)</td>
<td>0.075</td>
</tr>
<tr>
<td>Hypokalemia (&lt;3.0 mmol/L)</td>
<td>4 (1.6)</td>
<td>0 (0.0)</td>
<td>0.310</td>
</tr>
<tr>
<td>Hypercholesterolemia (&gt;110 mmol/L)</td>
<td>3 (1.2)</td>
<td>0 (0.0)</td>
<td>0.554</td>
</tr>
</tbody>
</table>

DISCUSSION

A preoperative evaluation may be an entry diagnosis of one previously unknown hypertension. A study in Indonesia found that the prevalence of prehypertension in the population above 40 years was 32.5%. Significant risk factors associated with prehypertension were advanced age, male gender, overweight, obesity, and increased waist circumference. This study found quite similar prevalence and risk factors for hypertension. A study Lydia et al, 2021 showed that the prevalence of hypertension was 23.7%, overweight at 47.5%, and smoking at 25.3%. The use of antihypertensive drugs in this study was low, at 39.1%. Preoperative antihypertensive drugs were not administered unless systolic blood pressure was above 180 mmHg and diastolic blood pressure was above 110 mmHg, according to the Association of Anesthetists of Great Britain and Ireland and the British Hypertension Society (AAGBI and BSH). Therefore, it is common practice in our hospital not to immediately administer antihypertensive drugs during the preoperative evaluation of hypertensive patients with no previous history of hypertension. There are several limitations to this study. Cross-sectional studies could not prove if the risk factors for old age and overweight occurred before hypertension in preoperative patients.

CONCLUSION

The prevalence of preoperative hypertension was 33.7%. Elderly patients had a 2.8 times increased risk, and overweight patients had a 3.3 times risk of developing preoperative hypertension. Future studies regarding the association of preoperative hypertension characteristics with intraoperative, postoperative, and long-term outcomes are essential.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

FUNDING

There was no funding for this study.

ETHICAL CLEARANCE

This study was approved by the research ethics committee of the West Nusa Tenggara General Hospital with certificate number 070.1/36/KEP/2022.

AUTHOR CONTRIBUTION

IGYA was responsible for the study's conception and design, data analysis, manuscript preparation, and review. CB was responsible for manuscript editing and review. IGNOA was responsible for...
study design and statistical analysis. All authors approved the final manuscript.

REFERENCES

The effect of the type of COVID-19 vaccines on the neutralization response

Mutia Lailani1,2*, Linosefa2,3, Andani Eka Putra2,3

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic led to the rapid advancement of various vaccine technologies, such as inactivated vaccines, mRNA vaccines, and virus vector vaccines.1-3 To assess the effectiveness of these vaccines, a crucial factor to consider is their capability to trigger a strong and effective neutralizing immune response, which plays a vital role in providing immunity against the virus.4,5

The electro-chemiluminescence assay (ECLIA) is now an important method for measuring the neutralizing antibodies produced by these vaccines.3,6 The ECLIA’s sensitivity, wide range, and ability to detect multiple types of antibodies make it the ideal tool for analyzing the subtleties of neutralization induced by vaccines.6 This study aimed to compare the differences in neutralization responses due to different types of COVID-19 vaccines in Indonesia, as analyzed using ECLIA.

METHODS

Sample collection and grouping

A neutralization test was done on 1,465 serum samples from a serosurvey collection conducted by the Ministry of Home Affairs and the Ministry of Health in the period of October - November 2021. The samples were divided into four groups: the group with a history of COVID-19 infection without the vaccine, the group with inactivated vaccine, the group with the viral vector vaccine, and the group with the mRNA vaccine. The proportion of samples with negative and positive neutralizing antibodies (NAb) was then compared. A serum neutralization test was performed using an electro-chemiluminescence immunoassay (ECLIA, lifotronic eCL8000 eCLIA system).

Neutralization antibody assessment

Neutralizing antibody evaluation was done using serum samples. ECLIA was used on the lifotronic eCL8000 system to determine the presence of neutralizing antibodies accurately.

Statistical analysis

We conducted a comparison of the proportions of negative and positive neutralizing antibodies (NAb) in different groups using a chi-square for trends test. We considered a p-value of less than 0.05 as significant, indicating a significant difference between the groups.

RESULTS

In our study, it was found that the majority of the participants (72%) had received the inactivated vaccine, followed by the viral vector vaccine (16%), and then the mRNA vaccine (9%). Only a small percentage of participants (3%) did not receive any vaccine (Figure 1).

This study found significant differences in the number of samples with positive neutralizing antibodies (NAb+) or with negative neutralizing antibodies (NAb-) among all vaccination groups, including those without a vaccine, those with an inactivated vaccine, those with a viral vector vaccine, and others (Figure 2). Particularly, the differences were statistically significant (p <0.001).

ABSTRACT

Background: In order to deal with the coronavirus disease 2019 (COVID-19) outbreak in the last 2 years, hundreds of vaccines have been developed. These vaccines use various technologies, such as inactivated vaccines, mRNA, virus vectors, and recombinant proteins. The method of evaluating the effectiveness of the vaccine in vitro can be conducted by the neutralization test. This study aims to compare the effect of the type of vaccine on the neutralization response in post-vaccination serum samples.

Methods: We conducted a neutralization test on 1,465 serum samples from a serosurvey collection conducted by the Ministry of Home Affairs and the Ministry of Health in the period of October - November 2021. The samples were divided into four groups: the group with a history of COVID-19 infection without the vaccine, the group with inactivated vaccine, the group with the viral vector vaccine, and the group with the mRNA vaccine. The proportion of samples with negative and positive neutralizing antibodies (NAb) was then compared. A serum neutralization test was performed using an electro-chemiluminescence immunoassay (ECLIA, lifotronic eCL8000 eCLIA system).

Results: There is a significant difference in the proportion of samples with NAb (-) and NAb (+) between each group (p<0.001). The group with the mRNA vaccine had the highest proportion of NAb (+), namely 92.42%, while the group with the inactivated vaccine had the lowest proportion of NAb (+), namely 83.13%.

Conclusion: The mRNA vaccine showed the highest effectiveness, while the inactivated vaccine showed the lowest effectiveness.

Keywords: COVID-19, neutralization, mRNA vaccines.
After analyzing NAb positivity in different vaccine categories, certain patterns were observed (Figure 2). The group that received the mRNA vaccine had the highest proportion of individuals with NAb, with an impressive prevalence rate of 92.42%. Conversely, the group that had received the inactivated vaccine had the lowest proportion of NAb presence, with a prevalence of 83.13%, which was even lower than the no-vaccine group. These distinctive patterns highlight how different vaccine types can impact the production of neutralizing antibodies.

**DISCUSSION**

We have conducted research to compare the effectiveness of different types of vaccines using the neutralization test. Our study revealed a predominance of inactivated vaccines among participants. This prevalence underscores the accessibility and acceptance of inactivated vaccines, possibly due to their established safety profile and distribution ease.2-3

Furthermore, our study revealed that the mRNA vaccine had the highest efficacy as the vaccine resulted in more positive neutralization antibody rates. Our research supports the consistent discovery of mRNA vaccines’ higher effectiveness when compared to inactivated, viral vector-based, and nanoparticle-based peptide vaccines.2-5 The mRNA vaccines have proven to be effective in controlling COVID-19. They have the distinct advantage of enabling customization of antigen design and the capability to combat new mutations by merging sequences from different virus variants. This innovation is anticipated to transform disease prevention and treatment.7-9

Furthermore, the efficacy and safety of mRNA COVID-19 vaccines have been conducted in susceptible populations, particularly children. COVID-19 vaccines successfully reduced the chances of children aged 5–11 years contracting the virus, falling ill, and being hospitalized.10 The occurrence of side effects was infrequent and brief. These discoveries provide crucial information to doctors, parents, and decision-makers regarding the safety and efficacy of mRNA vaccines.10,11

Nevertheless, our research had limitations as it was a descriptive study and did not investigate all possible factors that could have affected outcomes. It focused solely on individuals of Indonesian heritage, providing insights into this group but may not apply to other populations or situations. Thus, we aspire to further research in order to gain a comprehensive understanding of this particular field.

**CONCLUSION**

mRNA vaccine recipients had the highest NAb presence, while inactivated vaccine recipients had the lowest, even lagging behind the unvaccinated group. Further research is needed to understand the mechanisms behind these differences and their implications for public health strategies.

**CONFLICT OF INTEREST**

None.

**ETHICAL CLEARANCE**

This study has been approved by the Research Ethics Committee, Faculty of Medicine, Universitas Andalas number 463/UN.16.2/KEP-FK/2021.
FUNDING
The research was funded by the Center for Diagnostic and Research on Infectious Diseases, Faculty of Medicine, Universitas Andalas, Padang, Indonesia.

AUTHOR CONTRIBUTION
Mutia Lailani: conceptualization, data collection, data curation, methodology, formal analysis, writing the original manuscript. Linosefa: conceptualization, data analysis, statistical reviews, writing the original manuscript. Andani Eka Putra: supervision, conceptualization, data resources, methodology, writing review, validation. All authors have read and approved the manuscript.

REFERENCES
The relationship between haze and increased pneumonia at Mandau District Hospital in Sumatra 2015-2016

Rayhana*, Hanifah Amalia1

INTRODUCTION

Forest and land fires are not a new phenomenon in several regions in Indonesia. In the last 23 years forest and land fires have occurred every year in Sumatra and Kalimantan.1-5 The National Disaster Management Agency stated that the increase in particulate matter (PM$_{2.5}$) particulate pollution as of September 18, 2020 in Riau Province reached 301 ug/m$^3$ with 388 hotspots. This situation creates dense smog that reduces a person’s visibility when walking or driving.2-7 The 2018 Basic Health Research found that the national prevalence of pneumonia was 4.5%. This prevalence has increased when compared to the prevalence in 2013.8-10

In the prevalence of pneumonia, Riau province has a prevalence of 3.0%. In general, the most categories of pneumonia sufferers in Riau province are geriatrics and toddlers with the most age category of sufferers in toddlers being 1-4 years.4,11 Pneumonia kills at least more than 800,000 children under five every year and this number exceeds the number of deaths from other infectious diseases.9,11 Globally, there are more than 1,400 cases of pneumonia per 100,000 children, or 1 case per 71 children each year, with the largest incidents occurring in South Asia (2,500 cases per 100,000 children) and West and Central Africa (1,620 cases per 100,000 children).9-11 Therefore, this study aims to know the relationship between haze and pneumonia cases in Mandau District Hospital.

METHODS

This study used cross-sectional design which data collection was carried out in the period 2015–2016, using secondary data on admission to hospitalization of toddler patients due to Pneumonia in the period 2015–2016 by collecting sample data on the air pollution standard index (APSI) of Mandau District, carried out by accessing publication data. Spearman Correlation non-parametric was tested to determine the relationship between pediatric patients treated for pneumonia and haze.

RESULTS

Spearman’s correlation analysis of the relationship between the haze disaster and the increase in the number of hospitalizations for toddlers due to pneumonia at the Mandau District Hospital in 2015 – 2016 showed that the correlation value (-0.206) is at the degree of weak correlation with the direction of a negative relationship, as well as a significance value (0.334) which is greater than the specified significance value of 0.05, the correlation analysis is considered to have a weak correlation.

DISCUSSION

The results in Table 1 are in accordance with study which are similar to the results research conducted by Imran in Bangladesh in 2018, namely toddlers aged 12-23 months and toddlers aged 24-35 months have a 2.03 and 1.67 times higher probability of experiencing infection acute respiratory tract infection.8,9 Figure
shows a difference in the results of a study conducted by Ming in 2018 in Kuala Lumpur, Malaysia, that the number of hospital admissions with problems in the respiratory system in 2014-2015 increased in the July-October period (smog disaster incidents) and decreased in July-October. November – December each year with a prevalence of 37%. In Figure 2, the highest APSI results occurred in September 2015 - October 2015 of 306 and 281. In August 2016 and October 2016 APSI were 109 and 105. These results are in accordance with research that showed during the period August - November 2015 many areas in Indonesia, especially in Kalimantan and Sumatra, were again covered by thick smoke. One example is in the province of Central Kalimantan, the APSI of fine PM$_{2.5}$ has been reported to exceed 1500 (PM$_{2.5}$ > 1250 µg/m$^3$) far above the level of short-term exposure and is considered hazardous to health humans (PSI > 300, PM$_{2.5}$ > 250µg/m$^3$).

In the analysis of the increase in the number of inpatients under five due to pneumonia, it correlates weakly with the incidence of the haze disaster using the Spearman’s correlation that the correlation value (Spearman’s correlation = -0.206) is at the degree of a weak correlation with a negative relationship, as well as a significance value (0.334) which is higher greater than the specified significance value is 0.05. This is similar to research during the haze event period, an increase in particulate pollution was not associated with hospital admissions due to respiratory problems at all ages. However, different results the 2015 haze disaster period, the weekly frequency of several admissions due to respiratory problems correlated significantly, although daily admissions were found to be weakly correlated with the average per day (r = 0.35, p < 0.001).

CONCLUSION
Haze management is a serious problem, especially in Sumatra because it has an impact on health, especially the lung health of children under five.

CONFLICT OF INTEREST
All authors declare there is no conflict of interest regarding publication of this report.

FUNDING
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AUTHOR CONTRIBUTION
All authors had contributed in manuscript writing and agreed for the final version of the manuscript for publication.

REFERENCES
Role of nutritional status in multidrug-resistant tuberculosis in Indonesia: a systematic review

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ABSTRACT

Background: Tuberculosis (TB) remains a significant public health challenge in Indonesia, with high TB incidence, prevalence, and mortality rates. In recent years, there has been increasing evidence suggesting a potential relationship between the nutritional status of individuals and the development of multidrug resistance (MDR) in TB. This review aimed to elucidate the role of nutritional status in MDR-TB.

Methods: We conducted a systematic review according to Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) protocols. The literature was searched using keywords in Pubmed, Science Direct Scopus, and Google Scholar databases.

Results: We critically reviewed 150 articles and selected 17 studies that met the inclusion criteria. The data analysis found that 58% of patients had poor nutritional status, 36% were normal, and 7% were overweight and obese.

Conclusion: It can be concluded that malnutrition plays a role in the occurrence of MDR-TB through various mechanisms. Improving nutritional status is an absolute thing that must be done to suppress the occurrence of TB, especially MDR-TB.

Keywords: multidrug-resistant tuberculosis, nutritional status, underweight.

INTRODUCTION

One of the most pressing and challenging issues facing global TB control is the ongoing spread of drug-resistant tuberculosis (TB).1,5 Patients with multidrug-resistant (MDR) TB, or forms of the disease resistant to isoniazid and rifampicin, are essentially incurable by first-line conventional therapy. MDR-TB caused around 450,000 new cases and 170,000 deaths in 2012. TB remains a significant public health challenge in Indonesia, with high TB incidence, prevalence, and mortality rates.6,7 Several risk factors contribute to the development and spread of MDR-TB, including nutritional status such as malnutrition. Malnutrition has been identified as a risk factor for TB, and nutritional status has a role in the modulation of immunological responses to infections.8-12 The TB-causing agent, Mycobacterium tuberculosis (Mtb), can alter the host’s lipid metabolism and cause lipid buildup in macrophages, where the bacilli take on a dormant state.16-19 In recent years, there has been increasing evidence suggesting a potential relationship between the nutritional status of individuals and the development of multidrug resistance (MDR) in TB.11,15,16 This review aimed to elucidate the role of nutritional status in MDR-TB.

METHODS

We conducted a systematic review according to Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) protocols. The literature was searched using keywords in Pubmed, Science Direct Scopus, and Google Scholar databases. The keywords used were “multidrug-resistant tuberculosis” OR “MDR-TB” AND “nutritional status” OR “underweight.” We critically reviewed 150 articles and selected 17 studies that met the inclusion criteria (2-19).

RESULTS

From the 17 publications analyzed, 1793 patients with MDR-TB were found. More than half of the patients were male (56.3%). Then, data on nutritional status were collected, and it was found that the majority of MDR-TB sufferers in Indonesia were underweight 1053 persons (58.73%) followed by normal-weight 652 persons (36.36%). Only 122 persons (9.25%) were overweight or obese. Table 1 shows that most MDR-TB patients have an underweight nutritional status.

DISCUSSION

From the results of this systematic review, it was found that most MDR-TB sufferers in Indonesia are underweight. These results are evenly distributed for almost all regions in Indonesia. The results of

Table 1. Overview of nutritional status in MDR TB patients in Indonesia

<table>
<thead>
<tr>
<th>Nutritional status</th>
<th>MDR-TB</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>1053</td>
<td>58.73</td>
</tr>
<tr>
<td>Normal</td>
<td>652</td>
<td>36.36</td>
</tr>
<tr>
<td>Overweight/obesity</td>
<td>122</td>
<td>9.25</td>
</tr>
</tbody>
</table>
Malnourished people have weakened immune systems, which makes it harder for them to manage and get rid of the TB germs. Due to the body’s inability to properly combat the infection, immunological dysfunction raises the chance of treatment failure. Malnutrition can also interfere with the metabolism and absorption of anti-TB medications. Gastrointestinal problems and improper medicine absorption might result from nutritional deficits. Because of this, the concentration of anti-TB medications in the body may not be optimal, resulting in insufficient drug exposure and possibly promoting the emergence of drug resistance.

On the other hand, insufficient and inconsistent drug intake might result in inadequate drug levels in the body, raising the risk of treatment failure and establishing drug-resistant TB strains. It is common for malnutrition to cause general weakness and physical fragility. Treatment for TB is difficult, necessitating prolonged medicine intake and possibly producing negative effects. Malnourished people may have less physical stamina and strength, making it harder to tolerate and follow the demanding treatment plan. Further treatment failure and the emergence of drug resistance may result from this.

The severity of MDR-TB may be exacerbated by malnutrition. It can result in co-morbidities and complications, making controlling the condition more challenging. Malnourished people are more likely to experience respiratory conditions, anemia, and other health concerns that might make managing MDR-TB more challenging. Malnourished Patients with MDR-TB are more likely to experience major side effects and may have trouble managing the infection and drug side effects due to their weaker immune systems. In those with MDR-TB, it increases the chance of death.

Thus, malnutrition has a reciprocal effect on the treatment of MDR-TB.
A five-year retrospective study of ESBL-producing Escherichia coli: prevalence and antibiotic susceptibility pattern

Gajah Nauli Dalimunthe1, Dimas Seto Prasetyo2, Rika Febriana Pinem1, Suratno Lulut Ratnoglik3, Delly Chipta Lestari2*

INTRODUCTION

Escherichia coli, a versatile Gram-negative bacterium from the Enterobacteriaceae family, is an essential member of the normal intestinal flora but can also cause infection in humans. E. coli can evade the host immune system and develop resistance to antibiotics. Multidrug-resistant (MDR) E. coli is becoming a serious threat to public health worldwide due to the inappropriate use of antibiotics, especially third-generation cephalosporins. E. coli is intrinsically sensitive to almost all clinically relevant antimicrobial agents. This study aims to describe prevalence and antibiotic susceptibility patterns of extended-spectrum β-lactamases (ESBL)-producing E. coli during five years.

METHODS

This cross-sectional retrospective study uses secondary data from clinical specimens examined at the Clinical Microbiology Laboratory, Faculty of Medicine, Universitas Indonesia during 2017–2021 to determine the prevalence and susceptibility of antibiotics to E. coli, particularly ESBL-producing.

RESULTS

We found that 28.4% of the 800 E. coli isolates were ESBL-producing. In addition to a decrease in susceptibility to cefepime, there is a decrease in susceptibility to other antimicrobials classes, even up to <50%, including ampicillin, ampicillin-sulbactam, ciprofloxacin, trimethoprim/sulfamethoxazole, tetracycline, and tobramycin.

Conclusion: These data indicate the need to manage the use of antibiotics to control the spread of resistant bacteria in society, particularly ESBL-producing E. coli.

Keywords: antibiotic resistance, ESBL, Escherichia coli, MDR.

METHODS

This study employed a cross-sectional study design and used secondary data from the Clinical Microbiology Laboratory, Faculty of Medicine, Universitas Indonesia for five years, from 2017 to 2021, extracted using WHONET 2022 software, and then analyzed descriptively using the spreadsheet software to calculate the percentage and create graphs. Only clinical specimens were included in the analysis, while screening and environment samples were excluded. Because the identification and antimicrobial susceptibility test (AST) being used is an automated system, VITEK® 2 (bioMérieux), a positive ESBL is defined according to the results issued by the system.

RESULTS

Eight hundred E. coli isolates were identified within five years. Of these, 228 isolates (28.4%) were ESBL-positive. (Figure 1)
Subsequently, we stratified the ESBL producer by the type of specimens and revealed that the most common was urine, which was detected in over 50%, followed by tissue, pus, and blood (Figure 2). Several specimens counted only one or two within five years, including cerebrospinal fluid, broncho-alveolar lavage fluid, wound, et cetera; hence, they were grouped as others (Figure 2). Regarding the antibiotic susceptibility results, we found that isolates of *E. coli* that produce ESBL remained susceptible to carbapenem, amikacin, tigecycline, piperacillin/ tazobactam, and nitrofurantoin. However, other antibiotics showed high resistance (Table 1).

**DISCUSSION**

The study found the prevalence of ESBL-producing *E. coli* within five years on average to be 28.4%, with the highest annual prevalence in 2020 at 42.1%. This result was slightly higher than a meta-analysis reported in 2022. However, the prevalence was relatively low compared to an Ethiopian study published in 2020. From 5 years of observation, the prevalence of ESBL producers fluctuates. There is no definite reason why this could happen. However, what is certain is that ESBL producers never really disappear and still circulate in the community.

We must continue to increase our awareness since ESBL-producing *E. coli* was also reported with high prevalence in the food chain and the environment by the Tricycle Project, a collaborative effort between the Ministry of Health and the Ministry of Agriculture in Indonesia. Based on the specimen type, we revealed that urine was the most frequently found ESBL-producing *E. coli* detected in over 50% of cases. Other specimens were tissue, pus, and blood. Meanwhile, it is relatively low in sputum. These common sample types are consistent with similar studies done elsewhere. Some antibiotics showed high sensitivity, especially among carbapenem, tigecycline, and amikacin, while others showed high resistance levels. We assumed that was a good sign of antibiotic stewardship implementation in the clinical setting, specifically among hospitals or clinics in Jakarta and surrounding areas reflected by specimens that have been examined.

**CONCLUSION**

ESBL-producing *E. coli* prevalence varies yearly as these resistant bacteria are always present and distributed in the clinical setting and the environment, requiring proper antibiotic management and infection control.

**CONFLICT OF INTEREST**

The authors have no conflicts of interest to declare.

**FUNDING**

The authors are accountable for covering all financial aspects independently, without support from grants or external funding.

**ETHICAL CLEARANCE**

This study has been approved by The Ethics Committee of the Faculty of Medicine, Universitas Indonesia – Cipto

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**Table 1. Antimicrobial susceptibility of ESBL-producing *E. coli* isolates**

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>% Susceptible*</th>
<th>Antibiotics</th>
<th>% Susceptible*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin (AMP)</td>
<td>0</td>
<td>Ertapenem (ETP)</td>
<td>99.6</td>
</tr>
<tr>
<td>Ampicillin-sulbactam (SAM)</td>
<td>32.8</td>
<td>Meropenem (MEM)</td>
<td>99.6</td>
</tr>
<tr>
<td>Piperacillin/tazobactam (TZP)</td>
<td>85.6</td>
<td>Amikacin (AMK)</td>
<td>98.7</td>
</tr>
<tr>
<td>Cefazolin (CZO)</td>
<td>0</td>
<td>Gentamicin (GEN)</td>
<td>56.8</td>
</tr>
<tr>
<td>Cefazidime (CAZ)</td>
<td>39.7</td>
<td>Ciprofloxacin (CIP)</td>
<td>30.1</td>
</tr>
<tr>
<td>Ceftriaxone (CRO)</td>
<td>0.9</td>
<td>Tigecycline (TGC)</td>
<td>98.7</td>
</tr>
<tr>
<td>Ceftepime (FEP)</td>
<td>65.9</td>
<td>Sulfamethoxazole-trimethoprim (SXT)</td>
<td>32.3</td>
</tr>
<tr>
<td>Aztreonam (ATM)</td>
<td>14.8</td>
<td>Nitrofurantoin (NIT)</td>
<td>83.8</td>
</tr>
</tbody>
</table>

*The number of isolates tested for all respective antibiotics above was the same, i.e., 228
Mangunkusumo Hospital (No. KET-287/UN2.F1/ETIK/PPM.00.02/2023).

AUTHOR CONTRIBUTION
DCL contributed to the study concept and design, supervised data analysis, and edited the final manuscript. DSP performed an initial analysis of the WHONET data. GND performed advanced data analysis. GND and RFP wrote the initial draft of the manuscript. SRL gave valuable input to the manuscript. All authors read, reviewed, and approved the final article.

REFERENCES
**ABSTRACT**

**Background:** Acute and chronic otitis media were correlated with acute respiratory tract infection. If there was a perforation, the discharge came out to the outer ear and could be collected as a sample for coronavirus disease (COVID-19) testing. The aim of this study is to identify the COVID-19 antigen in the purulent discharge of patients with acute and chronic suppurative otitis media.

**Methods:** This study used cross-sectional design in Universitas Mataram Hospital and Medismart Clinic from October 1\(^{st}\) until December 31\(^{st}\), 2021; whereas the rapid antigen tests were done on middle ear discharge to detect the presence of COVID-19.

**Results:** There were 47 subjects included in this study, 36.7% were acute otitis media and the rest of them were chronic. All subjects in this study are negative for COVID-19 antigen. Otitis media is one of the most common infectious diseases in the ear, and is associated with significant medical resource use, medical visits, and antibiotic prescriptions. Since upper respiratory tract infections spread mostly throughout the ear canal to induce OM, OM will likewise become less common if the frequency of upper respiratory tract infections falls including the COVID-19 that enters through the upper respiratory tract.

**Conclusion:** COVID-19 antigen is not found in the purulent discharge of patients with acute and chronic suppurative media.

**Keywords:** COVID-19, middle ear discharge, rapid antigen test.

**INTRODUCTION**

Acute and chronic suppurative otitis media (AOM and CSOM) are common diseases in developing countries.\(^{1,5}\) It is usually altered by the acute respiratory tract infection (ARTI) through eustachian tubes. In the pandemic of coronavirus disease (COVID-19) era, ARTI may also be caused by this viral infection. Furthermore, the microbiota of the upper respiratory tract (URT) plays a significant role in respiratory health.\(^{6,8}\) The URT microbiome can affect the viral load, acute immune response, and host gene expression patterns linked to common respiratory viruses, as well as the short- and long-term clinical outcomes of these viruses (including acute disease severity).\(^9\)

The complicated viral and inflammatory diseases known as otitis media (OM) affect the middle ear. Different subtypes of OM present differently and respond differently to treatment. Acute otitis media (AOM), chronic suppurative otitis media (CSOM), and otitis media with effusion (OME) are only a few of the disorders that represents OM.\(^{10,11}\) Since upper respiratory tract infections spread mostly throughout the ear canal to induce OM, OM will likewise become less common if the frequency of upper respiratory tract infections falls.\(^{5,7}\) It presumably that COVID-19 viral antigen could be found in the purulent discharge of patient with acute and chronic otitis media. The study aims to prove whether the covid-19 antigen is found or not in middle ear discharge that is collected from patients with acute and chronic suppurative otitis media.

**METHODS**

This study was conducted in Universitas Mataram Hospital and Medismart Clinic from October 1\(^{st}\) until December 31\(^{st}\), 2021. The subjects were patients with acute or chronic otitis media that sign with the presence of eardrum perforation and mucopurulent discharge that analysed descriptively. The secret was collected with the sterile applicator then proceeded further with Entram rapid antigen kit\(^{15}\). The rapid antigen testing was done by following the manual instruction. After 5 minutes, the result can be read in the cassette. Positive if there were 2 red lines and negative if only 1 red line found in the cassette.

**RESULTS**

During the study periods, there were 47 subjects included in the study, 17 (36.7%) with acute otitis media and the rest were chronic otitis media. The average age of the subjects was 30.9 years old with the younger age was 2 years old while the oldest was 70 years old (Figure 1). Male and female ratio was 60:40 (Figure 2). In AOM, most of the subjects were documented triggered by ARTI (65%) while in CSOM only 37% (Figure 3).

According to 47 subjects, all samples found negative Covid-19 antigen. In this study, authors did not perform the comparison with the nasal or nasopharyngeal swab antigen testing.

**DISCUSSION**

In the middle ear, there is the angiotensin converting enzyme-2 (ACE-2) and transmembrane protease, serine 2 (TMPRSS2) receptor that known as a
In this study, antigen COVID-19 was not found in all subjects. The gold standard for diagnosing the COVID-19 was RT-PCR. The specificity and sensitivity of rapid antigen was lower than RT-PCR test. Furthermore, a previous report found that there was a decreased positivity rate of COVID-19 in the middle ear when compared with nasopharyngeal RT-PCR. Therefore, this result was logic. Although the result was negative, this finding is very important for the future strategy on detecting Covid-19 antigen from other body fluid sources. The simpler way to detect the Covid-19 compartment is still needed, not only for this pandemic but also for the future or another new emerging disease.

The limitation of this study including the middle ear antigen testing was not compared with the nasopharyngeal source and the use of the non-gold standard methods. Therefore, a future study should be conducted to make sure of this result with the gold standard testing and comparison with nasopharyngeal swabs.

CONCLUSION

There is no COVID-19 antigen identified in the purulent discharge of patients with acute and chronic suppurative otitis media. The use of rapid antigen was not suitable for detecting the presence of COVID-19 in an ear discharge. However, further research should be done to clarify this result.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

FUNDING

None.

ETHICAL CLEARANCE

This study was granted ethical clearance from the Ethical Committee, Faculty of Medicine, Universitas Mataram number 060/UN18.F7/ETIK/2021.
AUTHOR CONTRIBUTION
All authors equally contributed to this study.

REFERENCES
Leadership competency of hospital managerial: a literature review

Metta Octora1,2*, Ratri Wahyuningtyas3

INTRODUCTION

Hospital managerial is a business reality that has demand for human resources possessing exceptional service capabilities and a customer-centric approach aligned with the hospital’s vision and mission. The concept of customer value is of significant importance in the field of business and marketing.1 The hospital, as a service-oriented enterprise, heavily relies on the establishment of customer trust in the respective healthcare institution. The hospital industry places significant emphasis on values pertaining to customer satisfaction as its fundamental foundation. Consequently, it is imperative for the hospital to possess leaders who exhibit exceptional quality and reliability. It is imperative for hospitals to prioritise the enhancement of human resources, encompassing both leadership and subordinate roles, in order to enhance overall quality.2

The issue of incompetent hospital managers is a widespread global concern that can have detrimental effects on programme outcomes, quality health service and patient safety.3 Hospital managers play a crucial role in ensuring the successful implementation of an organization’s objectives, mission, and vision. The effective delivery of healthcare requires the acquisition of specific managerial competencies in health management. It is imperative to acknowledge that researchers in both developed and developing nations employ the managerial competencies concept as a means to enhance the efficiency and effectiveness of service delivery.4 Therefore this study aims to comprehend the leadership competency of hospital managerial.

MANAGERIAL COMPETENCY

The individuals occupying managerial positions within the upper echelons of an organisation are commonly referred to as top management. This group typically consists of directors and members of the board of commissioners. At this stage, managers necessitate a greater depth of knowledge and proficiency in cognitive abilities as opposed to technical skills.1-3 This is due to the necessity for top-level managers to possess the ability to engage in imaginative thinking and generate diverse ideas in order to adapt to contemporary circumstances. The acquisition of desired outcomes through effective management of personnel within an organisation is a crucial competency for a high-level executive.5

There exist five distinct approaches for the examination of leadership, namely the characteristic approach, the behavioural approach, the power-influence approach, the situational approach, and the integrated approach. The trait approach places significant emphasis on leader traits, encompassing aspects such as personality, motivation, values, and skills.5 The distinguishing features of a leader are those that set them apart from their followers. The various leadership characteristics, including self-confidence, ambition, enthusiasm, and intelligence. The behavioural approach focuses on the identification and analysis of effective leadership behaviours.6,7

Competency refers to a set of essential attributes possessed by an individual that directly impact their job performance or effectiveness in the workplace.9 There are five distinct categories of traits encompass both physical and mental characteristics, such as good eyesight and emotional regulation; self-concept

Keywords: competency, hospital, leadership, managerial.
encompasses one’s attitude, values, and self-image; knowledge that correlated to the information and understanding one possesses, while skills refer to one’s expertise in a particular area. Among the five attributes, knowledge and skills are competencies that possess observable manifestations. Self-concept, traits, and motives are latent competencies that have a greater propensity to shape an individual’s personality. The acquisition and enhancement of knowledge and skills are comparatively more straightforward, whereas the evaluation and cultivation of motives and traits, which form the foundational aspects of a person’s personality, are more difficult.

Competency motives, traits, and self-concept possess the ability to forecast an individual’s proficient behaviours, thereby enabling the prediction of their performance. There are total of 20 competencies, some of those as outlined below: (1) the individual’s propensity for achievement-oriented tasks, their emphasis on maintaining order, ensuring quality, and attaining accuracy, their willingness to take initiative, and their inclination to actively seek out information; (2) The ability to provide assistance and support in the field of human services, coupled with a strong aptitude for interpersonal understanding and a customer-centric approach; (3) the cluster of impact and influence encompasses various competencies, including impact and influence skills, organisational awareness, and relationship building abilities; (4) managerial skills encompass the ability to cultivate the growth and development of individuals, exercise directive decision-making, foster collaboration and teamwork, and demonstrate effective leadership within a team setting; (5) cognitive, with analytical thinking competency; conceptual thinking; technical/professional/managerial expertise; (6) personal effectiveness, with self-control competence; self-confidence; flexibility, organizational commitment.

The various positions of competency in HR management that can employ specific competency models across different positions at all organisational levels to effectively perform various functions such as recruitment, selection, placement, performance management, training and development, and compensation determination. From an organisational perspective, the inclusion of competency information is integral to an HR management strategy, enabling management to ensure the accuracy and reliability of the information pertaining to the skills and capabilities of its workforce.

**LEADERSHIP COMPETENCY**

The National Centre for Healthcare Leadership (NCHL) stated leadership competency is described as the combination of technical and behavioural attributes that leaders need to possess in order to achieve success in leadership roles within the health professions. It has formulated a comprehensive leadership competency model with the objective of enhancing the overall well-being of individuals within a nation by fostering effective leadership within the healthcare
sector. This competency model comprises a total of 26 competencies that are categorised into three primary sections. They are as follows: (1) transformation, which involves the observation, promotion, and facilitation of a transformative process that integrates the community, patients, and healthcare professionals within a novel framework of healthcare services. The competencies consist of achievement orientation, analytical thinking, community orientation, financial skills, information seeking, innovative thinking, strategic orientation; (2) execution translates company's vision and strategy into the most effective and efficient organisational performance. The competencies consist of accountability, change leadership, collaboration, communication skills, impact and influence, information technology management, initiative, organizational awareness, performance measurement, management/organizational design, project management; (3) people: establishing an organisational climate that fosters inclusivity and acknowledges the diverse backgrounds of employees, while cultivating a positive working environment (Figure 4).

The core competencies consist of eight key elements. (1) Adaptability/flexibility refer to the ability to maintain work effectiveness in the face of significant changes in tasks or the work environment. (2) Continuous learning: engaging in proactive identification of novel domains for knowledge acquisition. (3) Solution development: the process of formulating solutions by integrating analysis, wisdom, experience, and careful examination of prevailing issues. (4) Persuasiveness: suitable interpersonal styles and communication methods to garner support or acceptance for a product, service, or idea (5) Initiating action: promptly and accurately action to solve problem; over target style, proactive (6) Organisational: the purpose of the unit aligns with the larger organisation mission. (7) Service orientation and customer focus the needs of both external and internal customers is priority, sustaining positive relationships with customers. (8) value diversity involves the ability to collaborate effectively with individuals who possess different work styles, abilities, and motivations.

There are three primary components: personal character, social character, and organisational character (Table 1). The concept of leadership character encompasses a set of values, traits, and a clear sense of purpose that collectively shape an individual's aspirations and identity as a leader.

**CONCLUSION**

The process of acquiring and developing a competent leader can be achieved through two primary methods, specifically: (1) selection can identify the most suitable candidate for a leadership role to conduct an assessment or evaluation. It was used to identify potential leadership qualities; (2) training plays a crucial role in modifying an individual's behaviour to align with desired expectations.

**CONFLICT OF INTEREST**

The authors affirmed that there were no conflicts of interest in this study.

**FUNDING**

The authors were responsible for all research funding without obtaining financial support.

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**Table 1. Principal components of leadership character**

<table>
<thead>
<tr>
<th>Personal Character</th>
<th>Social Character</th>
<th>Organizational Character</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staying steadfast and</td>
<td>Showing others respect, being</td>
<td>Willingness to put organization and customer</td>
</tr>
<tr>
<td>decisive in the face of adversity</td>
<td>com-passionate, and valuing individual</td>
<td>needs ahead of personal needs</td>
</tr>
<tr>
<td>Risk-Taking</td>
<td>differences</td>
<td>Ethical</td>
</tr>
<tr>
<td>Initiative</td>
<td>Integrity</td>
<td>Customer Focus</td>
</tr>
<tr>
<td>Drive</td>
<td>Compassity</td>
<td>Leadership Courage</td>
</tr>
<tr>
<td>Sense of Urgency</td>
<td>Propriety</td>
<td>Organizational</td>
</tr>
<tr>
<td>Tenacity</td>
<td>Values Diversity</td>
<td>Commitment</td>
</tr>
<tr>
<td>Resilience</td>
<td>Cooperative</td>
<td></td>
</tr>
<tr>
<td>Flexibility</td>
<td>Accessible</td>
<td></td>
</tr>
<tr>
<td>Stress Management</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

**Figure 4.** NCHL Health Leadership Competency Model.
ETHICAL STATEMENT
This review article has followed the International Committee of Medical Journal Editors (ICMJE).

AUTHOR CONTRIBUTION
All authors contributed equally in this research and publication of this manuscript.

REFERENCES
ABSTRACT

Background: Methicillin Resistant Staphylococcus aureus (MRSA) is a pathogenic bacterium that causes infections in all parts of the body as reported worldwide. Individual management of carriers and patients infected with MRSA includes nasal decolonization using 2% mupirocin ointment. Extensive use of mupirocin may increase the risk of mupirocin resistance. The ability to form biofilm would increase antibiotic resistance in MRSA. This research was conducted to observe the mupirocin resistance, antibiotic sensitivity patterns and biofilm producer of MRSA isolates obtained from Dr. Moewardi General Hospital (RSDM) Surakarta.

Methods: This research is a descriptive study with a cross-sectional analytic approach using MRSA isolates from the Clinical Microbiology Laboratory of RSDM Surakarta. The samples we used were all MRSA isolates from the Clinical Microbiology Laboratory of RSDM Surakarta collected from May - October 2022. Mupirocin sensitivity test using the Kirby Bauer diffusion method. The ability to form biofilms using a microtiter plate assay, and the pattern of antibiotic sensitivity in MRSA using the results of the antibiotic sensitivity test from Vitek2.

Results: Sixty-four MRSA isolates were obtained from various clinical specimens based on the cefoxitin screen using Vitek2. There are 5 MRSA isolates that show high mupirocin resistance. The ability to form biofilms in MRSA isolates was found 40.6% weak, 21.9% moderate, and 37.5% negative biofilm. All MRSA isolates were resistant to benzylpenicillin and sensitive to tigecycline. Most of the MRSA isolates were resistant to ciprofloxacin and levofloxacin (70.3% and 68.7%), as well as gentamicin, erythromycin and tetracycline (64.1%; 59.4%; and 56.3%).

Conclusion: We should pay attention to the evidence of high-level mupirocin resistant, MDR and biofilm producers from MRSA isolates in this study. A comprehensive implementation of infection control and antimicrobial stewardship programs would be useful to manage MRSA infection.

Keywords: antibiotic sensitivity, MRSA, mupirocin, biofilm.

INTRODUCTION

Staphylococcus aureus (S. aureus) is pathogenic bacteria that causes infections in all parts of the body as reported worldwide. Widespread use of beta-lactam antibiotics has led to the emergence of beta-lactam antibiotic resistant bacteria called methicillin resistant S. aureus (MRSA). MRSA infections still remain challenging, because of limited therapy and high cost for prolonged treatment. Surveillance by SINAR in 2021 found that MRSA infection distribution among 51 hospitals in Indonesia are 38% at type A hospital and 40% at type B hospital. This data showed that the incidence of MRSA are remind high in Indonesia.

MRSA can colonize some parts of the human body as anterior nares, axilla, perineum and inguinal. Some studies said that MRSA carrier incidence are around 5.8% - 17.8%. Treatment for patient with MRSA infection as well as carrier are decolonization used 4% chlorhexidine for bathing and 2% mupirocin ointment for nasal decolonization. Mupirocin is also used as a drug of choice for skin and soft tissue infection caused by Staphylococcus spp and Streptococcus spp. The wide used of mupirocin cause resistance among MRSA as reported before.

Biofilm formation in bacteria will lead to antibiotic resistance. S. aureus (MRSA) is known as a biofilm producer in biotic and abiotic surfaces. Biofilm formation will inhibit antibiotic penetration and then increase the risk of antibiotic resistance. Study about mupirocin resistance, biofilm producer and antibiotic resistance pattern have not yet been conducted in Indonesia, especially at Dr. Moewardi general hospital. The aims of study are conducted to look at mupirocin resistance, antibiotic sensitivity patterns and biofilm production in MRSA isolates at Dr. Moewardi general hospital Surakarta.

METHODS

This research is a descriptive study with a cross-sectional analytic approach using MRSA isolates from various clinical specimens from the Clinical Microbiology Laboratory at RSDM Surakarta during May - October 2022. MRSA identifications were based on the cefoxitin screen from Vitek2. Mupirocin sensitivity test are using Kirby Bauer diffusion method with Muller Hinton agar, using mupirocin disk 5 µg for low level mupirocin resistance identification and 200 µg for high level mupirocin resistance, based on CLSI and some study before.
Biofilm producers among MRSA isolates use microtiter plate assay with *S. epidermidis* ATCC 12228 as negative control. The interpretation for capability of biofilm producers refers to Stepanovic criteria.13–15 MRSA biofilm formation 3D image use scanning electron microscope (SEM). Antibiotic sensitivity test for MRSA isolates data use antibiotic sensitivity results from Vitek2. Statistical analysis in this study uses fisher exact test.

### RESULTS

We obtained 64 MRSA isolates from various clinical specimens: 37 isolates from pus, 18 isolates from blood and 9 isolates from sputum, respectively. From 64 MRSA isolates, we find that 7.8% (5 isolates) are high level mupirocin resistance (3 from isolates from pus and 1 from sputum and blood specimens, respectively). Forty MRSA isolates (62.5%) are biofilm producers, where 14 (40.6%) isolates are moderate biofilm and 26 (21.9%) isolates are weak biofilm. Among mupirocin resistant MRSA isolates, we find that all MRSA isolates are resistant to benzylpenicillin and sensitive to vancomycin, linezolid, quinupristin-dalfopristin and tigecycline. More than half MRSA isolates are sensitive to clindamycin, trimethoprim-sulfamethoxazole, and rifampicin. MRSA isolates mostly resistant to ciprofloxacin, levofloxacin, gentamicin, erythromycin and tetracycline. From MRSA isolates with biofilm producer (moderate and weak biofilm), we find that mostly isolates resistant to ciprofloxacin (73.1% and 71.4%), levofloxacin (73.1% and 71.4%), and gentamicin (65.4% and 78.6%). Erythromycin resistance is mostly found in weak biofilm producer MRSA isolates (84.6%) and tetracycline resistance is also high in moderate biofilm MRSA isolates (78.6%). The result of the antibiotic sensitivity pattern is as seen in figure 2 above.

### DISCUSSION

We find 5 MRSA isolates that have high level mupirocin resistance. Most isolates that demonstrate high-level mupirocin resistance have been reported to carry acquired plasmid-mediated *mupA*, which encodes a novel isoleucyl tRNA synthetase. Mupirocin mechanism of action is by binding with bacterial isoleucyl tRNA synthetase and inhibit protein forming of bacteria. The change of the enzyme will make mupirocin binding isoleucyl tRNA synthetase fail and then bacterial protein synthetase still occurred.6,16,17 Since mupirocin still remain as topical

### Table 1. The results of biofilm producer from mupirocin sensitive and resistant MRSA isolates

<table>
<thead>
<tr>
<th>Specimen</th>
<th>Mupirocin sensitive (n: 59)</th>
<th>Mupirocin resistant (n: 5)</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Biofilm (+) (%)</strong></td>
<td><strong>Biofilm (-) (%)</strong></td>
<td><strong>Biofilm (+) (%)</strong></td>
</tr>
<tr>
<td>Pus (n:37)</td>
<td>22 (59.5)</td>
<td>12 (32.4)</td>
<td>3 (8.1)</td>
</tr>
<tr>
<td>Blood (n:18)</td>
<td>7 (38.9)</td>
<td>10 (55.6)</td>
<td>0</td>
</tr>
<tr>
<td>Sputum (n: 9)</td>
<td>7 (77.8)</td>
<td>1 (11.1)</td>
<td>1 (11.1)</td>
</tr>
<tr>
<td>Total</td>
<td>36 (61)</td>
<td>23 (39)</td>
<td>4 (80)</td>
</tr>
</tbody>
</table>

*: significant level p < 0.05
antibiotic for nasal decolonization in MRSA, this is only one step of MRSA eradication, so all steps of MRSA eradication must be comprehensive and mupirocin decolonization should be based on microbiological culture to prevent this antibiotic resistance. Almost half of MRSA isolates in this study are biofilm producers with moderate and weak biofilm capability. We find that almost all mupirocin resistant MRSA isolates are moderate biofilm producers and more than half of mupirocin sensitive MRSA isolates are moderate and weak biofilm producers, but this difference has no significance by statistic (table 1). MRSA is known as MDR bacteria, so that biofilm-forming genes will be suppressed by the antibiotic resistance genes expressed by these bacteria.10,18 Although biofilm producer MRSA isolates capability in this study were weak and moderate, these results need to be concern because it could increase the risk of antibiotic resistance spreading, affect in therapy, and also increase patient morbidity and mortality. All of MRSA isolates have beta lactam resistance as some studies before.5,5,19 This can be related to the presence of mecA gene in MRSA that encodes PBP2a enzyme. This enzyme has low affinity to beta-lactam antibiotics, so the bacteria are resistant to this class of antibiotics. Most MRSA isolates in this study have resistance to tetracycline, erythromycin and quinolone. MRSA is known as multi drug resistant (MDR) bacteria, because of the presence of mec A gene in SCCmec that is a mobile genetic element. In addition to beta lactam resistance genes, as mobile genetic element, SCCmec also carries another resistance genes to erythromycin, tobramycin, tetracycline and quinolone.7,8 SCCmec type could not be concluded in this study, as we did not make SCCmec identification. Drugs of choice for treating MRSA infection are vancomycin, rifampicin, linezolid and quinupristin-dalfopristin. Tigecycline could be used as 2nd or 3rd line for MRSA infection if there is resistance to all antibiotics for treatment options.8,9,20-22 Due to the limited choice of antibiotics in MRSA infections, we need to make consideration in prescribing vancomycin as 1st line drug for MRSA infection in hospitals, in order to reduce the risk of antibiotic resistance.

CONCLUSION
The presence of MRSA with high level mupirocin resistance and biofilm production in this study need to be concerned because of the risk of treatment failure. As for MRSA nasal decolonization, we should be aware of the extensive use of mupirocin to prevent resistance. Prescription of antibiotics for MRSA treatment must be based on microbiology culture results, so we can reduce antibiotic resistance by implementing the antimicrobial stewardship program. In order to control MRSA spreading, implementation of the infection prevention and control programs and also comprehensive management of MRSA infection should be done properly to prevent transmission.

ACKNOWLEDGMENTS
We would like to thank to laboratory staff of Microbiology Laboratory at Dr. Moewardi General Hospital; Department of Microbiology, Faculty of Medicine, Community Health and Nursing, Gadjah Mada University and Department of Microbiology, Faculty of Medicine Sebelas Maret University for isolates identification, storage and assistance this study.

CONFLICT OF INTEREST
The author reports no conflicts of interest in this study.

ETHICAL CLEARANCE
This study has been approved by Research Ethics Committee of Faculty of Medicine, Sebelas Maret University with the ethical clearance certificate no. 144/UN27.06.11/KEP/EC/2022.

FUNDING
The authors are responsible for all financing without grant or external funding sources.

AUTHORS CONTRIBUTION
DKS responsible for study’s conception and design, data analysis, statistical analysis, manuscript preparation, manuscript editing, final approval of the manuscript. LS responsible for study’s conception and design, manuscript review. ATA responsible for study’s conception and design, manuscript review. TN responsible for study’s conception and design, manuscript review.

REFERENCES
INTRODUCTION

Ventilator-Associated Pneumonia (VAP) is still the second leading cause of death in the Intensive Care Unit (ICU). Ventilator-Associated Pneumonia appears ≥48 hours after intubation with a mechanical ventilator, which is usually characterized by fever, tachycardia, leukocytosis, and infiltrates in the lungs. The VAP mortality rate in ICU of a tertiary referral hospital in Indonesia was 86.8%, that was associated with the duration of mechanical ventilator, an increased length of stay in the intensive care unit by ≥10 days, and the types of pathogens. Therefore, VAP is mostly associated with higher costs and mortality rates, as well as longer hospital stays, especially caused by multi-drug resistant organism. The study was aimed to analyze the characteristics and risk factors of VAP patient in ICU of tertiary referral hospital.

METHODS

This was a retrospective study using a cross-sectional design. It was conducted using medical records in the ICU of Tertiary Referral Hospital, RSUD Provinsi Nusa Tenggara Barat, from December 2022 – February 2023. The population in this study was all patients using mechanical ventilators in the ICU from January 2018 – June 2022. The inclusion criteria of samples were patients that have been using MV at least 2 x 24 hours in the ICU that have been diagnosed with VAP. Exclusion criteria were patients that already diagnosed pneumonia or sepsis before the installation of mechanical ventilation or diagnosed with pneumonia during the use of a mechanical ventilator for less than 2 x 24 hours. Data was analyzed using Chi Square, Contingency Correlation, and Spearman Test.

RESULTS

The total number of the samples was 46 patients who met the inclusion and exclusion criteria of 131 patients. The patient characteristics include age, sex, ICU admission, primary diagnosis, indication, and duration usage of MV, as listed in Table 1 based on its outcome. Some of these data do not include culture data. The culture samples obtained from these data were 32 isolates. In this study, the VAP patients were primarily male (54.3%), aged above 45 (76.1%), ICU admission with extrapulmonary disease (87%), and post major surgery (with sedation) more likely to have VAP.

DISCUSSION

Statistical tests conducted between VAP patients with/without COPD on the mortality rate showed a significant correlation. However, the number of VAP samples with COPD considered too
Table 1. Sample Characteristics and Analytic Result

<table>
<thead>
<tr>
<th>Category</th>
<th>Mortality</th>
<th>Mean (SD)</th>
<th>P value</th>
<th>Differences (95%CI)</th>
<th>r</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Survived (n=46)</td>
<td></td>
<td>Death (n=10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (n=46)</td>
<td>53.72(13.65)</td>
<td>0.61</td>
<td>49.66-57.77</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>26-45 year (11)</td>
<td>0 0 11 100</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;45 year (35)</td>
<td>3 9.38 32 91</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex (n=46)</td>
<td></td>
<td>0.1</td>
<td>0.49</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (25)</td>
<td>3 12 22 88</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female (21)</td>
<td>0 0 21 100</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICU Admission(n=46)</td>
<td></td>
<td>0.28</td>
<td>0.13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extrapulmonary (40)</td>
<td>2 5 38 95</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intrapulmonary (6)</td>
<td>1 16.7 5 83</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MV Indication(n=46)</td>
<td></td>
<td>0.81</td>
<td>0.95</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post Major Surgery (33)</td>
<td>2 6.06 31 94</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory Failure (10)</td>
<td>1 10 9 90</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary Oedema (3)</td>
<td>0 0 3 100</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MV Duration(n=46)</td>
<td></td>
<td>329.26(440.87)</td>
<td>0.56</td>
<td>198.33-460.18</td>
<td>0.09</td>
</tr>
<tr>
<td>48-120 hours (11)</td>
<td>1 9.09 10 91</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;120-192 hours (19)</td>
<td>0 0 19 100</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;192 hours (16)</td>
<td>2 12.5 14 88</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COPD (n=46)</td>
<td></td>
<td>0.00</td>
<td>0.49</td>
<td></td>
<td></td>
</tr>
<tr>
<td>With COPD (1)</td>
<td>1 100 0 0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without COPD (45)</td>
<td>2 4.44 43 96</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pathogens (n=25)</td>
<td></td>
<td>0.98</td>
<td>0.13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gram Positive Bacteria</td>
<td>0 0 2 100</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gram Negative Bacteria</td>
<td>1 5.56 17 94</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fungi</td>
<td>0 0 1 100</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polymicrobial</td>
<td>0 0 5 100</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Notes: Age and Duration of MV analyzed using Spearman test, MV: Mechanical ventilation; COPD: Chronic Obstructive Pulmonary Diseases

Table 2. Antibiogram of Pathogens Susceptibility Test

<table>
<thead>
<tr>
<th>Pathogens</th>
<th>Percentage of isolates sensitive to antibiotics</th>
<th>Patterns of Pathogens Susceptibility in VAP Patients to Antibiotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterobacter cloacae</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Staphylococcus haemolyticus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Notes:</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
greater risk which is related to weakening of immune system and regeneration in elderly patients.\(^2\) ICU admissions with extrapulmonary diagnoses were more likely to have VAP, that is related to the high incidence of trauma and post major surgery requiring MVs caused by sedation, as shown in other research.\(^7\) The duration of MV varied with the duration that had the highest incidence of VAP, which was >120-192 hours. Alfaray et al\(^8\) also state that duration >120 hours have 3.386 times more risk of VAP than those who have shorter duration. The most Gram-Negative bacteria found was A. baumannii, the same result shown in researches.\(^4,9\) Meanwhile, S. haemolyticus, the only Gram-Positive found in this study. However, no other adequate research has been found related to this. The discovery of this bacteria in the culture results is suspected as a bacterial contaminant, so data of blood culture is needed too.

**CONCLUSION**

The prevalence of VAP cases in the ICU of West Nusa Tenggara Provincial Hospital in 2019 was 23.1% with a mortality rate of 90.4%. VAP patients in ICU mostly do not have pulmonary disease and mostly are elderly patients (> 44 years), male, and have a history of surgery or use of sedation. There is a significant moderate correlation between COPD and mortality rate (p<0.05). Pathogens that are found in VAP patients mostly are Gram Negative bacteria (90.63%), Acinetobacter baumannii (50%) and Pseudomonas aeruginosa (37,51 %), Candida albicans (3.12%). The best antimicrobial susceptibility for Gram negative bacteria is Amikacin, but A. baumannii showed the best susceptibility to Cefoperazone-Sulbactam. Staphylococcus haemolyticus has the best susceptibility to Trimethoprim-Sulfamethoxazole and Vancomycin.

**CONFLICT OF INTEREST**

The author reports no conflicts of interest in this work.

**ETHICAL CLEARANCE**

Ethical clearance certificate number from RSUD Provinsi NTB is 070.1/67/KEP/2022.

**FUNDING**

Personal Funding.

**AUTHOR CONTRIBUTION**

Priyahita responsible for study conception and design, data collection, analysis and interpretation of results, and manuscript preparation. Octora, Dirja, and Hidayat served as scientific advisors.

**REFERENCES**

The potential of Allium sativum Linn as an inhibitor of Salmonella Typhi bacterial growth

Hasta Handayani Idrus1,2*, Yusriane Mangareng2, Wa Ode Sri Ariani Taufan3, Nesyana Nurmadilla4, Yani Sodiqah5, Amrizal Muchtar6, Sarwo Handayani1, C. S. Whinnie Lestari1, Hermiaty Nasrudin5

Background: Garlic has many properties in terms of curing various diseases due to the influence of the active ingredients it contains such as allicin, allylpropyl disulphide, allyl sulphide, allyl vinyl sulphoxide, allistan, sativine, garlicin and alkyl thioulsulphinate. The aim of this research is to see the potential of Allium sativum Linn as an Inhibitor of Salmonella Typhi Bacterial Growth.

Methods: This study used a laboratory experimental research design (laboratory experiment). This research is a true experiment posttest using the disc diffusion method to see the effectiveness of a single garlic extract (Allium Sativum L) as a medium for inhibiting the growth of Salmonella typhi bacteria. Garlic that is still fresh as much as 1 kg is done by separating the bulbs from the skin of the wrapper. Garlic is dried in direct sunlight so that the densest chemical compounds in the garlic bulbs are not damaged. Then the garlic bulbs are laid out in a tin with even thickness and put in the oven at 38°C to maximize the drying process.

Results: The disc diffusion method is used to measure the effectiveness or antibacterial activity of a substance against bacterial growth by placing paper discs soaked with the tested extract or substance on agar media that has been inoculated with bacteria. Results of the study show that the higher the concentration of Allium sativum, the larger the inhibition zone formed. At the highest concentration, which is 100% garlic extract, an inhibition zone of 14.4 mm was observed with an interpretation of sensitivity.

Conclusion: Based on the results of research regarding the antibacterial effectiveness test of garlic extract (Allium Sativum L) on the growth of Salmonella typhi bacteria and it was concluded that garlic extract (Allium Sativum L).

Keywords: Allium sativum Linn, Salmonella Typhi, in vitro experiment.
garlic oil (MBP), and garlic extract (EBP). Garlic possesses numerous therapeutic properties, owing to its active ingredients, including allicin, allylpropyl disulphide, allyl sulphide, allyl vinyl sulphoxide, allistatin, sativine, garlicin, and alkyldisulphinate. It is commonly used to treat conditions like colds, asthma, hyper tension, and intestinal worm infestations. Notably, one of its active ingredients, allicin, serves as an effective antibacterial agent. The central question in this study is whether garlic extract (Allium Sativum L) can effectively inhibit the growth of Salmonella typhi bacteria, considering the background information provided.

METHODS

This study used a laboratory experimental research design (laboratory experiment). This research is a true experiment posttest using the disc diffusion method to see the effectiveness of a single garlic extract (Allium Sativum L) as a medium for inhibiting the growth of Salmonella typhi bacteria. Garlic that is still fresh as much as 1 kg is done by separating the bulbs from the skin of the wrapper. The garlic is cut into small pieces to increase the surface area so as to speed up the drying process and make grinding easier. Garlic is dried in direct sunlight so that the densest chemical compounds in the garlic bulbs are not damaged. Then the garlic bulbs are laid out in a tin with even thickness and put in the oven at 38°C to maximize the drying process.

Garlic that has been dried is mashed using a grinding machine (Blender) so that a small and fine powder is obtained. Then the garlic powder was extracted by maceration. A total of 500 grams of single garlic powder (Allium sativum) was put into a large jar and 2500 ml of 96% ethanol was added and then soaked for 24 hours. Then after 24 hours of soaking the garlic simplicia was filtered using filter paper and the dregs obtained were macerated again with the same solvent 96% ethanol. This process and make grinding easier. Garlic is crushed or mashed, the odorless allin substance within it transforms into allicin, which is believed to possess potent antibacterial properties. This allin-containing garlic extract was shown to inhibit the growth of various bacteria. In particular, a 50% concentration of the extract effectively inhibited the growth of both gram-positive and gram-negative bacteria, including S. Aureus, S. Epidermidis, S. Pyogenes, S. Pneumonia, Enterobacter faecalis, P. Aeruginosa, Pseudomonas Fluorescens, Proteus Vulgaris, Proteus Mirabilis, E. Coli, Enterobacter aerogenes, K. Pneumonia, S. Typhi, and Acinetobacter. The study also revealed that the concentration of garlic juice had a proportional relationship with its inhibitory potential. Allicin, the active compound in garlic, disrupts the synthesis of DNA, RNA, and proteins in bacteria, leading to damage in the bacterial wall.

RESULTS

Researchers have conducted research on the effect of garlic extract (Allium sativum L) in suppressing the growth of Salmonella typhi bacteria in vitro. This study used a laboratory experimental research design (laboratory experiment). This research is a true experimental post test using the disc diffusion method to see the effectiveness of garlic extract (Allium Sativum L) as a medium for inhibiting the growth of Salmonella typhi bacteria. Based on the research that has been done, the results are.

In the study, the results were obtained based on positive and negative controls, the positive control formed an inhibition zone against Salmonella typhi while the negative control did not form an inhibition zone against Salmonella typhi. Negative control using distilled water showed negative results because there was no inhibition zone formed. Based on the inhibition zone of single garlic extract (Allium Sativum L) with a concentration of 25%, 75%, and 100% against Salmonella typhi bacteria, the results were obtained.

Inhibition zone of Garlic (Allium Sativum L) extract with concentrations of 25%, 75%, and 100% against Salmonella typhi bacteria. The inhibition zone of a single garlic extract (Allium Sativum L) with a concentration of 25% was obtained with an inhibition zone of 5.4 mm which was formed with a resistance interpretation. The inhibition zone of a single garlic extract (Allium Sativum L) with a concentration of 75% obtained an inhibition zone of 10.5 mm which was formed with a resistance interpretation. The inhibition zone of a single garlic extract (Allium Sativum L) with a concentration of 100% resulted in an inhibition zone of 14.4 mm which was formed with a sensitive interpretation. Inhibition zone of garlic extract (Allium Sativum L) with a concentration of 25% against Salmonella typhi bacteria.

<table>
<thead>
<tr>
<th>Number</th>
<th>Onion extract (%)</th>
<th>Obstacles zone</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25%</td>
<td>5.4 mm</td>
<td>Resistance</td>
</tr>
<tr>
<td>2</td>
<td>75%</td>
<td>10.4 mm</td>
<td>Resistance</td>
</tr>
<tr>
<td>3</td>
<td>100%</td>
<td>14.4 mm</td>
<td>Sensitive</td>
</tr>
</tbody>
</table>

DISCUSSION

A study conducted at the UP3M Laboratory, Faculty of Medicine, Indonesian Muslim University, in February to March 2023, aimed to assess the antibacterial properties of a single garlic extract (Allium Sativum L) against Salmonella typhi using the true experimental post-test disc diffusion method. The results demonstrated that the garlic extract exhibited a bacterial inhibition zone, and this inhibitory effect was directly correlated with the concentration of the extract. When garlic is crushed or mashed, the odorless allin substance within it transforms into allicin, which is believed to possess potent antibacterial properties. This allicin-containing garlic extract was shown to inhibit the growth of various bacteria. In particular, an 50% concentration of the extract effectively inhibited the growth of both gram-positive and gram-negative bacteria, including S. Aureus, S. Epidermidis, S. Pyogenes, S. Pneumonia, Enterobacter faecalis, P. Aeruginosa, Pseudomonas Fluorescens, Proteus Vulgaris, Proteus Mirabilis, E. Coli, Enterobacter aerogenes, K. Pneumonia, S. Typhi, and Acinetobacter. The study also revealed that the concentration of garlic juice had a proportional relationship with its inhibitory potential. Allicin, the active compound in garlic, disrupts the synthesis of DNA, RNA, and proteins in bacteria, leading to damage in the bacterial wall.
cytoplasmic membrane, and hindrance in protein and nucleic acid metabolism. This disruption prevents bacterial proliferation and growth. The largest inhibition zone diameter was found at a concentration of 80% with a value of 23 mm and was included in the category of very strong inhibition. It can be concluded that there is a proportional relationship between the concentration of garlic juice and the potential inhibition.

The quality factor of the garlic for the bacterial that I use is still clean and also white in color without any damage from the garlic that I use. The type factor of garlic, the previous researchers used compound garlic, while what I used was single garlic. Allicin can inhibit the proliferation of bacteria, fungi, or kill cells directly. Allicin blocks the synthesis of DNA (thymidine), RNA (uracil), and protein (leucine).

Allicin in garlic has antibacterial activity that attacks gram-positive and gram-negative bacteria. Allicin compounds can increase the permeability of the bacterial wall, when there is an increase in permeability on the bacterial wall, the SH groups (sulphhydryl and disulfide) on the amino acids cystine and cysteine are destroyed.

The SH group that is destroyed causes the synthesis of protease enzymes to be inhibited and the cytoplasmic membrane on the bacterial wall is damaged, as well as disruption of protein and nucleic acid metabolism so that proliferation does not occur in bacteria. Allicin also attacks DNA, RNA and protein synthesis, the main target of allicin is RNA. According to Murungan, when RNA cannot be produced, or is produced in insufficient quantities, protein synthesis will be greatly affected due to the absence of messenger RNA (mRNA), ribosomal RNA (rRNA), and transfer RNA (tRNA). If amino acids and proteins cannot be produced, growth and development of bacteria will not occur.

CONCLUSION

Based on the results of research regarding the antibacterial effectiveness test of garlic extract (Allium Sativum L) on the growth of Salmonella typhi bacteria and it was concluded that garlic extract (Allium Sativum L) with a concentration of 25% was not effective in inhibiting the growth of Salmonella typhi bacteria with a concentration of 75% was not effective inhibiting the growth of Salmonella typhi bacteria, 100% concentration effectively inhibited the growth of Salmonella typhi bacteria, azythromycin as a positive control effectively inhibited the growth of Salmonella typhi bacteria, distilled water as a negative control was not effective in inhibiting the growth of Salmonella typhi bacteria.

CONFLICT OF INTEREST

The author reports no conflicts of interest in this work.

ETHICAL CONSIDERATION

This study was conducted after obtaining an ethical clearance certificate from the Indonesian Muslim University Research Ethics Institute with certificate number LEP.234/LP2S-UMI/LP2S/H.IX/2023.

FUNDINGS

Thank you very much for the National Research and Innovation Agency (BRIN) for providing funding for me to participate in this activity and for providing a lot of support for the course of this research and also to the Universitas Muslim Indonesia (UMI) for providing a place and space for me to research.

AUTHOR’S CONTRIBUTION

The author reports in details the contribution of each author.

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17. Sheoran N, Kumar R, Kumar A, Batra K, Sihag S, Maan S, et al. Nutrigenomic evaluation of garlic (Allium sativum) and...


Prevalence and antimicrobial susceptibility patterns of ESBL-producing *Klebsiella pneumoniae*: A five-year retrospective cross-sectional study

Aiman Idrus Alatas1, Dimas Seto Prasetyo2, Conny Riana Tjampakasari2, Tjahjani Mirawati Sudiro2, Delly Chipta Lestari2

ABSTRACT

**Background:** *Enterobacteriaceae*, which are resistant to carbapenem and produce extended-spectrum β-lactamase (ESBL), has become a priority pathogen by the WHO. ESBL is frequently found in *Klebsiella pneumoniae*. The first case of ESBL-producing *Klebsiella pneumoniae* was reported in 1983, and currently, its cases continue to increase and become a serious threat to patient management. This study was conducted to add to the data on the prevalence of ESBL-producing *Klebsiella pneumoniae* in Indonesia.

**Methods:** This research is a retrospective descriptive study with a cross-sectional approach to examine the prevalence and antimicrobial susceptibility patterns of *Klebsiella pneumoniae* by utilizing secondary data taken from the WHONET 2022 software. The samples studied consisted of routine diagnostic results sent to the Clinical Microbiology Laboratory Faculty of Medicine, Universitas Indonesia (LMK FKUI), Jakarta, from 2017 to 2021.

**Results:** We found that the prevalence of ESBL-producing *Klebsiella pneumoniae* was 24.1% of the total 531 *Klebsiella pneumoniae* isolates, with one isolate also resistant to carbapenem. Based on the sample type, ESBL-producing *Klebsiella pneumoniae* was mainly found in urine samples, followed by sputum and tissue samples.

**Conclusion:** ESBL-producing *Klebsiella pneumoniae* has been found in many countries, including Indonesia, and even isolates resistant to carbapenem have been identified, although their number is still small. This condition remains a serious problem and a global challenge, requiring the control of antimicrobial use to prevent the spread of resistance.

**Keywords:** *Klebsiella pneumoniae*, ESBL, antibiotic resistance.

INTRODUCTION

World Health Organization (WHO) released the list of priority pathogens in 2017, including *Enterobacteriaceae*, which are resistant to carbapenem and produce extended-spectrum β-lactamase (ESBL) as the critical group. ESBLs are enzymes that render many beta-lactam antibiotics ineffective, including penicillin, cephalosporins, and monobactams. ESBL is frequently found in *Klebsiella pneumoniae*. The initial case of ESBL-producing *K. pneumoniae* was documented in 1983, and the cases continue to increase and become a significant challenge to patient care and management.1,2 ESBL-producing *K. pneumoniae* is increasingly prevalent worldwide, presenting a significant challenge to healthcare systems. Such infections are associated with higher rates of illness and mortality, prolonged hospital stays, and increased healthcare expenses. Furthermore, the limited treatment options for these infections complicate patient management and contribute to the spread of these resistant strains.3

Therefore, a comprehensive five-year retrospective cross-sectional study was conducted to determine the prevalence and analyze antimicrobial susceptibility patterns of ESBL-producing *K. pneumoniae* from specimens examined in Clinical Microbiology Faculty of Medicine Universitas Indonesia (LMK FKUI). By analyzing an extensive dataset spanning five years, we hope the results will provide valuable insight into the epidemiology of ESBL-producing *K. pneumoniae* and contribute to the knowledge of antibiotic resistance patterns.

**METHODS**

This research is a retrospective descriptive study with a cross-sectional approach to examine the prevalence and antimicrobial susceptibility patterns of *K. pneumoniae* by utilizing secondary data from the WHONET 2022 software from all clinical specimens examined at LMK FKUI, Jakarta, from 2017 to 2021. We used spreadsheet software to calculate the percentage and create graphs. We include only clinical isolates for analysis. Since the identification and antimicrobial susceptibility test (AST) at LMK FKUI uses an automated system, VITEK® 2 (bioMérieux), a positive ESBL is defined according to the results released by the system.

**RESULTS**

In total, 531 isolates of *K. pneumoniae* were discovered during the investigation. Among these isolates, we identified 128 as ESBL-positive. We examined the distribution of ESBL-producing *K. pneumoniae* isolates over different years and found that the highest number of such isolates occurred in 2019, with 46 samples.
This result accounted for a prevalence rate of 35.9% during that particular year. The findings were visually presented in Figure 1, which depicts the annual trends in ESBL-positive *K. pneumoniae* isolates.

Next, we investigated the distribution of *K. pneumoniae* isolates based on the type of samples collected. Sputum samples were the most frequently encountered among the various samples, followed by urine and tissue samples. Furthermore, we delved into the prevalence of ESBL-producing *K. pneumoniae* isolates based on the type of samples. Interestingly, urine samples demonstrated the highest prevalence of ESBL-producing *K. pneumoniae*, 30.4%, surpassing all other sample types, followed by sputum and tissue samples (Table 1).

ESBL-producing *K. pneumoniae* isolates exhibited a notable and reassuring susceptibility profile towards carbapenem-class antibiotics and amikacin, with an impressive susceptibility rate exceeding 95%. We observed a noteworthy decline in susceptibility to gentamicin and tigecycline, as shown in Table 2.

**DISCUSSION**

Within five years, we found the overall prevalence rate of ESBL-positive among *K. pneumoniae* clinical isolates was 24.1%, indicating a substantial presence of ESBL resistance in the bacterial population. This discovery underscores the importance of monitoring and understanding the prevalence of ESBL-producing strains, as they present a significant challenge in treating infections caused by *K. pneumoniae*. We also investigated the distribution of ESBL-producing *K. pneumoniae* isolates across different years. These findings suggest that ESBL-producing *K. pneumoniae* remains a significant concern, albeit with some variation in prevalence over time.

Compared to previous studies, ESBL-producing *K. pneumoniae* isolates can differ significantly across various regions and healthcare settings. A study conducted in China reported a prevalence rate of 31.9%. In contrast, in West Africa, the prevalence rate of ESBL-producing isolates reached 84% among all detected *K. pneumoniae* strains in clinical specimens. In Indonesia, the prevalence of ESBL-producing *K. pneumoniae* also varied between areas. It ranges from 52.98% to 69.2%. Antibiotic usage, infection control practices, and patient demographics influence region variations prevalence. In this study, we observed that the ESBL-producing *K. pneumoniae* remains susceptible to carbapenem and amikacin. However, other antibiotics showed decreasing sensitivity. Moreover, we identified one specimen that exhibited resistance to carbapenems, a class of potent antibiotics used as a last resort for severe infections.

**CONCLUSION**

ESBL-producing *K. pneumoniae* has emerged as a concerning global health issue. Alarming trends have been observed, including growing isolates demonstrating resistance to carbapenem. The results of this study have important implications for clinical practice, infection control strategies, and the urgent need for continued antibiotic resistance surveillance and monitoring.
CONFLICT OF INTEREST
The authors have no conflicts of interest to declare.

ETHICAL CLEARANCE
This project was conducted after approval from the ethics committee of the Health Research Ethics Committee of the Faculty of Medicine, Universitas Indonesia/ Cipto Mangunkusumo National General Hospital (RSCM) with certificate number KET-287/UN2.F1/ETIK/PPM.00.02/2023.

FUNDING
The authors manage all financial aspects independently, without grants or external funding.

AUTHOR CONTRIBUTION
DCL contributed to the study concept and design, supervised data analysis, and edited the final manuscript. DSP performed an initial analysis of the WHONET data. AIA performed advanced data analysis and wrote the initial draft of the manuscript. TMS and CRT gave valuable input to the manuscript. All authors read, reviewed, and approved the final article.

REFERENCES
Comparison of DNA extraction modification using QIAamp DNA mini kit vs boiling methods for *M. Tuberculosis* isolate

Deby Kusumaningrum¹,²,³,⁴, Ni Made Mertaniasih²,³,⁴*, Soedarsono Soedarsono³,⁴,⁵

### ABSTRACT

**Background:** The innovation of commercial DNA extraction kits and the application of molecular technology have recently been utilized in our understanding of microbial genomics. DNA extraction is a crucial step for molecular methods like Polymerase Chain Reaction. This study aimed to compare the modification of QIAamp DNA mini kit and a cheap, rapid, non-commercial method, the boiling method for extraction of *Mycobacterium tuberculosis* (*M.tb*) isolate. 

**Methods:** Both experimental protocols were applied to ten mycobacterial isolates from TB patients. The extracted DNA's purity and concentration with a spectrophotometer were evaluated, continued by electrophoresis to ensure the DNA's integrity.

**Results:** The process of boiling was shown to be more effective, easy, affordable, and acceptable for all of these isolates. The mean purity of DNA A260/280 by modification of the QIAamp DNA mini kit and boiling were 1.48 and 1.76. And the DNA yield were 22.8 and 116.39 µg/ml respectively.

**Conclusion:** Boiling method for *M.tb* isolates DNA extraction is a promising method that should be further explored and validated.

### Keywords: *M.tuberculosis*, DNA extraction, modification of QIAamp, boiling method.

### INTRODUCTION

Tuberculosis (TB) is a serious infectious illness that predominantly affects the lungs. In Indonesia, as per WHO global report issued Indonesia as second high burden TB country.¹ Thus, controlling the spread of TB involves rapid diagnosis. Several studies have indicated and advised for the use of molecular methods in the diagnosis of TB.² The first crucial step in Polymerase chain reaction (PCR) is the extraction of DNA from mycobacterial cells, which provides enough pure DNA for an effective PCR test.³

Although several TB genomic DNA extraction techniques have been developed previously, they are frequently specimen-specific. Some processes are expensive, long-time procedures unsuitable for PCR-based downstream applications. Furthermore, one of the physical methods used to extract mycobacterial DNA is boiling in enough buffer, damaging the connections between the cell wall lipids, resulting in adequate DNA extraction. In this study we performed and analyzed the results of DNA extraction using the modified method for QIAmp and boiling.

### METHODS

Ten isolates of *M.tb* in the clinical Microbiology Laboratory of Soetomo Hospital were used (Figure 1). A two-loopful colony of *M.tb* isolate was transferred to each of two tubes containing 5 ml 7H9 broth. The modification method was performed with used lysozyme buffer to resuspend the pellet, lysis at 37°C incubation for a night (12 hours).⁴ Finally, one tube was processed using QIAamp DNA Mini Kit as mentioned by manufacturer’s instructions (QIAGEN, Hilden, Germany), and the other tube processed for boiling method for 10 min in distilled water then centrifugation was done at 12000 g for 3 minutes. The results of extraction DNA were analyzed.

The absorbance was measured using The Thermo Scientific NanoDrop™ 1000 Spectrophotometer. The A260/A280 ratio for pure DNA extract should be between 1.8 and 2.0. and assessed by electrophoresis.⁵

### RESULTS

The DNA concentration resulting from ten samples with two modification methods is shown in Table 1, and Figure 2 indicates the visualization band in 0.7 % agarose gel electrophoresis.

### DISCUSSION

In our study, we have evaluated the boiling method, and one commercial kit for *M.tb* DNA extraction. The yield of DNA was higher with the boiling method (116.39 ± 272.89 µg/ml) and was significantly compared to extraction DNA by QIAamp DNA mini kit (p<0.05).
In parallel, comparing the purity of the DNA extracted by two methods showed that boiling produced the most pure DNA (1.76). This can be caused by the modification process with the addition of a lysozyme buffer. Lysozyme effects on cell wall bacterial lysis. Supported EDTA in lysozyme buffer can be used to prevent degradation of DNA and RNA and to inactivate nucleases that require metal ions. The results of the DNA and purity of the boiling method of DNA extraction in our study are almost higher than the research of Koentjoro et al., that used M.tb H37Rv isolate.

Several studies mentioned that boiling extract is recommended as a suitable method for M.tb DNA extraction from cultured isolates especially in developing countries with many samples to be done. Although other studies have shown that DNA extraction using boiling has a lower yield compared to the Qiagen and heliosis methods.

Results of purity extraction DNA by QIAamp show a lower average than the Boiling methods, it may indicate the presence of protein, phenol, or other contaminants that absorb strongly at or near 280. This study is a preliminary experiment with few samples. Furthermore, due to the costs of molecular tests in developing countries and the unavailability of diagnostic tools in every laboratory, this simple method used to extract DNA of M.tb, becomes an alternative method.

**CONCLUSION**

Boiling method for *Mycobacterium tuberculosis* isolates DNA extraction is a promising method that should be further explored and validated.

**ACKNOWLEDGMENT**

All authors thank laboratory technicians at Clinical Microbiology of Soetomo Hospital and Institute of Tropical Disease, University Airlangga, Indonesia, for their assistance.

**ETHICAL CLEARANCE**

The study was approved by the Dr Soetomo Hospital research ethics committee (approval number 0324/KEPK/XII./2021).

**AUTHOR CONTRIBUTIONS**

All the authors contributed equally.

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**Table 1. Comparison of the DNA yield in ug/ml and Purity between Two Extraction Methods**

<table>
<thead>
<tr>
<th>Extraction Method</th>
<th>DNA yield Mean</th>
<th>DNA yield Stdv</th>
<th>Statistics</th>
<th>DNA purity Mean</th>
<th>DNA purity Stdv</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boiling</td>
<td>116.39 ± 272.89</td>
<td>P = 0.003</td>
<td>1.76 ± 0.26</td>
<td>P = 0.071</td>
<td></td>
<td></td>
</tr>
<tr>
<td>QIAamp DNA mini kit</td>
<td>22.88 ± 25.43</td>
<td></td>
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**Figure 2.** Agarose gel electrophoresis of DNA extract by QIAamp DNA mini kit methods, (b). Visualization in 0.7% agarose gel electrophoresis.
INTRODUCTION

Coagulase-negative staphylococci (CoNS) are a large group of Gram-positive cocci united by the lack of coagulase virulence factors that constitute the skin commensal microbiota. Although considered less pathogenic than *S. aureus*, CoNS represents a classic opportunistic pathogen that has been established as a common cause of various healthcare. CoNS has emerged as a major pathogen in healthcare facilities, such as *S. epidermidis, S. haemolyticus*, and, more recently, *S. lugdunensis*, the most clinically relevant species. Studies reveal that antimicrobial resistance (AMR) is widespread among human commensal CoNS, many of which were detected as MDR-resistant isolates. The study found methicillin-resistant *Staphylococcus epidermidis* (32.7% vs. 2.6%) and methicillin-resistant *S. haemolyticus* (90.5% vs. 10%) of preterm mothers compared with term neonates. Marincola found that Multidrug-resistance (MDR) was observed in 23% of the isolates, with 33% of the individuals colonized with MDR-ConS in the community. The prevalence of methicillin-resistant coagulase-negative *Staphylococci* (MRCoNS) is 10%-29%. Determining the incidence could benefit for prevention. This study aims to determine the incidence of MRCoNS in breastfeeding mothers and their babies. We also wanted to see the antibiotic sensitivity pattern of CoNS.

METHOD

A cross-sectional study involving breastfeeding mothers and their babies from July to September 2022 in the work area of the South Tangerang City Health Office. The inclusion criteria for this study were breastfeeding mothers who did not suffer from mastitis or breast abscess infection, did not take antibiotics for the last two weeks, had babies aged 0-6 months in good health, and only gave exclusive breastfeeding. While the exclusion criteria were breastfeeding mothers had severe infections, samples were not met from the mother's nasal swabs, areola, and breast milk. We collected mother and baby nose swabs, areola swab, and breast milk samples. Identification and antibiotic sensitivity test using the VITEK®2 System. We present data descriptively using tables and diagrams.

RESULTS

We obtained 47 CoNS isolates from 36 pairs of mothers and babies aged 1 to 5 months. Of the 47 CoNS isolates, 62% were MRCoNS. Most breastfeeding mothers are housewives. Based on the results of Vitek-2 (Table 1), the species of coagulase-negative *Staphylococcus* that we found included *S. epidermidis, S. haemolyticus, S. capitis, S. hominis ssp hominis, S. warneri, S. gallinarum, S. auricularis, S. saprophyticus, S. lugdunensis, and S. lentus*. The most species found from the mother's nasal swab, baby's nasal swab, areola swab, and breast milk were *S. epidermidis* (40%) and *S. haemolyticus* (30%). Figure 1 shows the pattern of antibiotic sensitivity to coagulase negative *Staphylococcus*. Most of the isolates were resistant to the antibiotics benzylpenicillin, clindamycin,
ERYTHROMYCIN, and OXACILLIN. VANCOMYCIN, LINEZOLID, AND OXACILLIN WERE NOT COMPLETELY RESISTANT TO ALL COAGULASE NEGATIVE STAPHYLOCOCCI.

**DISCUSSION**

ASSOCIATED CONS INFECTIONS FROM THE HEALTHCARE SETTING ARE TYPICALLY CHARACTERIZED BY METHICILLIN AND MULTIDRUG RESISTANCE. HOWEVER, MORE RESEARCH STILL NEEDS TO BE DONE ON THE AMR PATTERN OF CONS COLONIZING THE GENERAL POPULATION. THIS STUDY DEMONSTRATES THAT METHICILLIN- AND MULTIDRUG-RESISTANT CONS IS ALSO PRESENT IN THE COMMUNITY IN HEALTHY VOLUNTEERS WHO ARE NOT HOSPITALIZED. MOST OF THE ISOLATES (62%) WERE MRCONS. THIS RESULT IS HIGHER THAN OTHER STUDIES, WHICH FOUND A PREVALENCE OF MRCONS OF 16% TO 50%. THIS RESULT IS HIGHER THAN OTHER STUDIES, WHICH FOUND A MAJORITY OF MRCONS OF 19.2% AND 24%.8

HIGH LEVELS OF RESISTANCE ARE ORDINARY AND TYPICAL AMONG CONS FROM HEALTHCARE SETTINGS. CONS WAS CONSIDERED A COMMENSAL FOR A LONG TIME AND HAS RARELY BEEN REPORTED TO CAUSE SEVERE INFECTIONS. HOWEVER, DUE TO THE COMBINED EFFECT OF INCREASED USE OF INTRAVASCULAR DEVICES AND AN INCREASE IN IMMUNOCOMPROMISED HOSPITALIZED PATIENTS, CONS HAS EMERGED AS A MAJOR CAUSE OF NOSOCOMIAL BLOODSTREAM INFECTIONS.9

IN THIS STUDY, MORE ISOLATES WERE RESISTANT TO ERYTHROMYCIN THAN SENSITIVE ONES (FIGURE 1). MACROLIDES SUCH AS ERYTHROMYCIN ARE THE MOST FREQUENTLY PRESCRIBED ANTIBIOTICS FOR MILD AND SEVERE STAPHYLOCOCCAL INFECTIONS.10 THE INCREASING PREVALENCE OF ERYTHROMYCIN RESISTANCE LIMITS THERAPEUTIC OPTIONS FOR STAPHYLOCOCCAL INFECTIONS. FORTUNATELY, WE DID NOT FIND RESISTANCE TO NEWER ANTIBIOTICS SUCH AS LINEZOLID.4 HOWEVER, IN ITALY, CFR PLASMID-MEDIATED LINEZOLID RESISTANCE HAS BEEN REPORTED IN S.EPIDERMIS. LINEZOLID IS AN OXAZOLIDINONE ANTIBACTERIAL AGENT THAT INHIBITS PROTEIN SYNTHESIS.11 S. HAEMOLYTICUS AND S.EPIDERMIS ARE THE MOST COMMON CONS ISOLATED FROM CLINICAL SAMPLES, AS IN THIS STUDY. MOREOVER, AMONG THE CONSS FOUND, WE OBSERVED DIFFERENCES IN ANTIMICROBIAL RESISTANCE. HIGH RESISTANCE TO BENZYLPLINICILLIN AND OXACILLIN HAS BEEN WELL DOCUMENTED PREVIOUSLY IN VARIOUS STUDIES. IN THIS STUDY, ALL CONS ISOLATES (100%) WERE SENSITIVE TO VANCOMYCIN. SIMILARLY, ANOTHER STUDY SHOWED THAT ALL NASAL CONS ISOLATES WERE SUSCEPTIBLE TO VANCOMYCIN BY PHENOTYPIC TESTING.10

**CONCLUSION**

THE PREVALENCE OF MRCONS NASAL CARRIERS IS HIGH IN LACTATING MOTHERS AND INFANTS ON A COMMUNITY BASIS. SEVERAL ISOLATES WERE ALSO FOUND TO BE MULTI-DRUG RESISTANT.

**CONFLICT OF INTEREST**

THE AUTHOR REPORTS NO CONFLICTS OF INTEREST IN THIS STUDY.

---

**Table 1. Coagulase-negative Staphylococcal Species Finding**

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>Specimen</th>
<th>N CoNS</th>
<th>N CoNS (%)</th>
<th>N MRCoNS</th>
<th>N MRCoNS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S.epidermidis</td>
<td>mother's nasal swab</td>
<td>6</td>
<td>3</td>
<td>2</td>
<td>13 (45)</td>
</tr>
<tr>
<td></td>
<td>baby's nasal swab</td>
<td>4</td>
<td>19 (40)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Areola swab</td>
<td>6</td>
<td>5</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Breast milk</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>S.haemolyticus</td>
<td>mother's nasal swab</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>13 (45)</td>
</tr>
<tr>
<td></td>
<td>baby's nasal swab</td>
<td>1</td>
<td>14 (30)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Areola swab</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Breast milk</td>
<td>7</td>
<td>6</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>S.capitis</td>
<td>baby's nasal swab</td>
<td>1</td>
<td>1 (2)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>S.hominis ssp hominis</td>
<td>baby's nasal swab</td>
<td>1</td>
<td>3 (6)</td>
<td>-</td>
<td>1 (3)</td>
</tr>
<tr>
<td></td>
<td>Areola swab</td>
<td>2</td>
<td>1</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>S.warneri</td>
<td>mother's nasal swab</td>
<td>2</td>
<td>2 (4)</td>
<td>-</td>
<td></td>
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<tr>
<td>S.gallinarum</td>
<td>Areola swab</td>
<td>1</td>
<td>1 (2)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>S. auricularis</td>
<td>baby's nasal swab</td>
<td>1</td>
<td>1 (2)</td>
<td>1</td>
<td>1 (3)</td>
</tr>
<tr>
<td>S.saprophyticus</td>
<td>baby's nasal swab</td>
<td>1</td>
<td>1 (2)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>S.ludgunensis</td>
<td>mother's nasal swab</td>
<td>1</td>
<td>3 (6)</td>
<td>1</td>
<td>1 (3)</td>
</tr>
<tr>
<td></td>
<td>Areola swab</td>
<td>2</td>
<td>2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>S.lentus</td>
<td>baby's nasal swab</td>
<td>2</td>
<td>2 (4)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

MRCONS: Methicillin-resistant Coagulase-negative Staphylococci

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**Figure 1.** Pattern of Antibiotic Susceptibility to coagulase-negative Staphylococcus.
ETHICAL CLEARANCE
This study has been approved by Research Ethics Committee of Faculty of Medicine and Health, Universitas Muhammadiyah Jakarta, Indonesia.

FUNDING

AUTHORS CONTRIBUTION
All authors contributed equally with regards to this research.

REFERENCES
Correlations between Ki-67 biomarkers and grading meningioma

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ABSTRACT

Background: Meningioma is one of the most common types of intracranial tumors. A biological marker, such as Ki-67 is needed to predict the risk of tumor recurrence and development. The purpose of this research is to know the correlation between expressions Ki-67 with grading meningioma.

Methods: The cross-sectional study used meningioma samples of Risa Sentra Medika Hospital at Mataram City. Total number of samples were 9 samples from 3 different grades of meningioma. The samples consist of 3 samples from grade 1 meningioma, 3 samples from grade 2 meningioma, and 3 samples from grade 3 meningioma.

Results: The mitotic activity were differ in every grade of meningioma, 1 samples shown 15% mitosis/hpf, 3 samples 10% mitosis/hpf, 2 samples 5% mitosis/hpf, 2 samples 3% mitosis/hpf, and 1 samples 1% mitosis/hpf. Meningioma classification can be determined based on meningioma mitotic activity by using markers such as Ki-67 markers and there are also several factors that could be used to diagnose meningioma grading.

Conclusion: It concluded that the Ki-67 marker cannot be the main parameter for determining grading meningioma.

Keywords: meningioma, Ki-67, mitotic activity, parameter.

INTRODUCTION

Meningioma is one of the most common types of intracranial tumors.1,2 The latest World Health Organization (WHO) classification 2021, meningiomas are grouped into three groups based on their level, grade I (benign), grade II (atypical), and grade III (anaplastic).3,4 Regulation of cell proliferation identified with protein markers can be used to predict the characteristics of meningioma.5 Ki-67 is one of the most often immunohistochemical marker (IHC) used to measure cell proliferation6 which has a very high expression ability in meningioma. Surgical treatment in meningioma patients mostly provide better postoperative results.7 However, recurrence and re-development of postoperative tumor cells are still common which causes patients to return and have a poor prognosis.8 Therefore, a biological marker, such as Ki-67 is needed to predict the risk of tumor recurrence and development.

METHODS

This research is a type of observational analytic research using the method cross sectional to determine the correlation between the level of Ki-67 with grading meningioma. It was conducted using meningioma samples of Risa Sentra Medika Hospital, Mataram City, from 2021 – 2022. The inclusion criteria of samples were all meningioma samples at Risa Sentra Medika Hospital, Mataram 2021 – 2022. Exclusion criteria were samples that were not suitable for examination using a microscope and samples of tumors other than meningioma. Data was analyzed using the Friedman Test.

RESULTS

The total number of the samples were 9 samples who met the inclusion and exclusion criteria out of 30 samples. Each grade of meningioma has 3 samples with the mitotic activity shown after being stained with Ki-67 markers. The results of the normality test show that the distribution of the data is not normal so that a nonparametric test is needed to analyze the correlation between grading meningioma by Ki-67 immunohistochemical staining. Nonparametric test is needed to determine the correlation between

Table 1. Meningioma Samples with Staining of Ki-67 Markers

<table>
<thead>
<tr>
<th>Sample Number</th>
<th>Grade</th>
<th>Mitotic Activity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>949/22</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>999/22</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>631/22</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>1255/21</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>333/21</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>69/22</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>1798/21</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>2387/21</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>1241/22</td>
<td>3</td>
<td>15</td>
</tr>
</tbody>
</table>

Table 2. Friedman Test Results

<table>
<thead>
<tr>
<th>Test Statistic</th>
<th>df</th>
<th>Asymptotic Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total N</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Test Statistics</td>
<td>3.800</td>
<td></td>
</tr>
<tr>
<td>df</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Asymptotic Sig.</td>
<td>0.150</td>
<td></td>
</tr>
</tbody>
</table>
grading meningioma with Ki-67 staining due to abnormal data distribution. Based on the results of the Friedman test, it was found that the asymptotic sig. 0.150 (> 0.05). Based on the value of the Friedman test, the null hypothesis (H0) in the study is accepted and the alternative hypothesis (Ha) is rejected. H0 in the study is that there is no correlation between Ki-67 and grading meningioma while Ha in the study was a correlation between Ki-67 and grading meningioma.

DISCUSSION

Meningioma tumor progression can be determined based on the diagnosis grading meningioma. Meningioma classification according to WHO in 2021 can be determined based on meningioma mitotic activity which is divided into three grading, namely meningiomas grade 1, grade 2, and grade 3. Meningioma grade 1 had mitotic activity < 4 mitosis/hpf, meningioma grade 2 with mitotic activity of 4 – 19 mitosis/hpf, and meningioma grade 3 with mitotic activity > 20 mitosis/hpf.9

No positive correlation was found between the Ki-67 marker and grading meningioma in this study. Friedman test results show value p = 0.150 (> 0.05) so that H0 is accepted and Ha is rejected. Based on the research, no correlation was found between the Ki-67 marker and grading meningioma. The results found may differ from several studies that have carried out immunohistochemical staining tests on grading meningioma because the number of samples tested differed from those studies. In addition, there are other pathological parameters that can be used to determine grading meningioma. Upgrading meningioma can not only be determined based on one parameter only.

The results of the study may be influenced by several things that affect meningioma mitotic activity.9 Therapeutic interventions that have been performed on previous patients, such as radiation therapy can affect meningioma mitotic activity to be lower.10,11 In addition, physical status patients, such as body mass index (BMI) included in the classification of obesity and therapeutic interventions hormone replacement can also affect the mitotic activity of meningioma patients.12,13 Therefore, mitotic activity in meningioma patients can be influenced by several factors.

CONCLUSION

The Ki-67 marker cannot be the main parameter for determining grading tumors or meningiomas. This shows that other parameters are needed to be considered in determining grading tumors or meningiomas. Therefore, further research is needed regarding other parameters that can be used to determine grading meningioma.

CONFLICT OF INTEREST

The author reports no conflicts of interest in this work.

ETHICAL CLEARANCE

Ethical clearance certificate number from Mataram University UNRAM0970822.

FUNDING

Personal Funding.

AUTHORS CONTRIBUTION

Bharata responsible for study conception and design, data collection, analysis and interpretation of results, and manuscript preparation. Rosyidi, Prihatina, and Djannah served as scientific advisors.

REFERENCES

Association between asphyxia neonatorum and neurodevelopmental delay in children aged 1-3 years

Rizqi Al Kasiron¹*, Titi Pambudi Karuniawaty², Herpan Syafii Harahap³

ABSTRACT

Background: Neonatal asphyxia is defined as failure to initiate or maintain spontaneous breathing in neonates. The most common complications of neonatal asphyxia is hypoxic-ischemic encephalopathy which is typically associated with neurodevelopmental disorders in later life. Therefore it is very important to monitor the neurodevelopmental achievement of children at risk. This study aims to analyze the association between neonatal asphyxia and neurodevelopmental delay in children 1-3 years old.

Methods: This study used a retrospective cohort study design. Subjects aged 1-3 years old without any congenital malformation were selected. Neurodevelopmental level was assessed using Denver II test. Perinatal history collected as secondary data based on the MNCH Record on the selected sample. Data analysis was performed using the Chi Square test.

Result: There were 62 children selected as research subjects. The results showed 18 children (29.0%) with asphyxia and 2 children (3.2%) without asphyxia with a significant difference (p=0.000). There was a significant difference in gross motor development delays in 8 children (12.9%) with asphyxia and 1 children (1.6%) without asphyxia (p=0.026), fine motor developmental delay in 7 children (11.3%) with asphyxia (p=0.011) and 0 child without asphyxia, language development delay in 9 children (14.5%) with asphyxia and 1 children (1.6%) without asphyxia (p=0.006). There was no significant difference in personal-social delay which only found in 1 child (1.6%) with asphyxia.

Conclusion: There is a significant association between asphyxia neonatorum and neurodevelopmental delay in children aged 1-3 years. There is a significant association between asphyxia neonatorum and the development of fine motor, gross motor, and language in children aged 1-3 years.

Keywords: Asphyxia Neonatorum, Neurodevelopment, Denver II Test, Developmental Disorder.

INTRODUCTION

Neonatal asphyxia is a significant problem in Indonesia, being the second leading cause of death among newborns, accounting for 27% of deaths in 2019 (5,464 deaths).¹ It results from breathing difficulties and has a mortality rate of 1.3 deaths per 1000 births, rising to 2.5 deaths per 1000 births in premature cases.² This condition leads to hypoxemia and hypercapnia, causing various complications. One severe complication is hypoxic-ischemic encephalopathy, linked to neurodevelopmental disorders.³ Early identification is crucial to prevent severe neurological abnormalities through appropriate management.⁴

Asphyxia-related complications can lead to neurodevelopmental disorders affecting approximately 52.9 million children worldwide.⁵ These disorders include Global Developmental Delay (GDD), Cerebral Palsy, speech and language issues, and mental retardation. Research shows that about 41.5% of children experiencing neonatal asphyxia suffer from these disorders.⁶ Motor and cognitive delays are also prevalent, affecting children at various ages. For infants with ischemic hypoxic encephalopathy, a complication of neonatal asphyxia, delays in all aspects of development were observed, according to Adhikari and Rao (2017).⁷ This analysis explores the link between neonatal asphyxia and neurological development in children aged 1-3 years, a topic not previously studied in NTB Province, particularly in Lombok.

METHODS

This study used a retrospective cohort design to collect data from December 2021 to November 2022 in Mataram City and West Lombok Regency. It focused on children aged 1-3 years in a specific location and timeframe. Simple random sampling was used, including children meeting inclusion criteria (aged 1-3 and consent from parents) and excluding those with congenital abnormalities or incomplete Maternal Neonatal and Child Health (MNCH) records. The children were divided into asphyxia and control groups based on their neonatal asphyxia history recorded in MNCH records. Statistical analysis was performed with SPSS version 26.0 software. Non-Parametric Kolmogorov-Smirnov test was used to determine data normality. Pearson’s Chi Square test, Fisher’s Exact test, and Two-sample Kolmogorov-Smirnov Test was used to determine statistically significant relation between variables.

RESULTS

The study involved 62 children, with 31 in the asphyxia group and 31 in the non-asphyxia group. Most subjects fell into the 25-36 months age group, with 32 children...
in total, including 20 with asphyxia (32.3%) and 12 without (19.4%). Of the subjects, 31 were female (50%), comprising 14 in the asphyxia group (22.6%) and 17 in the non-asphyxia group (27.4%). There were also 31 male subjects (50%), with 17 in the asphyxia group (27.4%) and 14 in the non-asphyxia group (22.6%). The majority of participants came from West Lombok Regency, totaling 56 children, with 25 (40.3%) having a history of asphyxia and 31 (50%) without.

In this study, most research subjects were born at full term gestation, with 37 children falling into this category, including 18 with asphyxia (29.0%) and 19 without (30.6%). The majority of subjects had adequate birth weight, totaling 57 children, with 27 having asphyxia (43.5%) and 30 without (48.4%). Normal delivery was the most common method of childbirth for the subjects, with 45 cases, including 18 with asphyxia (29.0%) and 27 without (30.6%). Midwives were the most common labor assistants, with 39 children having midwives assist, including 26 with asphyxia (41.9%) and 13 without (21.0%).

The mean gestational age for all subjects was 38.94 ± 1.3 weeks, with similar averages in both the asphyxia (38.74 ± 1.39 weeks) and non-asphyxia groups (39.13 ± 1.2 weeks). The mean birth weight for all subjects was 3088 ± 448 grams, with the asphyxia group having a mean birth weight of 3032 ± 507 grams, and the non-asphyxia group having a mean birth weight of 3143 ± 380 grams.

According to the Denver II test, 32.3% of children (20 in total) showed developmental delays, with 29.0% (18) having a history of asphyxia and 3.2% (2) without. These delays were found in personal social, language, gross motor, fine motor, and GDD categories. Children with a history of asphyxia showed a significant difference in gross motor (8 vs. 1, p=0.026), fine motor (7 vs. 0, p=0.011), language (9 vs. 1, p=0.006), and GDD (6 vs. 0, p=0.024) delays compared to the control group. However, there was no statistically significant difference in personal and social aspects (1 vs. 0, p=0.000) between the asphyxia and control groups.

### DISCUSSION

The majority of participants in this study lived in West Lombok Regency and had socioeconomic characteristics indicating low income levels and limited parental education. These socio demographic conditions can impact family life and child development. The study revealed a significant link between child development and neonatal asphyxia (p=0.001), which aligns with findings by Nguefack et al (2013), highlighting perinatal factors like neonatal asphyxia and hypoxic ischemic encephalopathy (HIE) as primary causes of developmental delays. However, they also noted challenges in identifying the causes of delays in some children (17%). Meena et al (2011) suggested that immediate interventions for infants with asphyxia can lead to positive outcomes in all aspects of child development at age 1. This study further examined the relationship between different developmental aspects.

The study found no statistically significant relationship between neonatal asphyxia and children's personal-social development (P=1.000). This lack of association may be influenced by various factors, including environmental elements and parental psychological conditions. Personal-social development pertains to a child's attitude and emotional state towards themselves and their surroundings, closely linked to their psychological well-being. Parental involvement and the surrounding environment play a crucial role in stimulating a child's personal-social development. Research by McDonald et al (2018) highlighted risk factors for delays in personal-social development, primarily connected to parental psychological disorders such as maternal depression, low parenting self-efficacy, and insufficient play interaction with the child. Another study by Kaur et al (2021) also failed to establish a significant relationship between personal-social development and biological factors like gestational age and newborn weight. Therefore, it is suggested that a child's personal-social development is less likely to be affected when parents are psychologically healthy, and the child's environment provides a positive influence.
ample developmental stimulation.

The results of this study highlight significant connections between neonatal asphyxia and both fine motor and gross motor development in children. In terms of fine motor skills, the study found a statistically significant relationship (p=0.011), aligning with Charan and Vaghá’s (2016) research that linked neonatal asphyxia to Global Developmental Delay (GDD), including fine motor delays. However, the relationship between delayed motor development and various factors, such as perinatal and socioeconomic influences, remains complex, as demonstrated by Arabiat et al’s (2021) meta-analysis. Similarly, Bortagarai et al (2021) emphasized the influential role of factors like maternal and obstetric conditions, biological factors, sociodemographics, and psychosocial factors in fine motor and gross motor delays. In the context of gross motor development, a statistically significant relationship with neonatal asphyxia (P=0.026) was established, consistent with prior research, including Hanrahan and Mangunatmadja’s (2019) findings, which highlighted asphyxia as an intrinsic risk factor for delayed gross motor development in children aged 6-24 months. Nevertheless, Hanrahan and Mangunatmadja’s study revealed that microcephaly and birth age below 37 weeks were also significant predictive factors. Furthermore, Sutapa and Suharjá’s (2019) research underscored the positive impact of physical activities like walking, running, jumping, kicking, and ball play on gross motor development, enhancing nerve-muscle coordination and overall motor skills.

This study established a statistically significant link (P=0.053) between neonatal asphyxia and child language development, corroborating findings by Sundereran and Kanhere (2019) and Tan et al. (2019). Neonatal asphyxia emerged as a medical risk factor for language delay, alongside family and environmental factors such as multilingual backgrounds and low parental education.

By definition, Global Developmental Delay (GDD) is a disorder of developmental delay in more than one aspect of development. In this study, it was found that there was a statistically significant relationship between GDD and neonatal asphyxia (p=0.005). This is in accordance with the findings in a study conducted by Charan and Vaghá (2016), which explains that GDD is more common in children born preterm, LBW, intrauterine growth restriction (IUGR), and neonatal asphyxia.

CONCLUSION

There is a significant relationship between history of neonatal asphyxia and developmental conclusions based on the Denver II Test assessment in children aged 1-3 years. More specifically, there is a significant relationship between the history of neonatal asphyxia and the development of fine motor, gross motor, language, and GDD in children aged 1-3 years.

ETHICAL CLEARANCE

This study was conducted after obtaining an ethical clearance certificate from the Health Research Ethics Committee of the Faculty of Medicine, University of Mataram / University of Mataram General Hospital No: 394/UN18.F7/ETIK/2021.

FUNDINGS

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CONFLICT OF INTEREST

The author reports no conflicts of interest in this work.

AUTHORS CONTRIBUTION

All authors had contributed in manuscript writing and agreed for the final version of the manuscript for publication.

REFERENCES


INTRODUCTION

Tuberculosis poses a significant health problem in the world, particularly in Indonesia as the second rank country with the highest number of TB cases. Obtaining accurate statistical data on Tuberculosis (TB) cases in children presents challenges due to inadequate specimen collection and problems in collecting appropriate specimens. Current diagnostic methods that aimed at detecting bacteria in children are insufficient, primarily because most pediatric TB cases are paucibacillary. So diagnosis confirmation is difficult and requires clinical judgements. Effective diagnostic tools play a vital role in establishing TB diagnosis, enabling the prompt initiation of treatment and prevent unnecessary morbidity and mortality.

Immunology assay approaches such as the tuberculin skin test and interferon-γ release assay (IGRA) contribute in establishing pediatric TB. Nevertheless, the tuberculin test exhibits low sensitivity. Various factors can lead to false positive result due to non-tuberculosis mycobacterial infection and BCG vaccination. On the other hand, IGRA is a test that measures the level of IFN-γ released by T lymphocytes when exposed to M.tuberculosis antigenic peptide. This assay offers an advantage in sensitivity compared to the tuberculin test.

A simplified version of the IGRA tool is required to extend its accessibility for suspected pediatric TB patients across diverse regions. Therefore, a testing tool was developed based on the Lateral Flow Immunoassay (LFA) method. This method offers portability and ease of use in remote laboratory settings. Interferon-γ (QIAreach®) represents a digital fluorescence LFA that employ nanoparticle technology to quantify the levels of IFN-γ released by CD4 and CD8 T cells in the plasma, eliminating the necessity for an ELISA. This study was carried out to address the need for a simplified IGRA testing tool that can be utilized by healthcare personnel in rural area.

MATERIAL AND METHODS

Data Collection

The study was conducted between November 2021 and May 2023, involving both outpatients and inpatients within the Pediatric department of RSUPN Dr. Cipto Mangunkusumo, and the Clinical Microbiology Laboratory of FKUI. The criteria for inclusion encompassed pediatric patients aged 5 to 18 years old, who were suspected of pulmonary tuberculosis and sought consultation from the respirology division of RSUPN Dr. Cipto Mangunkusumo’s pediatric department. Miliary tuberculosis cases were excluded from the study. The collected specimen for this study included peripheral venous blood for Interferon-γ (QIARach*®) and either sputum or gastric lavage for genexpert® MTB/RIF assay.

Specimen Collection and Processing

The amount of 1 ml peripheral venous blood was taken and accommodated in a special QIAreach QFT tube containing heparin. Specimens were homogenized...
by shaking the tube for 10 times. Further incubation was carried out for 16-24 hours in 37 ±1°C. After the incubation period, plasma was separated by centrifugation at a velocity of 2000-3000 times the force of gravity (RCF) for 15 minutes. Into the processing tube, 150 ul of QIAreach diluent buffer was introduced, after which 150ul of plasma was added, and subsequent homogenization was manually performed. A total of 150 ul of samples from the processing tube were transferred into the sample port and qualitative test results become readable after a span of 20 minutes. TheGeneXpert® analysis were conducted using sputum or gastric lavage specimen. Beforehand, the buffer was homogenized and then allowed to incubate for a duration of 10-15 minutes. Results would be observed after 2 hours.

**Statistical Analysis**

All statistical analyses were performed using IBM Statistical Package for the Social Sciences (SPSS) version 22 software and Microsoft excel.

**RESULTS**

During the study period, there were 45 patients who met the inclusion criteria. More than half of the study subjects were female (68.9%), with common symptoms of stagnant or weight loss (60%), chronic cough (51.1%) and long fever (44.4%). Chest X-ray with suggestive TB were 68.8%. Mantoux test was performed on 51% of study subjects and about 15.6% (7 of 23) gave positive results. TB scoring with suggestive results were obtained at 19 (42.2%) study subjects.

QIAreach® exhibited a sensitivity of 100% and specificity of 68.4%, with a positive predictive value of 36.8% and a negative predictive value of 100%, positive likelihood ratio 3.17, negative likelihood ratio 0, and diagnostic accuracy 73.3%.

**DISCUSSION**

The sensitivity of Interferon-γ (QIAreach®) assay against ESAT-6 and CFP-10 protein in patients with suspected pulmonary tuberculosis obtained in this study was 100%. IGRA measures the cellular immune response to specific MTB antigens. A positive result indicates TB infection. Because MTB is a prerequisite for TB disease, a negative IGRA result may rule out active TB disease. A positive IGRA can provide additional value in establishing the diagnosis in pediatric patients with clinical features consistent with active TB, such as the use of the Mantoux examination which has been used so far. The accuracy of IGRA in children aged less than 5 years is difficult to assess because blood sampling is more difficult in younger children, microbiological confirmation is difficult to obtain. The immunological response is highly dependent on the child’s age, one of which is due to the low production of Interferon-γ against the TB antigen response.

The specificity value in this study was 68%. The low specificity value of Interferon-γ (QIAreach®) obtained in this study could be caused by paucibacillary tuberculosis infection making it difficult to find bacteriological evidence in pediatric patients. The best way to minimize false positive results is to only have IGRA examined in patients with TB risk factors such as children with TB symptoms. So that in Indonesia a scoring system for children’s TB was developed which is a guideline for diagnosing children with TB. With the right diagnosis of TB in children, it can provide appropriate treatment and care for children who suffer from TB. Children who are in contact with adult TB patients will have a higher risk of TB infection. This is in line with the results of this study, that 36% of patients with positive Interferon-γ (QIAreach®) results showed a history of contact with TB patients. A history of close contact with a TB patient who also has a cough will increase the risk of infection and the number of droplets inhaled into the alveoli. Children aged 5-14 years with a history of close contact with adult TB patients are almost 3 times more likely to become infected with TB than children aged 15 years and over.

**CONCLUSION**

The characteristics of pediatric TB subjects in this study were found similar with the tuberculosis patients in the world. The sensitivity and specificity of the Interferon-γ (QIAreach®) are 100% and 68.4%. The positive predictive value and negative predictive value of Interferon-γ (QIAreach®) are 36.8% and 100%. IGRA should be done together with other examination modalities such as history, physical examination and chest X-ray. IGRA can be performed to replace Mantoux as a pulmonary TB screening in children.

**CONFLICT OF INTEREST**

All authors have no conflicts of interest to declare and certify that the submission is original work and is not under review at any other publication.

**ETHICAL CLEARANCE**

This study has obtained an ethical clearance certificate from the Health Research Ethics Committee of the Faculty of Medicine, Universitas Indonesia/ Cipto Mangunkusumo National General Hospital (RSCM) with certificate number KET/862/UN.F1/ETIK/ PPM.00.02/2021 and ND-255/UN2.F1/ ETIK/PPM.00.02/2023.

**FUNDINGS**

PT UBC Medical Indonesia provided the QIAreach QFT test kits free of charge. PT UBC had no role in study design, collection, analysis and interpretation of data.

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**Table 1. Accuracy Analysis of Interferon-γ (QIAREACH®) Examination Results with Genexpert® MTB/Rif in Pediatric Patients with Suspicion of Pulmonary Tuberculosis**

<table>
<thead>
<tr>
<th>Assay</th>
<th>GeneXpert®</th>
<th></th>
<th>Cohen’s Kappa</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>INTERFERON-γ (QIAREACH®)</td>
<td>Positive</td>
<td>7</td>
<td>12</td>
<td>0.403</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>0</td>
<td>26</td>
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</tbody>
</table>

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**PROCEEDING**

AUTHORS CONTRIBUTION

AK and NK designed and directed the project; NK and FAN contributed to specimen collection; TAS performed the measurements and data analysis; AK and FAN supervised the findings of this works; AK, YRS and NK contributed to the interpretation of the results and verified the analytical findings; AK and TAS wrote the paper with input from all authors.

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Knowledge of nasopharynx and nasopharyngeal carcinoma during the COVID-19 pandemic among the Indonesian community and the lesson learnt for the future management

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INTRODUCTION

Nasopharyngeal carcinoma (NPC) is one of the most common malignancies in Asian countries, including Indonesia with the overall incidence of 5.6/100,000.1 The origin of this malignancy is at the posterior part of the nasal cavity, called nasopharynx. The structure of nasopharynx is hidden and difficult to observe directly. So far, the knowledge about NPC in health workers is considerably low, only 51% of 106 general practitioners know the symptoms of NPC.2 Knowledge on NPC among the community might be lower than health workers. Low knowledge of NPC is correlated to the delay in seeking medical treatment,3 which may lead to late diagnosis of NPC.4 As a result, cases of NPC are frequently found at an advanced stage.5

The World Health Organization (WHO) has declared the end of COVID-19 pandemic in May 2023. There are many lessons to learn that the world has gained from this pandemic. There are many negative impacts of COVID-19 such as the restrictions of activities, high morbidity and mortality rates, as well as economic and social impacts.5,6 However, the positive impact of COVID-19 is rarely discussed and is hidden behind the magnitude of its negative impact.7 With the massive information on COVID-19 in the community, the knowledge on COVID-19 including how it is diagnosed might be very high. One of the COVID-19 diagnostic methods that are popularly known and to be the most reliable technique is to take a swab sample in the nasopharynx for either rapid antigen or polymerase chain reaction (PCR) examination,8 because the viral load was found to be most abundant in the nasopharynx.9 Earlier studies showed that the public knowledge and perception of COVID-19 were found to be good and very good in several countries.10,11 This might affect the knowledge on nasopharynx and NPC as well.

This study aims to explore the community’s knowledge about the nasopharynx and NPC in the COVID-19 pandemic era and the benefit of this trend to be implemented in the future.

METHODS

Data collection was conducted in several regions in Indonesia, including Sumatra, Java, Sulawesi, and Nusa Tenggara to represent the huge variability of the Indonesian population. These provinces were categorized into the western, middle, and eastern parts. Sumatra and Java are part of the Western, while West Nusa Tenggara (WNT) and South Sulawesi are in the middle part. Respondents were recruited using consecutive sampling and the participation was voluntary. The inclusion criteria were to be at least 17 years old, have access to a smartphone, and the participation was voluntary.  The participation was voluntary.

ABSTRACT

Background: Nasopharynx is a hidden structure inside the nasal cavity. Nasopharyngeal carcinoma (NPC) originated from nasopharynx and is one of the most common malignancies in Asian countries. Previously, the knowledge of the community regarding this disease was notably low. Massive news on nasopharyngeal swab (NS) during the pandemic COVID-19 era may increase the community's knowledge about the nasopharynx and NPC origin. Furthermore, a future strategy can be proposed on tackling the NPC in the post pandemic era.

Methods: A multi-region study was done with an online questionnaire. A figure of nasopharynx was included in the questionnaire. The participant should choose one of the correct locations of the nasopharynx, the origin of NPC, and the sign and symptoms of NPC.

Results: There were 377 subjects who fulfilled the questionnaire. The origin of subjects was from 4 main regions in Indonesia. Knowledge of NS was very high (98%) while the knowledge of nasopharynx location was 82% and NPC origin was 77%.

Conclusion: The knowledge about nasopharynx location and origin of NPC was relatively high in the pandemic COVID-19 era. It is assumed that this may become one of the positive impacts of NS knowledge. This phenomenon could be a lesson to learn on combating NPC in the future.

Keywords: Nasopharyngeal carcinoma, Nasopharyngeal swabs, COVID-19, Lessons learn.
and be willing to participate in this study. Respondents were excluded if they did not complete or submit the electronic questionnaire or had a history of NPC.

Data collection was conducted online using an electronic questionnaire by sending the links of the form to prospective respondents from 1st June – 30th September 2022. The questionnaire included knowledge on the nasopharynx location, swab nasopharynx, and NPC, a figure of nasopharynx was included in the questionnaire. Respondents were asked to choose one of the correct locations of the nasopharynx, swab nasopharynx sampling site, and the origin of NPC. The questionnaire was piloted to ensure the validity and reliability of this tool. The validity and reliability were 0.77 and 0.6, respectively. Data analysis was done using IBM SPSS. Descriptive and correlation analysis was done to describe the pattern of knowledge of the nasopharynx swab, the location of the nasopharynx, and the origin of NPC.

**RESULT**

A total of 377 respondents completed the questionnaire. By regions, there were 79, 134, 33, and 131 respondents from West Sumatra, Yogyakarta, South Sulawesi, and West Nusa Tenggara, respectively. More than half were aged between 20-29 years (58%). Most respondents had undergraduate education (73%) followed by junior-high school (15%) and post-graduate education (11%). More respondents lived in urban areas than in rural areas and this was observed both at provincial and national level. The average income of respondents was 1.5-4.9 million rupiah (100-300 USD) per month. By occupation, the proportion of respondents were quite evenly distributed with one third were government employers, private employees 25%, and some were unemployed or work at home (41%). More than one third of all respondents were health workers.

Most respondents had knowledge about nasopharyngeal swabs (98%), and the symptoms of COVID-19. The most frequent source of information was from health workers (81%) and followed by social media (65%). Most respondents (82%) were able to correctly locate the nasopharynx. Knowledge about the origin of NPC was also high (77%). Half respondents also recognized various signs and symptoms of NPC although the history of their family suffering from NPC was very low (5%).

The distribution of knowledge of NPC based on the region was shown in Figure 1.A. In the Western part, the knowledge was higher than in the middle part. There was no data in the eastern part of Indonesia. The highest knowledge was in the Special region of Yogyakarta (SRY) then followed by West Sumatera, South Sulawesi, and WNT consecutively at 89%, 85%, 70%, and 62%.

Knowledge on swab nasopharynx facilitated the respondents to know better about NPC. More than 60% (254) of respondents said that the knowledge of NS affected their insight into NPC. More than half of them said that the influence was very strong and strong. The nasopharyngeal swab also increased the respondent’s knowledge about NPC. More than 50% of respondents said that their knowledge increased after knowing the nasopharyngeal swab and the location of the nasopharynx (Figure 1.B).

**DISCUSSION**

The study found that knowledge of NPC in the community was remarkably high. The proportion of respondents with knowledge of NS and NPC was higher compared to previous studies. The present study found the pattern of knowledge of NPC in the community was relatively increased. Due to the exponential effect of the COVID-19, the news from formal and informal sources regarding this disease was spreading massively to the entire world.

Several scientific meetings also addressed this topic, as well as an increase in articles published in local and international journals. All of those activities promoted public knowledge regarding the term of nasopharynx, which explains the high proportion of respondents who know the location of nasopharynx.

The highest viral load is located in the nasopharynx. The nasopharynx could be a source of examination for several diseases. On the other hand, the nasopharynx could be the origin of certain diseases. Previous study showed that social media have a cardinal effect in increasing community attention to health information. The news from the mass media could influence the perception of psychology and medical students of a certain disease and public awareness.
health behavior. Informal and formal systematic and massive news regarding the NS is one of the strategies that could affect the perception of the population regarding NPC. Moreover, the multicenter awareness program in Indonesia reported that it can significantly increase NPC knowledge among health workers, especially after education and training programs.

We found that the knowledge of NPC was higher in the western part than in the middle part. There are many reasons that support this finding. The SRY has the highest human development index in Indonesia, while West Sumatera and South Sulawesi were in the middle, and West Nusa Tenggara was in lower rank based on the national statistics bureau.

After the COVID-19 pandemic has already ended, the community knowledge regarding the swab nasopharynx will be retained until a certain time. The study on knowledge of NPC found that it will be retained for more than 1.5 years. Therefore, the physicians and stakeholders who are responsible for managing the NPC should take advantage of this phenomenon. The better population's knowledge about a certain disease the better awareness will occur.

According to this finding, the authors proposed the strategy on NPC management should include social media to promote community knowledge. There was a relationship between the use of social media to the better health behavioral intention via self-efficacy due to health literacy and health related social media. Furthermore, the continuous use of health-related social media may affect the consciousness of family member to implemented a better healthy behavior.

There are several limitations in this research including the unequal distribution of sample size between the regions, no data in the eastern part of Indonesia, and the use of an online questionnaire. Although the use of online questionnaires in the era of COVID-19 is common, it is advisable to conduct focus group discussion to explore the knowledge of respondents. Future research should be addressed to gain a better result to check the reliability of this result. Research in the eastern part of Indonesia and other countries is needed to complete the pattern.

CONCLUSION
The high knowledge of NPC and nasopharynx in this study might be a positive impact of the COVID-19 pandemic. The influence of the massive information regarding COVID-19 and nasopharyngeal swab procedures is one of the factors that may affect this pattern. The strategy on combating NPC should include the social media platform to increase the community knowledge. Therefore, preventive action and early case detection can be promoted.

CONFLICT OF INTEREST
All authors stated that they don't have any competing of interest.

ETHICAL CLEARANCE
The ethical clearance was granted by the ethical committee, Faculty of Medicine, University of Mataram (No: 348/UN18.F7/ETIK/2021). All participants were recruited voluntarily.

FUNDING
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AUTHORS CONTRIBUTION
HK, DAZ, FRA, CW: drafted the manuscript; HK, DY, DAZ, SR, CH, NAP: data collection; DAZ: statistical analysis; HK, CW, FRA: finalized the manuscript; all authors agree with the final manuscript.

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ABSTRACT

Background: Scabies is a skin disease caused by *Sarcoptes scabiei varieties hominis*. The prevalence of scabies in Indonesia in 2018 is 5.6% - 12.95%. Scabies is often found in nursing homes, dormitories, orphanages and Islamic boarding schools. Even though the students have good knowledge of scabies, the incidence of scabies in Islamic boarding schools is still high and is an unresolved problem. The purpose of study was to find out how the management of Islamic boarding schools views the incidence of scabies in students.

Methods: This is a qualitative study with a phenomenological design that examines the views of Islamic boarding school managers on the incidence of scabies in students at the Al-Raisiyah Islamic boarding school, Mataram, Indonesia.

Results: The manager of the Al-Raisiyah Islamic boarding school considers that scabies is a common disease in Islamic boarding schools. Islamic boarding school managers have not been optimal in providing attention related to scabies, even though the number of cases of scabies at Al-Raisiyah Islamic boarding school has been large. Prevention efforts that have been carried out by the management of Islamic boarding schools are related to public sanitation, such as cleaning schedules in classrooms and dormitories, as well as handling efforts by bringing scabies-infected students to the nearest health service.

Conclusion: There are no specific regulations or policies regarding the prevention and treatment of scabies in students at the Al-Raisiyah Islamic boarding school, Mataram, Indonesia.

Keywords: scabies, perception, policy, Islamic boarding school management.

INTRODUCTION

Scabies public health disease caused by *Sarcoptes scabiei varieties hominis*. The World Health Organization (WHO) reports 300 million cases around the world each year. The prevalence of scabies is high in hot and densely populated tropical countries such as Indonesia, around 5.6% - 12.95% (ranks 3rd out of the 12 most common skin diseases). Scabies can reduce the quality of life of sufferers due to feelings of shame in social interactions, interfere with the concentration of study, work, and rest, and also can cause secondary infection by *Streptococcus* and post streptococcal acute glomerulonephritis. About 40% of glomerulonephritis sufferers are the result of scabies with secondary infection.

Many factors trigger scabies infection, such as: age, gender, level of personal hygiene, use of shared items, economic level, culture, residential density, level of education and knowledge about scabies. Scabies is often found in densely populated areas where people live together in one building, such as nursing homes, dormitories, orphanages and Islamic boarding schools.

Several Islamic boarding school studies concluded that the level of knowledge of students about scabies is in the good category but the incidence of scabies is still high. The prevalence of scabies infection at Al-Aziziyah Islamic Boarding School, Gunung Sari, West Nusa Tenggara Province in 2015, is 95.69%. Based on this background, scabies is still an unresolved problem in Islamic boarding schools, so that the perceptions and actions of managers of an Islamic boarding school are needed to fight scabies. The study aims to find out views of Islamic boarding school managers against the incidence of scabies in students, as well as to find out the policies that have been implemented by Islamic boarding school managers in handling scabies. The study took place at the Al-Raisiyah Islamic Boarding School, Mataram, Indonesia which had been established since 1987 and had many students.

METHODS

This qualitative research with a phenomenological design was done by using the form of the views of the management of the Islamic boarding school on the incidence of scabies in students at the Al-Raisiyah Islamic boarding school, Mataram, Indonesia. The collected data were analyzed descriptively in the form of written words from study informants in July - August 2023.

This study used a purposive sampling technique. The criteria for informants in this study were the managers of the Al-Raisiyah Islamic boarding school who were considered to have authority, policies, and authority related to aspects of student activities. There were 9 informants in this study consisting of 6 managers, 2 male students and 1 female student.

RESULTS

The result of deep interview with the managers of the Al-Raisiyah Islamic boarding school are as follows:
1. Knowledge and perceptions of managers about causes of scabies
   “...in my opinion, scabies is a disease that should not be considered normal in Islamic boarding schools because it can interfere with students' learning activities and rest, which is worrying that it can affect academic grades. ...from what I've read, the cause of scabies is a type of parasitic flea, but I don't know more specifically about its name.”

2. Knowledge of Islamic boarding school managers about scabies transmission
   “...scabies can be transmitted through the sharing of items, such as towels, clothes, gloves, shoes, bedding, toiletries, and when they come into contact with the patient's skin.”

3. Knowledge of Islamic boarding school managers about symptoms of scabies
   “The symptom is itching, then what I feel most often is at night. The areas that itch most often are around the groin and hands.”

4. Number of scabies cases at Al-Raisiyah Islamic boarding school
   “...all of the students of the Al-Raisiyah Sekarbela Islamic boarding school have had scabies. For example, if a new student enters after a few weeks, they will definitely get scabies, so both old students and new students must have had scabies. “...as far as I can remember there are 3-6 students who have had scabies every year.”

5. Handling carried out by boarding school managers for students infected scabies
   “...If there are students who are sick, we first contact the parents/guardians of the students for independent medical treatment. But sometimes the parents/guardians of the students bring the medicine directly to the hut so there is no need to take it to the public health center.”

6. Prevention carried out by Islamic boarding school managers against scabies
   “In my opinion, there are a number of preventive measures that have been implemented at the Islamic boarding school, namely the picket schedules in classrooms and dormitories, collaboration with the local health center for counseling and we always remind students not to lend each other things such as clothes and towels.”

7. Regulation implementation by Al-Raisiyah manager regarding scabies
   “I think there is no specific policy related to scabies at the Al-Raisiyah School, the leadership of the Islamic boarding school is not too concerned about this scabies disease. They think the scabies problem can be handled by the supervisor of the Islamic boarding school so that the leadership of the Islamic boarding school does not need to intervene until they make special regulations regarding this disease.”

8. Suggestions for clean water at Al-Raisiyah Islamic boarding school
   “We are here using water from drilled wells, and there are 2 wells. Water is used for various things such as washing, bathing, ablution and cooking. Even one of our wells has potable water.”

DISCUSSION
Most of the informants knew that scabies transmission could be through contact with infested objects such as towels, blankets, or upholstery of furniture and could also be through direct skin-to-skin contact. Overcrowding in a dormitory can increase the risk of direct or indirect physical contact, thereby increasing a person's risk of being infected with scabies. The manager of the Islamic boarding school has made regulations related to sanitation such as the prohibition on the use of personal equipment such as towels, clothing and toiletries together, as well as a schedule for cleaning classrooms and dormitories for students. These results are in line with several studies which state that scabies is most often found in densely populated environments, and the density of a residence can increase the risk of direct or indirect physical contact, thereby increasing the risk of scabies. Sharing items such as sleeping equipment, toiletries and clothing also increases the risk of spreading scabies.9-11

Itching was the most common symptom and the symptoms were most often felt at night, that caused by the activity of mites that increases in humid temperatures, hot weather or when sweating. The itching often appears in areas such as between the fingers, around the armpits, elbow folds, thigh folds, around the buttocks, navel area, as well as around the chest or papilla mammae in women.12

The students who are infected by scabies would be taken for treatment to the public health center by the boarding school manager or parents of the students when picking up their children for self-medication purposes. The school managers only prevent scabies infestation by asking students to always maintain personal hygiene (not borrowing clothes, towels, toiletries, prayer equipment and other personal items) and sanitation (maintain the cleanliness of the environment of class and dormitory regularly, but the evaluation of regulation have not yet been implemented. The collaboration with the public health center has not been carried out regularly. Clean and Healthy Living Behavior is one of the efforts that can be made to prevent scabies. Preventing scabies among dense community can be done by avoiding direct contact (skin to skin) each other who suffer scabies.13,14

The results showed there were no specific regulations related to the prevention of scabies as well as the personal and environmental hygiene were not done under strict control. The prevention of scabies specifically such as mass drug administration (permethrin) to students has not been carried out. This drug administration technique can be carried out at each return and arrival of the students to break the cycle of scabies spreading from inside and outside the hut.15

CONCLUSION
The manager of the Islamic boarding school considers scabies as a common disease among students and does not require special treatment efforts. The hygiene and sanitation regulations have not been carried out strictly, and evaluation of regulation have not yet been implemented. Efforts to prevent scabies by mass drug administration such as permethrin have not been carried out.

CONFLICT OF INTEREST
The authors affirmed that there were no conflicts of interest in this study.
FUNDING
The authors were responsible for all research funding without obtaining financial support.

ETHICAL CONSIDERATIONS
Certificate from Faculty of Medicine, University of Mataram with No: 276/UNI8.F8/ETIK/2023.

AUTHOR CONTRIBUTION
All authors contributed equally in this research and publication of this manuscript.

REFERENCES
ABSTRACT

Background: *Staphylococcus aureus* is a highly pathogenic Gram-positive bacterial group that has resistance to antimicrobial agents. In Indonesia, the prevalence of *Staphylococcus aureus* infection is 28% of the total cases of infection and exhibits an upward trend annually. The escalation of treatment and care expenses poses a significant challenge for global healthcare. Sumbawa honey (*Apis dorsata*) is a viable natural antimicrobial option that exhibits the potential to prevent the resistance tendencies of *Staphylococcus aureus*.

Methods: It is a laboratory experiment to compare effectiveness of Sumbawa honey (*Apis dorsata*) as an antibacterial therapy against *Staphylococcus aureus* isolates (ATCC 25923).

Results: The study indicates that *Apis dorsata* exhibited antibacterial properties against *Staphylococcus aureus* (ATCC 25923). The inhibition zone observed was 8 mm at a concentration of 100%, 18.4 mm at a concentration of 75%, 9 mm at a concentration of 50%, and 5.4 mm at a concentration of 25%. Vancomycin as a positive control shows an inhibition zone measuring 23 mm. The best antibacterial efficacy of *Apis dorsata* is found at a concentration of 75% (compared to a concentration of 100%).

Conclusion: The concentration of 75%, exhibits the most potent antibacterial activity in inhibiting the growth of *Staphylococcus aureus* isolates.

Keywords: *Apis dorsata*, *Staphylococcus aureus*, zone of inhibition.

INTRODUCTION

*Staphylococcus aureus* is widely recognized as a highly pathogenic microorganism within the Gram-positive bacterial group, known for its propensity to cause both nosocomial and community-acquired infections. *Staphylococcus aureus* is classified as an opportunistic bacterium that typically resides within the human microflora. However, it exhibits a propensity to initiate infection when the host has impaired immune system. The incidence of *Staphylococcus aureus* in Indonesia reaches 28% of all cases of infection and will continue to increase every year. The prevalence of *Staphylococcus aureus* infection and the emergence of antibacterial resistance contribute to elevated hospitalization expenses and heightened rates of patient morbidity and mortality.

Sumbawa honey (*Apis dorsata*) is known to possess antibacterial properties including hydrogen peroxide, flavonoids, essential oils, and a variety of other organic compounds. The antibacterial properties of honey are influenced by factors such as high osmolarity effects, low water activity, and low pH, resulting in a high level of acidity. Several studies stated that honey has been found to contain natural antibacterial compounds such as flavonoids, saponins, and tannins, which exhibit antibacterial properties.

METHODS

A laboratory experimental study was conducted at the Microbiology and Pharmacology laboratory, Faculty of Medicine, Universitas Mataram, from March to August 2023. The aim of the experiment was to investigate the potential antibacterial effect of Sumbawa Honey (*Apis dorsata*) against *Staphylococcus aureus* isolates (ATCC 25923). The Sumbawa Honey has obtained certification under the identification number IDM000168988. Honey consisted of concentrations of 25%, 50%, 75%, and 100%, Vancomycin as a positive control, and Aquadest as a negative control, each groups consist of four replicants. The data was subjected to analysis using a one-way ANOVA test, employing the SPSS software. The objective was to investigate the impact of Sumbawa as an antibacterial agent on the growth of *Staphylococcus aureus* (ATCC 25923).

RESULTS

In general, the outcomes of antibacterial research experiments indicated that different concentrations of the Sumbawa honey exhibited inhibitory effects on *Staphylococcus aureus* (ATCC 25923). The zone of inhibition test demonstrates the inhibition of bacterial growth. All concentrations of *Apis dorsata* 25%, 50%, 75%, and 100% showed inhibitory effects to the growth inhibition of *Staphylococcus aureus*. The highest level of antibacterial efficacy is observed
at a concentration of 75% (Table 1). Phytochemical screening was conducted to identify the constituent compounds present in Sumbawa Honey (Apis dorsata). The tube test observed alterations in color and the formation of precipitates subsequent to the introduction of test reagents (Table 2 and Figure 1).

According to the results of the phytochemical screening test, it was determined that Sumbawa honey (Apis dorsata) contains flavonoid compounds. This was confirmed by the presence of black tannins, which indicated a positive result, as well as the formation of dark red flavonoids, also indicating a positive result. Additionally, the presence of violet/brown saponins, accompanied by the formation of stable froth, further supported a positive result. The presence of a brown ring formation serves as an indicator for a positive outcome in the detection of steroids.

### DISCUSSION

The experiment conducted involved testing the antibacterial activity of various concentrations of Apis dorsata against Staphylococcus aureus (ATCC 25923). The results indicated that there was a discernible variation in the diameter of the inhibition zone. The zone of inhibition resulting from the concentration of Apis dorsata increases proportionally with its concentration, except for a honey concentration of 100%. A hohudaney concentration of 75% exhibits a larger zone of inhibition compared to a honey concentration of 100%. A honey concentration of 75% exhibits superior antibacterial activity compared to a honey concentration of 100%, because the viscosity of Sumbawa honey caused its limited ability to permeate the disc paper and disperse within the medium. The highest level of antibacterial efficacy of Musi Rawas Forest honey exhibited an increase in the inhibition zone when used at concentrations ranging from 10% to 70%. However, at concentrations of 80% and 90%, a decrease in the zone of inhibition was observed.

The zone of inhibition is attributed to the presence of flavonoids, saponins, and tannins in honey. Flavonoids can be attributed to their lipophilic nature, which leads to the disruption of microbial membranes and interference with the activity of peptidoglycan transpeptidase. Consequently, the formation of the bacterial cell wall is disrupted, resulting in cell lysis. Saponin exhibits antibacterial properties by interacting with the bacterial wall, causing its disruption and the subsequent breakdown of surface tension. This disruption facilitates the entry of antibacterial substances into the bacterial cell, ultimately leading to bacterial death. Tannin exhibits the activity of reverse transcriptase and DNA topoisomerase.
enzymes, thereby impeding the formation of bacterial cells. Tannins possess the ability to impede bacterial proliferation through their interference with protein transportation, inactivation of cell adhesins and enzymes within bacterial cells.\textsuperscript{10-13}

The zone of inhibition is attributed to the elevated levels of sugar present in honey, which effectively hinder the growth and progression of \textit{Staphylococcus aureus} by exerting osmotic pressure. The presence of high sugar molecules, a low acidic pH ranging from 3 to 4, and a low water content ranging from 0.562 to 0.620 has been observed to result in the loss of bacterial viability to survive.\textsuperscript{14} Moreover, honey is known to possess radical hydrogen peroxide ($H_2O_2$) compounds that exhibit antibacterial properties, capable of eliminating bacteria and various pathogenic microorganisms. These compounds exhibit reactivity towards the functional groups present in biomolecules within bacterial cells, resulting in their damage. The catalase enzyme present in honey rapidly catalyzes the decomposition of hydrogen peroxide ($H_2O_2$), a substance commonly employed for bactericidal purposes, into water and oxygen.\textsuperscript{15} Variations in the duration of honey storage can also impact the magnitude of the clear zone observed in honey concentrations. This phenomenon is influenced by the composition of honey’s reducing sugar content, which in turn affects the functional characteristics of honey. Specifically, it affects the water-holding capacity of honey, and its ability to prolong its life, and the hygroscopic properties derived from glucose and fructose. Consequently, in cases where honey exhibits low compound content and insufficient honey storage during the incubation process at 37°C for a duration of 24 hours, it is expected that the diameter of the inhibition zone will decrease at varying concentrations of honey.

**CONCLUSION**

There is antibacterial effect of Sumbawa Honey (\textit{Apis dorsata}) at concentrations of 25\%, 50\%, 75\%, and 100\% against \textit{Staphylococcus aureus} isolates. The best antibacterial effect against \textit{Staphylococcus aureus} isolates is Sumbawa Honey (\textit{Apis dorsata}) with a concentration of 75%.

**CONFlict of Interest**

All authors declare there is no conflict of interest regarding publication of this report.

**Ethical Clearance**

Ethical clearance certificate number from Faculty of Medicine No: 285/UN18.F8/ETIK/2023.

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None.

**Authors Contribution**

All authors had contributed in manuscript writing and agreed for the final version of the manuscript for publication.

**References**

Examining referral communication in maternal healthcare: Perceptions, gaps, and opportunities for improvement

Dian Puspita Sari1*, Yoga Pamungkas Susani1, Rizkinov Jumsa1, Mohammad Rizki1

ABSTRACT

Background: Effective communication is crucial for high-quality and continuous maternal care. However, a lack of communication between providers often cited in the literature. Exploring maternal Primary Care Providers’ (PCPs) perspectives on referral communication in Indonesian setting can uncover barriers, facilitators, and potential solutions for the problem. This study aimed to explore the frequency and content of referral and reply letters as perceived by maternal PCPs and to examine PCPs’ perspectives and experiences with referral communication, focusing on reply letters and feedback.

Methods: A convergent parallel mixed-methods approach was used, including a survey assessing the frequency and content of referral and reply letters, and semi-structured interviews. Participants were GPs and midwives from ten purposively selected CHCs in West Lombok.

Results: Among 117 respondents, 76.1% consistently sent referral letters containing patient history, examinations, diagnoses, and treatment details. However, 41.9% reported infrequent receipt of reply letters. Interviews with 20 PCPs identified various communication channels and the role of local government in facilitating the communication. Nonetheless, there was a lack of timely and adequate feedback. PCPs perceived an imbalance of responsibility in referral communication with specialists, with more responsibility placed on communication prior to referral than on the feedback.

Conclusion: This study highlights a gap in referral feedback, emphasizing the need to establish specific mechanism for feedback delivery and to address the perceived responsibility imbalance.

Keywords: referral communication, maternal healthcare, primary healthcare provider, reply letters, referral feedback.

INTRODUCTION

Appropriate referrals are necessary for women and newborns with conditions that cannot be effectively managed with available resources. To achieve it, appropriate information exchange and feedback between involved healthcare personnel is crucial.1 However, the literature highlights a lack of communication between care providers during the referral process,2 leading to delayed and inappropriate referrals3 and poor maternal health outcomes.4 Exploring Primary Care Providers (PCPs) perspectives on referral communication can uncover barriers, facilitators, and potential solutions for the problem. Thus, this study aims to examine the frequency and content of referral and reply letters as perceived by maternal PCPs and to explore PCPs’ perspectives and experiences with referral communication, focusing on reply letters and feedback. This study will answer the following research questions: (1) What are the frequency and content of referral and reply letters in maternal care? (2) What are PCPs’ perspectives and experiences with referral communication, particularly focusing on post-referral feedback?

METHOD

This study used a mixed-methods design with a convergent parallel approach.5 Participants in this study were GPs and midwives actively providing maternal healthcare in Community Health Centers (CHCs) in West Lombok district, Indonesia. Ten CHCs were purposively selected from 20 CHCs to represent each sub-district, rural and urban areas, and CHCs with and without inpatient care. A survey was used to assess the frequency and content of referral and reply letters, and the data was analyzed descriptively. Semi-structured interviews were conducted with ten GPs and ten coordinating midwives to explore experiences of referral communication and perceptions of reply letters. The interview transcripts were analyzed thematically6 using an inductive approach. The study was conducted from July to September 2022.

RESULTS

A total of 119 PCPs completed the survey, with only two being male. The median respondent age was 35 years with an age range from 22 to 55 years, and their median professional experience was 12 years, varying from 0 to 35 years. Among the participants, 117 (98.3%) had referred patients to hospitals, hence underwent the analysis.

Eighty-nine (76.1%) participants consistently sending referral letters containing patient history, physical exams, diagnoses, and treatment details. The majority also specified referral purposes (105, 89.7%) and timing (103, 88%). Despite this, 49 (41.9%) reported frequent receipt of referral letters, and 117 (98.3%) had referred patients to hospitals, hence underwent the analysis. Eighty-nine (76.1%) participants consistently sending referral letters containing patient history, physical exams, diagnoses, and treatment details. The majority also specified referral purposes (105, 89.7%) and timing (103, 88%). Despite this, 49 (41.9%) reported frequent receipt of referral letters, and 117 (98.3%) had referred patients to hospitals, hence underwent the analysis. Eighty-nine (76.1%) participants consistently sending referral letters containing patient history, physical exams, diagnoses, and treatment details. The majority also specified referral purposes (105, 89.7%) and timing (103, 88%).

Residual

follow-up plans (41.9%).

Four main themes emerged from the interviews regarding referral communication. The first theme, “Communication with patients,” pertains to informing patients and their families about the necessity and urgency of the referral, the process, outcomes, and subsequent follow-up. In contexts where rural patients were hesitant to be referred outside their village, referral replies’ informative content gained significance.

The second theme, “Communication with specialists” portrays one-way communication from PCPs to specialists to obtain referral approval. This interaction utilized diverse channels such as referral notes, text messages and phone calls to hospital numbers, and group WhatsApp. The establishment of a Group WhatsApp consisting of PCPs and specialists in the district is facilitated by the local government, aimed to streamline the communication process from primary care to the hospital and reduce waiting times. Despite these channels, feedback on referral was rare. The PCPs felt an imbalance of responsibility in referral communication, as indicated by a GP: “When referring we always send referral letters. However, so far, the hospital is not required to send referral replies to us.”

The “Referral Communication Artifacts” theme includes various forms of communication between CHCs and hospitals during referrals. Referring facilities typically provide referral letters, the pink book, the patient’s partograph, and text messages to convey the referral plan. In the absence of reply letters, PCPs used alternative sources for patient information, such as hospital handover notes brought back by the health professionals who assisted the referred patients, discharge summaries, and consultation appointment letters. We summarized the interactions among the four themes in figure 1.

**DISCUSSION**

Despite the formal requirement for referral facilities to inform patients’ condition back to the referring facilities, our findings indicate the lack of referral feedback. Several issues contribute to the lack of feedback in this study: depending on patients for delivering the reply letter, inadequate information in referral replies, illegible handwriting, and the perceived imbalance of responsibility in referral communication with specialists, with more responsibility placed on communication prior to referral than on the feedback.

The lack of referral feedback was also reported by another study in Indonesia as well as in other countries, particularly in low- and middle-income countries. Assumption of patient’s problem being solved is mentioned as the reason hospitals tend to neglect providing referral feedback. In addition, the lack of specific feedback mechanisms, i.e. how the feedback should be delivered to the referring facilities hinder the implementation of referral feedback.

The current study reveals availability of various communication channels between PCPs and specialists, including a group WhatsApp, and the government’s role in facilitating referral communication. The use of private WhatsApp group for referral communication have been proven to be feasible in low-resource settings. However, align with the current study, this platform is mainly used for pre-referral communication and notification to higher facilities, with feedback accounting for less than 10%. The government can encourage two-way communication between hospitals and PCPs through the existing WhatsApp group to address this issue.

**CONCLUSION**

This study highlights a gap in communication feedback, emphasizing the need to establish specific mechanisms for feedback delivery and to address the perceived responsibility imbalance. These measures can enhance referral processes and contribute to more efficient and patient-centered maternal healthcare referrals.

**CONFLICT OF INTEREST**

All authors declare no conflict of interest.
FUNDING
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ETHICS
Ethical clearance certificate was obtained from the Health Research Ethics Committee of the Faculty of Medicine, University of Mataram No. 124 / UN18.F7 / ETIK / 2022.

AUTHOR CONTRIBUTIONS
DPS and YPS contributed to the design of the study, conducted the interviews and analysis, and write the manuscript. RJ and MR provided input to the manuscript.

REFERENCES
Analysis of referral characteristics of obstetric cases and maternal outcomes at the University of Mataram Hospital, Indonesia

Theophany Margareta Kurniawan¹, Meilisva Audila Anggraini², Muhammad Rizkinov Jumsa³, Dian Puspita Sari*³

ABSTRACT

Background: The Maternal Mortality Rate (MMR) in Indonesia shows a downward trend but is still above the target. Various efforts to reduce MMR have been carried out, including a tiered referral system. However, multiple factors affect its implementation hence also the outcomes. This study aimed to investigate the relationships between characteristics and outcomes of obstetric referrals in a type-C hospital in Mataram, Indonesia.

Methods: We retrospectively reviewed the medical records of obstetric patients referred to the University of Mataram Hospital from January 2020 to July 2022. Patients' demographics, obstetric history, referral characteristics, mortality and morbidity outcomes were collected from the medical records.

Results: Out of 353 referrals, 52.1% were between 20-29 years old, 38.5% completed senior high school; 86.4% were referred by a community health center; 60.9% from outside Mataram; 45% were nulliparous; 86.7% were in the third semester of pregnancy; 86.1% were in labor, and 36.3% were late referrals. All mothers were alive, but 10.8% stayed for >3 days. A significant association was found between maternal age and referring facility with length of stay (p < 0.001 and p = 0.001, respectively).

Conclusion: Patients' age and the referring facility were related to maternal morbidity.

Keywords: obstetric referral, maternal outcome, fetal/neonatal outcome.

INTRODUCTION

Despite the downward trend in Maternal Mortality Rate (MMR) from 1991 to 2015, Indonesia's MMR has not reached the target of the 2030 Sustainable Development Goals and is still three times higher than the 2015 Millennium Development Goals' target. In West Nusa Tenggara in 2020 there were 122 cases and increased to 144 cases in 2021.¹

The most common problem is due to delays in the referral process.² Various factors affect referral process, such as pregnancy conditions, demographics, geography, socio-economic, competence of health workers, and the ability of health facilities.²,³ Effective referrals play significant roles in improving the quality of maternal care to prevent death due to late management of complications.¹

The objective of this study is to evaluate the relationship between referral characteristics and maternal outcomes of patients referred to the University of Mataram Hospital, an academic hospital in West Nusa Tenggara, Indonesia.

METHODS

We conducted a retrospective review of the medical record of maternal patients referred to the University of Mataram Hospital from January 2020 to July 2022. Data collected were patients' demographics (age, education, region), obstetric history (parity and gestational age), and referral characteristics (referring facility and referral time). Maternal outcomes studied were patient mortality, and morbidity as indicated by length of stay in the hospital: ≤3 days or >3 days. Statistical analysis was carried out using Chi-square and Fisher's exact test.

RESULT

A total of 353 maternal patients were referred to the hospital from 1 January 2020 to 31 July 2022. The mortality of the referred patients was zero, but 10.8% were hospitalized more than three days, indicating maternal morbidity. Patients' characteristics and morbidity outcomes are presented in table 1. A significant association was found between maternal age, referral origin, and maternal morbidity.

DISCUSSION

This study aims to determine the relationship between the characteristics and outcomes of maternal patients referred to the University of Mataram Hospital.

More than half (52.1%) of referred patients were between 20-29 years, which is the best age for pregnancy.⁴ Patients below or above the age range have a greater risk of pregnancy,⁴ due to physical, mental, and reproductive readiness factors.⁵ In this study, the patient's age significantly impacted hospitalization duration; a higher proportion of those below 20 and above 40 stayed more than three days. This finding aligns with another study conducted in Indonesia⁶ which also found a significant relationship between maternal age and complications during pregnancy.

Studies showed that education affects...
risk perception, healthcare utilization, understanding of health information, and Antenatal Care adherence.\textsuperscript{37} This finding aligns with another study in Indonesia,\textsuperscript{8} which also found a significant relationship between education and knowledge of high-risk pregnancy factors.

Although we did not find a significant association between regions and morbidity outcome, the literature suggests mortality risks increase as the distance between patients’ homes and health facilities increases.\textsuperscript{9} In addition, the possible absence of an association between parity and maternal morbidity is due to variations in the clinical conditions of patients in this study.

Referring facilities impact patient morbidity, as secondary care referrals show higher morbidity (34.6%). This is probably due to more complex issues, inadequate screening, and referral delays.\textsuperscript{8} For the referral timing matters, 86.1% were referred during intrapartum. Intrapartum referrals can be anticipated by recognizing the risk factors that can occur in pregnant women so as to reduce the risk of complications due to intrapartum referrals.\textsuperscript{11}

\section*{CONCLUSION}
Younger and older maternal age, and being referred from secondary healthcare facilities are associated with longer hospitalization.

\section*{CONFLICT OF INTEREST}
All authors declares that they have no conflict interest.

\section*{FUNDING}
No funding.

\section*{ETHICS}
This study was approved by the Health Research Ethics Committee Faculty of Medicine, University of Mataram (No.266/UN18.F7/ETIK/2022).

\section*{AUTHOR CONTRIBUTION}
TMK and DPS conceptualized this study. TMK carried out data collection, analysis and wrote the manuscript. All authors analyzed the data and revised the manuscript.

\section*{REFERENCE}
5. Komariah S, Nugroho H. Hubungan pengetahuan, usia dan paritas dengan kejadian

\begin{table}[h]
\centering
\caption{Characteristics and maternal referral outcomes} 
\begin{tabular}{|l|c|c|c|c|}
\hline
Variable & Maternal Morbidity & Treat & Total (100\%) & \multicolumn{1}{c|}{p-value} \\
 & Age (N=353) & Treated ≤ 3 days & Treated > 3 days & \\
\hline
Age & & & & \\
< 20, ≥ 40 y.o. & 41 (75.9\%) & 13 (24.1\%) & 54 & 0.001** \\
20 – 29 y.o. & 173 (94\%) & 11 (6\%) & 184 & \\
30 – 39 y.o. & 100 (87.8\%) & 14 (12.2\%) & 114 & \\
\hline
Education (N=287) & & & & \\
Low & 107 (87\%) & 16 (13\%) & 123 & 0.677 a \\
Middle & 123 (90.4\%) & 13 (9.6\%) & 136 & \\
High & 25 (89.3\%) & 3 (10.7\%) & 28 & \\
\hline
Region (N=351) & & & & \\
Mataram & 117 (86\%) & 19 (14\%) & 136 & 0.132 a \\
Outside Mataram & 196 (91.2\%) & 19 (8.8\%) & 215 & \\
\hline
Parity (N=353) & & & & \\
Nulliparous & 143 (89.9\%) & 16 (10.1\%) & 159 & 0.906 a \\
Primiparous & 98 (89.1\%) & 12 (10.9\%) & 110 & \\
Multiparous & 74 (88.1\%) & 10 (11.9\%) & 84 & \\
\hline
Region (N=353) & & & & \\
1st and 2nd trimester & 30 (96.8\%) & 1 (3.2\%) & 31 & 0.227 b \\
3rd trimester and postpartum & 285 (88.5\%) & 37 (11.5\%) & 322 & \\
\hline
Referring facility (N=352) & & & & \\
Primary care facility & 297 (91.1\%) & 29 (8.9\%) & 326 & 0.001** \\
Secondary care facility & 17 (65.4\%) & 9 (34.6\%) & 26 & \\
\hline
Referral time (N=353) & & & & \\
Intrapartum & 271 (88.6\%) & 35 (11.4\%) & 306 & 0.298 a \\
Ante and postpartum & 44 (93.6\%) & 3 (6.4\%) & 47 & \\
\hline
Total & 315 (89.2\%) & 38 (10.8\%) & 353 & \\
\hline
\multicolumn{4}{l}{a = Chi-square Test; b = Fisher’s Exact Test; *p<0.05; **p<0.01} \\
\end{tabular}
\end{table}


INTRODUCTION

Fungi are significant in causing opportunistic infections in HIV/AIDS patients. Some fungal infections may have mild clinical manifestations or severe clinical manifestations with poor prognosis. The incidence of opportunistic fungal infections is a significant problem related to the ability to detect these fungal infections and the availability of antifungal drugs.

The spectrum of opportunistic fungal systemic infections in Indonesia has not been widely studied. This study aims to detect opportunistic fungi in HIV/AIDS patients' blood samples. The success of detecting the presence of fungi in the blood will provide clinicians with information that can be used in dealing with HIV/AIDS patients, resulting in improved clinical outcomes for HIV/AIDS patients.

METHODS

This was a cross-sectional observational study. The study sample consisted of blood samples from HIV/AIDS patients with suspected bloodstream infections who were over 18 years old and had complaints of fever for more than three days, as well as CD4+ counts of <200 cells/ul. HIV/AIDS patients taking 200 mg of Fluconazole were excluded from this study.

Blood samples were taken per regular operating protocols. Blood was inoculated into a BacT/Alert FA Plus bottle and incubated on the BACT/ALERT automatic culture machine for ten days. Positive blood cultures were subcultured onto Sabarouds Dextrose Agar (SDA) media and incubated at 25°C and 37°C, up to four weeks. Microscopic and macroscopic morphological observations were used to identify hypha. The microscopic morphology of the fungal hypha was evaluated using Lactophenol cotton blue staining. The yeast colonies were identified using VITEK 2 systems (bioMérieux).

RESULTS

Fungal isolates were found in 7 (22.6%) of the 31 research subjects who underwent blood culture, while fungal growth was not found in 77.4% (24/31) of the blood specimens. The fungi isolated included 5 (16.1%) isolates of *Penicillium marneffei*, 1 (3.2%) isolates of *Cryptococcus laurentii*, and 1 (3.2%) isolates of *Histoplasma capsulatum*. Of the 7 HIV/AIDS patients with fungaemia, 100% (7/7) had weight loss, 85.7% (6/7) had oral ulcers, 71.4% (5/7) had cough, 57.1% (4/7) had skin lesions, and 71.4% (5/7) had received antiretroviral therapy and 100% (7/7) had CD4+ counts < 100 cells/ul. Total CD4+ levels among HIV patients with fungaemia were as low as six cells/ul and as high as 99 cells/ul, with an average CD4+ count of 28.7 cells/ul.

DISCUSSION

The profile of opportunistic fungi among HIV patients varies by region. Opportunistic fungal infections among HIV patients remain a significant concern in high-HIV-prevalence areas, hospitalised patients with advanced HIV stage and low CD4+ cell counts, or patients with persistently low CD4+ cell counts due to noncompliance with antiretroviral therapy, resistant to antiretroviral drugs.
or both. In a 12-year study at a Swiss tertiary hospital, *Cryptococcus ssp* (5), *Candida ssp* (4), *Histoplasma capsulatum* (2), and *Penicillium marneffei* (2) were isolated from HIV patients with fungaemia. In a 2004-2008 Thai retrospective cohort study of 140 HIV patients with bloodstream infection (BSI), 24% of fungal isolates were isolated from positive blood cultures. The most common fungal isolate, *Cryptococcus neoformans* (28%), *Penicillium marneffei* (2.7%) and *Histoplasma capsulatum* (0.7%) were also isolated. In this study, 7 (22.6%) isolates of fungi were isolated from 31 HIV patients' blood specimens, including 5 (16.1%) isolates of *Penicillium marneffei*, 1 (3.2%) isolates of *Cryptococcus laurentii*, and 1 (3.2%) isolates of *Histoplasma capsulatum*.

Systemic mycoses caused by *Penicillium marneffei* are known to be endemic in South and Southeast Asia. Talaromycosis is still a health problem in Vietnam and China; it is found in 5-15% of AIDS cases each year and is the cause of HIV-associated bloodstream infection. A review of 407 Histoplasmosis cases in Southeast Asia from 1932 to 2018 revealed that only East Timor and Brunei were disease-free. The most cases were in Malaysia (76), Indonesia (48), Singapore (21), and Thailand (233). Other countries reported only a few cases. Data from 48 cases of Histoplasmosis in Indonesia, 24 cases presented with HIV infection, and 28 cases with disseminated histoplasmosis. According to research on various opportunistic infections of HIV patients conducted in Kuala Lumpur (2001-2002) and Bangkok (2002), 1.5% of HIV patients in Kuala Lumpur and 1% of HIV patients in Bangkok had histoplasmosis.

In this study, from the blood of HIV patients with CD4+ counts of <100 cells/ul, one isolate of *Cryptococcus laurentii* was isolated. A literature review revealed 44 non-neoformans cases, with *Cryptococcus laurentii* being responsible for 18 of them. Several studies have reported isolating *Cryptococcus laurentii* from the blood and cerebrospinal fluid of HIV patients with meningitis.

Our results follow a study by Kawila (2013) that reported clinical symptoms in 86 HIV patients with penicilliosis at Chiang Mai University Hospital in Thailand. Mootsikapun and Srikulbutr (2006) found the same clinical picture in AIDS patients with *Histoplasma capsulatum* and *Penicillium marneffei* infections. This study found three HIV patients with *Penicillium marneffei* fungaemia and one HIV patient with *Histoplasma capsulatum* fungaemia with skin lesions. Siregar C (2018) reported that 49% of fungal isolates were isolated from 43 skin lesions of HIV patients at the Adam Malik General Hospital Medan, with 16 isolates of *Penicillium marneffei* and five isolates of *Histoplasma capsulatum*. The average CD4+ cell count of HIV patients with fungaemia in this study are consistent with those published by WHO (2009) regarding CD4+ levels and the incidence of opportunistic infections, namely Histoplasmosis with CD4+<150 cells/ul and Cryptococcosis and Penicilliosis with CD4+<100 cells/ul. Several approach, for instance zinc supplementation could improve the immunological response (CD4+ cell count). This study found fungaemia in HIV/AIDS patients with CD4+ counts of <100 cells/ul.

**CONCLUSION**

*Penicillium marneffei*, *Cryptococcus lauranteii*, and *Histoplasma capsulatum* were isolated from blood specimens of HIV/AIDS patients at the Adam Malik General Hospital in Medan.

**CONFLICT OF INTEREST**

The author reports no conflicts of interest in this work.

**ETHICAL CLEARANCE**

This study has been approved by the Health Research Ethics Committee of the Faculty of Medicine, Universitas Sumatera Utara, with certificate number 663/TGL/KEPK FK USU-RSUP HAM/2019.

**FUNDING**

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**AUTHORS CONTRIBUTION**

All authors have made intellectual contributions and approved it for publication.

**REFERENCES**

Modulating effect of Heat Shock Protein-70 (HSP 70) in acute ischemic stroke: A review to the recent knowledge

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INTRODUCTION

Stroke is a neurological disorder due to arterial defect in the brain and a life-threatening condition.1 Ischemic stroke is the highest incidence of stroke.2 Blockade brain arterial resulting in decreased blood flow, causing a reduced oxygen supply and neuronal damage.1 Cerebral ischemia causes neuronal signal failure, oxidative stress, production of Reactive Oxygen Species (ROS), and activation of intracellular proteases, lipases, and ribonucleases, which damage cellular integrity resulting in the apoptotic cascade.1,3 Various mechanisms of apoptosis both intra and extracellular involved Heat Shock Protein (HSP). HSP 70 is a chaperon that catalyzes the refolding of protein denaturation. HSP can prevent protein denaturation and aggregation to modulate various signal pathways. Induced HSP 70 can modulate multiple cell death and inflammatory pathways.3 We will discuss the modulating HSP 70 in acute ischemic stroke and the potential mechanism applying to clinical level and therapeutic target.

METHODS

Literature relevant to this review was identified by systematic searches on Pubmed, Pubmed Central, and Google Scholar from 2012 to 2022. Searches used the keywords Heat Shock Protein, Heat Shock Protein 70, Stroke, and Cerebral Ischemia. Experimental and clinical studies and case reports published in the last ten years were included. All research found in electronic databases was screened for titles and abstracts. Articles that do not meet the eligible criteria are excluded.

RESULTS

From a total of 7857 studies discovered across the databases, 38 studies from Pubmed, 35 studies from Pubmed Central, and 45 studies from Google Scholar were included in this study. All of which were studies regarding the role of HSP-70 in neuroinflammation and it’s neuroprotective effect in stroke and cerebral ischemia or infarction.

DISCUSSION

Heat Shock Protein was discovered by Ferruccio Ritossa in 1962.5,6 HSP is a protein that is formed in response to stress and plays an essential role in the synthesis of new proteins and the refolding of damaged proteins. In ischemia, a coordinated stress response will occur to prevent further damage.7 HSP 70 can catalyze brain cells

Keywords: HSP 70, Acute Ischemic Stroke.

ABSTRACT

Background: Stroke is an acute neurological condition that causes death and disability. Cerebral ischemia results in multiple cellular changes. This condition results in the activation of the heat shock protein including Heat Shock Protein 70 (HSP 70), to reduce neuronal damage. The purpose of writing this review is to describe the role of HSP 70 modulation in acute ischemic. Methods: Comprehensive Literature review with search for all the roles of HSP-70 and cerebral ischemia in Pubmed, Pubmed Central, and Google Scholar with keywords Heat Shock Protein, Heat Shock Protein 70, stroke, cerebral ischemia. All past ten years’ experimental, clinical, and case reports were included. Results: Heat Shock Protein (HSP) is a chaperon that can prevent protein denaturation and aggregation and modulate various signal pathways. Ischemic stroke causes hypoxia in cells that activate the HSP-HSF complex. This activation causes oligomerization, translocation to the nucleus, and binding to the promoter region of various HSPs, accelerating the mRNA transcription and translation. Research shows that overexpression of HSP 70 has a neuroprotective effect against neuronal cell death, so HSP 70 increases neuroprotection, improves functional stress in cells during stroke, and improves functional outcomes. Modulation of HSP 70 can be carried out, one of which is by administering anti-oxidants and anti-apoptotic drugs, which can increase HSP 70 expression so that it increases the neuroprotective effect in cerebral ischemia conditions to improve neurological deficits. Conclusion: HSP 70 is neuroprotective. Modulating HSP 70 levels in cerebral ischemia can increase neuroprotection’s effect and improve functional outcomes in ischemic stroke.
and influence the expression of the HSP 70 family chaperones. Ischemic stroke model induce a robust expression of HSP 70 in brain neurons, the penumbra, and blood, which occurs within 24-48 hours after ischemia. Studies using immunohistochemistry show that HSP 70 protein is expressed in neurons in the cortex around the infarct area and in the blood vessels of the ischemic area. Research shows that overexpression of HSP 70 has a neuroprotective effect against neuronal cell death, so HSP 70 increases neuroprotection and improves functional stress during a stroke and improve functional outcome.

Neuroinflammation induces an increase of cytokines and chemokines, glial cell activation, and leukocyte infiltration. Neuroinflammatory activation begins with activating pattern recognition receptors (PRR) such as Toll-like receptors (TLR). These receptors recognize any signal that induces an immune response. Tissue damage due to stroke, triggers the release of danger-associated molecular patterns (DAMP), which causes an inflammatory response. HSP 70 can modulate various inflammatory pathways. Overexpression of HSP 70 can reduce the formation of pro-inflammatory mediators in glial cells and reduces neuronal damage. Brain cell damage, intracellular HSP 70 acts as an anti-inflammatory capable of blocking proinflammatory molecules such as Matrix Metalloproteinase (MMP) and inhibiting Nuclear Factor Kappa Beta (NFκβ). Extracellular HSP 70 has anti-inflammatory and neuroprotective effects like intracellular HSP 70. It shows that an increase in intracellular HSP 70 levels is always accompanied by a rise in extracellular HSP levels, thereby reducing the inflammatory process. HSP 70 can downregulate Tumor Necrosis Factor-Alpha (TNF-α), lower Interleukin (IL)-6, IL-8, and Monocyte Chemoattractant Protein-1 (MCP-1) levels.

HSP 70 can modulate the inflammatory response by recruiting microglial cells and astrocytes, such as recruitment of peripheral inflammatory cells and regulation of NFκβ. Cellular damage will cause the release of DAMPs and activate TLRs to stimulate the release of proinflammatory mediators and activate transcription factors NFκβ and caspase 1; NFκβ activation is a master regulator of inflammation and apoptosis, both of which play a role in releasing IL-1. Barriers to TLR 2 and TLR 4 will provide a protective effect in cerebral ischemia. In acute ischemic stroke, ROS formation will activate IkB Kinase (IKK) to induce the formation of NFκβ, where the activation of NFκβ will cause the release of inflammatory mediators. Cerebral ischemia will trigger the release of HSP 70 and its family, both intracellular and extracellular, which can inhibit the IKK and NFκB complexes and reduce release of inflammatory mediators.

Hypoxia in brain cells will trigger apoptosis. HSP 70 plays a dual role in the process of apoptosis, inhibiting release of cytochrome C by forming a Bax-HSP 70/HSP 40 complex, weakening mitochondrial Bax translocation. HSP 70 reduces the apoptotic process by activating and stabilizing the AKT signal pathway. Besides that, HSP 70 inhibits the apoptotic process through the inhibition of caspase 3/9 and interacts with DR 4/5 to suppress the formation of TNF related apoptosis inducing ligand (TRAIL), which mediates the occurrence of Death Inducing Signal Complex (DISC). The intrinsic pathway of apoptosis is initiated by mitochondrial damage. Mitochondrial damage will release cytochrome-C, caspase 9, and apoptosis-inducing factor (AIF). HSP 70 plays a role in stopping the process of apoptosis by inhibiting the translocation of cytochrome C from mitochondria to the cytosol and inhibiting the translocation of AIF to the nucleus.

CONCLUSION

HSP 70 is neuroprotective. Modulation of HSP 70 levels in cerebral ischemia can increase neuroprotection’s effect and improve functional outcome in ischemic stroke.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ETHICAL CLEARANCE

This study requires no approval from the ethical committee due to the nature of this review.

FUNDING

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

AUTHORS CONTRIBUTION

All contributors contributed equally in concept, design, literature search, data analysis, manuscripts preparation, editing and review.

REFERENCE

Hypertension in mortality and morbidity of COVID-19: A systematic review and meta-analysis of prospective cohort study

Lalu Hizrian Rizkika Abtartu1*, Hamsu Kadriyan1, Yusra Pintaningrum1

ABSTRACT

**Background:** COVID-19 is an infectious disease and quickly becoming a major pandemic. Hypertension, characterized by elevated systolic and diastolic blood pressure. The objective of our study is to evaluate the prognostic of hypertension on mortality and morbidity in individuals diagnosed with COVID-19.

**Methods:** We search the latest five years studies using PubMed, ResearchGate and Google scholar database. The process of selecting articles was conducted using a search strategy aligned with the guidelines of PRISMA.

**Results:** This article showed a significant increase of morbidity (RR: 1.33 [1.01 – 1.74], p=0.04) in homogenous data (I² = 0%, p=0.26). However, this disease did not show significant increase of mortality (RR: 0.69 [0.37 – 1.31], p=0.26) in heterogeneous data (I² = 91%, p<0.00001).

**Conclusion:** Based on this meta-analysis, we concluded that hypertension increases the risk of morbidity in patients with COVID-19 and no significant increase of mortality.

**INTRODUCTION**

COVID-19 has emerged in global public health. Recent estimates indicate that 2% of healthy individuals carry Coronaviruses. Since the onset of the epidemic, there have been over 2,241,359 confirmed cases reported worldwide. Individuals diagnosed with COVID-19 commonly exhibit symptoms such as fever, myalgia, and a dry cough.1,2 While the overall prognosis for most patients is favorable, but individuals with preexisting hypertension are believed to significantly contribute to disease severity and risk of mortality such as acute respiratory distress syndrome (ARDS) or organ failure.3

Investigating this correlation can contribute to improved management strategies for COVID-19 patients at higher risk of developing complications, by implementing proactive and vigilant monitoring at an early stage. Therefore, the objective of this meta-analysis is to evaluate the relationship between hypertension and the severity of the disease.

**METHODS**

The methods utilized in this study with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

**Data Sources and Searches**

We searched PubMed, ResearchGate and Google scholar from May, 29th 2023 to June, 3rd. 2023. The search syntax is in the following: “Hypertension”, “Severity”, “Mortality” AND "COVID-19".

**Study type**

We pooled data from published only that included COVID-19 with hypertension that also included mortality and severity of the disease.

**Population**

The inclusion criteria for this research are patients with hypertension and COVID-19, Cohort study, the research paper showed mortality and severity of COVID-19. The exclusion criteria are COVID-19 without hypertension, Non Cohort study (review article, case report, editorial letter), and The research paper did not show mortality and severity of COVID-19.

**Intervention/comparison**

Patients with hypertension and without hypertension in COVID-19.

**Outcome**

The outcome for this meta-analysis is mortality and morbidity rate of COVID-19.

**Data Extraction**

We extracted the following data from each inclusion criteria study: author, year, population, mortality rate and morbidity rate.

**Data analysis**

The data were analyzed using RevMan 5.4.1 for forest plot of dichotomous data.

**RESULTS**

**Study selection**

We found a total of 2,039 records from the database. Record removed before screening (n = 143) due to duplication (n = 103) and not publication article (n = 40). Records screened for further evaluation were excluded (n = 284) because no full text was available (n = 189) and invalid DOI (n = 95). Record assessed for eligibility (n = 1,602), excluded for many reasons. We used ten publications to establish this systematic review and meta analysis.
**PROCEEDING**

**Table 1.** Mortality and morbidity rates based on all studies analyzed\(^{3–11}\)

<table>
<thead>
<tr>
<th>Author, Years</th>
<th>(n)</th>
<th>Survival</th>
<th>Non Survival</th>
<th>Mortality Rate</th>
<th>Author, Years</th>
<th>(n)</th>
<th>Critical</th>
<th>Non Critical</th>
<th>Morbidity Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total HTN</td>
<td></td>
<td>Total HTN</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yuan, et. al. 2020</td>
<td>27</td>
<td>17</td>
<td>0</td>
<td>10</td>
<td>Kalligeros, et al. 2020</td>
<td>103</td>
<td>44</td>
<td>31</td>
<td>59</td>
</tr>
<tr>
<td>Huang, et. al. 2020</td>
<td>310</td>
<td>197</td>
<td>30</td>
<td>113</td>
<td>Huang, et. al. 2020</td>
<td>41</td>
<td>13</td>
<td>2</td>
<td>28</td>
</tr>
<tr>
<td>Sun, et al. 2020</td>
<td>244</td>
<td>121</td>
<td>76</td>
<td>123</td>
<td>Shi, et al. 2020</td>
<td>487</td>
<td>49</td>
<td>26</td>
<td>438</td>
</tr>
<tr>
<td>Du et al. 2020</td>
<td>179</td>
<td>158</td>
<td>45</td>
<td>21</td>
<td>Liu et al. 2020</td>
<td>78</td>
<td>11</td>
<td>2</td>
<td>67</td>
</tr>
</tbody>
</table>

**Figure 1.** Mortality of hypertension in COVID-19 patients with hypertension.

**CONCLUSION**

Hypertension is one of the comorbidities for COVID-19. According to our meta-analysis, individuals with COVID-19 and hypertension demonstrated a notable increase in morbidity, but no significant increase in mortality was observed.

**CONFLICT OF INTEREST**

The author reports no conflicts of interest in this work.

**ETHICAL CLEARANCE**

Meta-analysis did not apply the ethical clearance.

**FUNDING**

The are no funding on this research.

**AUTHORS CONTRIBUTIONS**

YP and LHRA concept and drafting manuscript, HK critical review the manuscript, all authors agree with the final manuscript.

**REFERENCES**


**TABLE 1.** Mortality and morbidity rates based on all studies analyzed\(^{3–11}\)

<table>
<thead>
<tr>
<th>Study Subgroup</th>
<th>Survival Events</th>
<th>Non Survival Events</th>
<th>Total Events</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total HTN</td>
<td>221</td>
<td>110</td>
<td>331</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Figure 2.** Morbidity of hypertension in COVID-19 patients.


Dominant gut microbiota profile in pediatric and adult patients with diarrhea

Resti Hardianti Lestari1, Yeva Rosana2*, Fera Ibrahim2, Conny Riana Tjampakasari2, Dimas Seto Prasetyo2

INTRODUCTION

The gut microbiota plays an important role in maintaining gut health and is linked to various intestinal disorders. Antibiotic use for hospitalized patients can have several negative effects on the gut microbiota, including reduced species diversity, altered metabolic activity, and the development of antibiotic resistance. Dysbiosis of gut microbiota corresponded with dominant microbiota will trigger diarrhea in both adults and children.

METHOD

Stool specimens from hospitalized patients with complaints of diarrhea were examined at Clinical Microbiology Laboratory of FMUI Jakarta during the period 2018 to 2022. The specimens were inoculated on SS and EMB agar. Selenite Broth was used as an enrichment medium for the isolation of salmonellas. The media were then incubated at 35°C – 37°C for 18-24 hours. The dominant colony was identified using Gram staining and VITEK2 compact system (bioMeriéux®).

RESULTS

A total of 367 stool specimens, of which only 325 samples were included in the study. Two microorganisms were found most in adult and pediatric patients, Escherichia coli and Klebsiella pneumoniae were 119 (43.90%) and 56 (20.66%) respectively. The third most common microorganism was found to be different between adult and pediatric patients. The third dominant microbiota in pediatric patients were Enterobacter cloacae, while in adults were Candida albicans, 23 (8.49%) and 18 (6.64%) respectively.

Conclusion: Overall, the dominant microbiota in children and adults is E. coli and K. pneumoniae. The third dominant microbiota in pediatric patients were E. cloacae, while in adults were C. albicans. The differences in intestinal microbiota profiles in adult and pediatric patients found in this study provide new insights into guidelines for the management of diarrhea in hospitalized adults and children.

Keywords: Gut microbiota, pediatric patients, adult patients, diarrhea.

ABSTRACT

Background: The gut microbiota plays an important role in maintaining gut health and is linked to various intestinal disorders. Antibiotic use for hospitalized patients can have several negative effects on the gut microbiota, including reduced species diversity, altered metabolic activity, and the development of antibiotic resistance. Dysbiosis of gut microbiota corresponded with dominant microbiota will trigger diarrhea in both adults and children.

Methods: This retrospective study used a cross-sectional approach to determine the profile of the dominant gut microbiota. Stool specimens from hospitalized patients with complaints of diarrhea were examined at Clinical Microbiology Laboratory of FMUI Jakarta during the period 2018 to 2022. The specimens were inoculated on SS and EMB agar. Selenite Broth was used as an enrichment medium for the isolation of salmonellas. The media were then incubated at 35°C – 37°C for 18-24 hours. The dominant colony was identified using Gram staining and VITEK2 compact system (bioMeriéux®).

Results: A total of 367 stool specimens, of which only 325 samples were included in the study. Two microorganisms were found most in adult and pediatric patients, Escherichia coli and Klebsiella pneumoniae were 119 (43.90%) and 56 (20.66%) respectively. The third most common microorganism was found to be different between adult and pediatric patients. The third dominant microbiota in pediatric patients were Enterobacter cloacae, while in adults were Candida albicans, 23 (8.49%) and 18 (6.64%) respectively.

Conclusion: Overall, the dominant microbiota in children and adults is E. coli and K. pneumoniae. The third dominant microbiota in pediatric patients were E. cloacae, while in adults were C. albicans. The differences in intestinal microbiota profiles in adult and pediatric patients found in this study provide new insights into guidelines for the management of diarrhea in hospitalized adults and children.
PROCEEDING

**DISCUSSION**

Dysbiosis of gut microbiota characterized by dominant one microbiota is widely identified in diarrhea. This study showed that the dominant microbiota in pediatric patients with diarrhea are bacteria as members of the normal gut flora of many humans and are not usually primary pathogens. *Escherichia coli* is a type of facultative anaerobic Gram-negative bacteria and causes diarrhea. Different diarrheal *E. coli* strains exhibit different epidemiology and have been classified as Enteropathogenic *E. coli* (EPEC, the main cause of infant diarrhea), Enterohemorrhagic *E. coli* (EHEC/STEC, the cause of hemorrhagic colitis and hemolytic uremic disease), Enteroaggregative *E. coli* (EAEC), Enterotoxigenic *E. coli* (ETEC, the main cause of travelers’ diarrhea and infant diarrhea) and Enteroinvasive *E. coli* (EIEC, the main cause of dysentery) according to the pathological types, colonization sites, virulence mechanisms, and clinical symptoms. After infection, *E. coli* adheres to the intestinal epithelial cells through the adherent fimbriae, and then produces toxins and exerts pathogenic effects.1,4,8-10

*Candida albicans* is one of the dominant microbiota in adult patients with diarrhea in this study. Although *C. albicans* is a normal microbiota in the human gut, it has been often considered documented as a cause of diarrhea, but its mechanism of inducing diarrhea is still unclear. The role of *C. albicans* and diarrhea has been controversial for many years. While in mouse model, it was found that *C. albicans* could cause intestinal dysbiosis and enhance the severity of DSS-induced colitis. The mechanisms may be associated with dectin-1, which is a C-type lectin-like receptor that mediates the fungal immune response. Dectin-1 expression is positively correlated with (1,3)-β-Glucan and mediates fungal infections by recognizing the (1,3)-β-glucan structure on the fungal cell wall. In addition, *C. krusei*, *C. tropicalis*, *C. glabrata*, *C. guilliermondii*, *C. parapsilosis* are also the main pathogens that cause invasive candidiasis that may be implicated in diarrhea, but the detailed mechanisms need to be further studied.1,4,11-15

**CONCLUSION**

The differences in intestinal microbiota profiles in adult and pediatric patients found in this study provide new insights into guidelines for the management of diarrhea in hospitalized adults and children. Giving probiotics is one of the recommendations for children who are hospitalized with diarrhea, whereas in adult patients it must be accompanied by restrictions on the long and excessive use of broad-spectrum antibiotics.

**ACKNOWLEDGMENT**

We sincerely thank Prof. dr. Pratiwi P. Sudarmono, Ph.D, Sp.MK (K), head and staf of Clinical Microbiology Laboratory, Microbiology Department, Faculty of Medicine Universitas Indonesia (FMUI)/ RSCM for providing a conducive environment for completing this study. Our deepest appreciation is extended to our dedicated laboratory personnel from Clinical Microbiology Laboratory FMUI for technical assistance and supporting this study.

**CONFLICT OF INTEREST**

The author reports no conflicts of interest in this work.
ETHICAL CLEARANCE

This study was conducted after obtaining an ethical clearance certificate from the Health Research Ethics Committee of the Faculty of Medicine, Universitas Indonesia/ Cipto Mangunkusumo National General Hospital (RSCM) with certificate number KET-940/UN2.F1/ETIK/PPM.00.02/2022.

FUNDING

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AUTHORS CONTRIBUTION

RHL and YR designed the study. FI and CRT supervised fieldwork. DSP input and collected data and samples. RHL and YR analyzed the results and wrote the first draft of the report, with revisions and input from FI, CRT and DSP. All authors contributed to revisions and approved the final version.

REFERENCES


