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**Tohid Vahdatpour**

PhD, Assistant Prof., Physiology, Islamic Azad University, Iran ([Website](#); [Scopus](#); [Google Scholar](#); [Emails: vahdatpour@iaushab.ac.ir](mailto:vahdatpour@iaushab.ac.ir))

**Veghar Hejazi**

MD, Tabriz University of Medical Sciences, Tabriz, Iran ([Email: vegharhejazi@gmail.com](mailto:vegharhejazi@gmail.com))

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PhD, Professor of Plant Biology, Atatürk University, Erzurum, Turkey ([Email: ykaya@atauni.edu.tr](mailto:ykaya@atauni.edu.tr))

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## Volume 9 (5); September 25, 2019 [Booklet]

**Research Paper****Analysis of the post-partum vaginal repair by injecting platelet-rich plasma; a study undertaken in Saudi German hospital K.S.A.**

Hassan Soliman HE-MAA

*J. Life Sci. Biomed.*, 9(5): 122-125, 2019;

pii:S225199391900019-9

**Abstract**

**Aim.** The research was based on the objective of vaginal recovery after vaginal delivery of women. PRP was used to determine whether the effects of the injecting PRP on vagina made any difference on vaginal prolapse repair or not. Therefore, the primary goal was to find the application of the PRP on the case of vaginal tear recovery of the mothers. **Methods.** The observational approach was utilized to conduct the following research. We examined (P=210) participants, while study duration was 10 months from November 2017 to August 2018. **Results.** The outcomes were 100% positive in the researcher's cohort since all the participants responded well while recovered fast than the usual estimated time. **Conclusion.** Injecting PRP for repairing vaginal tear is considered to be optimizing for the general medical background patients whereas, for the long-term follow-up, the study requires to get the large numbers of participants in order to make the research generic.

**Keywords:** Post-Partum, Vaginal Tear, Vaginal Repair, Platelet-Rich Plasma, Gynecological Study



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**Research Paper****Results of cytokine research of pregnant women with the risk of premature birth.**

Khakimovna RN.

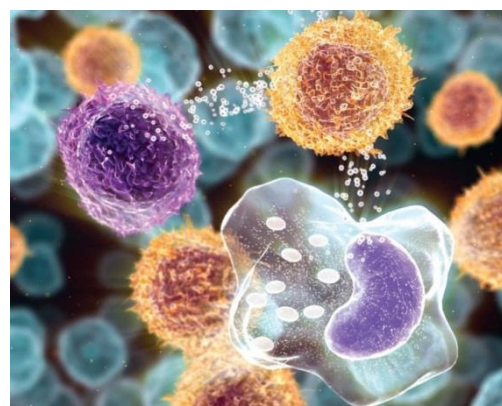
*J. Life Sci. Biomed.*, 9(5): 126-129, 2019;

pii:S225199391900020-9

**Abstract**

**Aim.** The aim of the research is to study the content of pro-inflammatory and anti-inflammatory cytokines of pregnant women with the risk of preterm birth (PB). **Methods.** Examined 42 women in the third trimester of gestation with the risk of preterm birth. Determination of the cytokine status of IL-1 $\beta$ , IL-4, IL-6, IL-8, IL-10 and TNF- $\alpha$  in the serum of peripheral blood was performed by Enzyme immunoassay. **Results.** The systemic cytokine status was studied in pregnant women with the risk of PB. An imbalance of cytokines has been established, characterized by an increase in the content of pro-inflammatory cytokines and a decrease in anti-inflammatory interleukins, indicating an increased inflammatory response of the organism in the genesis of premature birth. **Conclusion.** The study of cytokine balance is important to assess the direction of the immune response, as well as the outcome of pregnancy for the mother and fetus. Excessive stimulation of the systemic humoral immune response as a result of increased activity of peripheral pro-inflammatory cytokines and low secretion of anti-inflammatory cytokines are one of the fundamental mechanisms underlying the development of premature birth.

**Keywords:** Preterm birth, Pro-inflammatory, Anti-inflammatory cytokines, Cytokine status



[Full text-[PDF](#)] [[XML](#)]

**Research Paper****Assessment of antibacterial efficacy of Lugol's iodine compared with commercial hand sanitizers of Bangladesh.**

Rahman Md.N, Abdullah-Al-Shoeb M, Huq S and Abul Kalam Azad M.

*J. Life Sci. Biomed.*, 9(5): 130-137, 2019;

pii:S225199391900021-9

**Abstract**

**Introduction.** Hand disinfection is an essential step to prevent infection, reduce morbidity and minimize health care costs in a

Rahman Md.N, Abdullah-Al-Shoeb M, Huq S and Abul Kalam Azad M. Assessment of antibacterial efficacy of Lugol's iodine compared with commercial hand sanitizers of Bangladesh. *J. Life Sci. Biomed.*, 2019; 9(5): 130-137; [www.jlsb.science-line.com](http://www.jlsb.science-line.com)



community. **Aim.** In this study, the Lugol's iodine (2%) solution was evaluated to use as an emergency hand sanitizer and compared with the three commercially available hand sanitizers (Hexisol, Sepsil and Handirub) of Bangladesh. **Methods.** These hand sanitizers were examined and analyzed by susceptibility test, minimum bactericidal concentration test and efficacy determination test. The agar diffusion test was used to assess the efficacy of the products against pathogenic *Escherichia coli*, *Shigella flexneri*, *Staphylococcus aureus*, *Salmonella typhi* and *Streptococcus pneumoniae*. **Results.** Handirub has inhibited all the test organisms with highest zones of inhibition ranging between 24.38 mm and 28.63 mm while Hexisol zone of inhibition was ranging from 13.3 mm to 15 mm. Unfortunately, Sepsil was inactive against *Salmonella typhi*, with very poor performance against other test organisms. All the three commercial hand sanitizers were only bacteriostatic at 100% concentration, while both 2% and 1% iodine were 100% bactericidal. The comparative study of the efficacy determination tests revealed that the Hexisol, Sepsil and Handirub are 93.05%, 85.99% and 96.57% effective against microorganism, respectively. Interestingly, both 2% and 1% of iodine solutions gave 100% reduction of viable bacteria during the efficacy determination test. **Conclusion.** It is concluded that 1% iodine showed better results against infection when compared to the other hand sanitizers used in this study. **Recommendation.** Lugol's iodine could be an effective alternative to hand washing to achieve asepsis for the health-care professional in emergency outreach program and water scarcity areas.

**Keywords:** Hand sanitizer, Lugol's iodine, Hand hygiene, Minimum inhibitory concentration

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## Research Paper

### Esophagus extirpation in the surgical treatment of neglected stages of esophageal achalasia.

Nazirov FG, Nizamkhodjayev ZM, Ligay RE, Tsoi AO, Shagazatov DB, Nigmatullin EE and Babadjanov KB.  
*J. Life Sci. Biomed.*, 9(5): 138-143, 2019;  
pii:S225199391900022-9

#### Abstract

**Aim.** The surgical treatment experience of patients with neglected stages of esophageal achalasia has been presented in the article.

**Methods.** The esophagus extirpation with simultaneous gastroesophagoplasty due to esophageal achalasia of stage III-IV was performed in 28 patients. **Results.** The results of the research, identifies indications for surgical intervention, features of intra- and postoperative complications, immediate and long-term results of esophageal extirpation. Cardioplasty remains the main treatment method for patients with esophageal achalasia, but its efficiency is significantly reduced in patients with neglected stages. **Conclusion.** Esophagus extirpation in patients with neglected stages of achalasia is pathogenetically reasonable surgical intervention when there is severe esophagoectasia and S-shaped deformity of the esophagus and cardio-esophageal junction. Further control randomized trials and multicentric studies should be performed.

**Keywords:** Achalasia, Neuromuscular diseases of the esophagus, Esophageal extirpation, Gastroplasty.

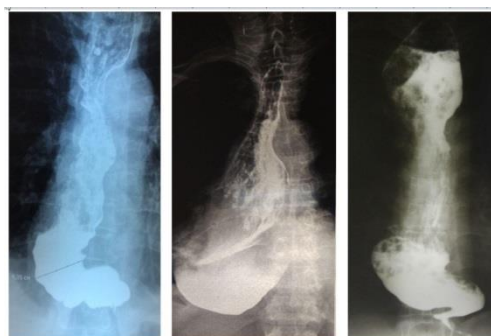


Figure 1. X-ray pattern of the esophagus (achalasia of stage IV).  
Nazirov FG, Nizamkhodjayev ZM, Ligay RE, Tsoi AO, Shagazatov DB, Nigmatullin EE and Babadjanov KB. Esophagus extirpation in the surgical treatment of neglected stages of esophageal achalasia. *J. Life Sci. Biomed.* 2019; 9(5): 138-143. [www.jlsb.science-line.com](http://www.jlsb.science-line.com)

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## Review

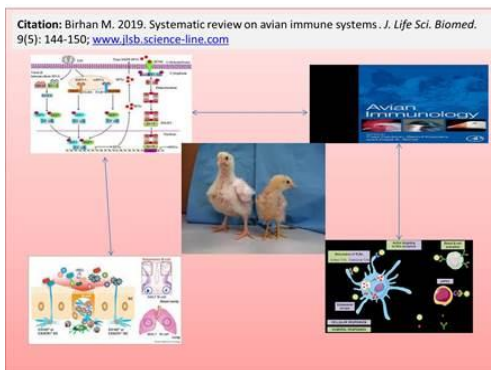
### Systematic review on avian immune systems

Birhan M.  
*J. Life Sci. Biomed.*, 9(5): 144-150, 2019;  
pii:S225199391900023-9

#### Abstract

**Aim.** The aim of this review paper is too summarized and compares avian immune systems to the other domestic animals as comparative immunology type of review. Appreciation of the avian immune systems and their functions are very critical for disease diagnostics and new vaccine developments. Some of the avian immune systems are differ from mammalian immune systems, based on their production sources of immune cells like B-cells production site bursa of fabrics, but in mammalian is bone marrow. When we see the antibody type of birds; there are three principal classes of antibodies: IgM, IgG, IgY and IgA. Antibody diversity is achieved by gene re-arrangement. The other effector immune cell of birds is T cells. There are two distinct pathways that are  $\alpha/\beta$  and  $\gamma/\delta$ , avian T-cell diversity is probable made through combinatorial and junctional mechanisms. Recently, genes of several avian cytokines have been cloned and expressed. A number of naturally occurring viruses cause immunosuppression in chickens. **Conclusion.** There is much current interest in understanding the mechanisms of immunosuppression and developing strategies to enhance immune responsiveness in commercial poultry.

**Keywords:** Antibody, Avian, T cells, Vaccine



Citation: Birhan M. 2019. Systematic review on avian immune systems. *J. Life Sci. Biomed.* 9(5): 144-150; [www.jlsb.science-line.com](http://www.jlsb.science-line.com)

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Emails:

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[saeid.azar@atauni.edu.tr](mailto:saeid.azar@atauni.edu.tr)

# Analysis of the post-partum vaginal repair by injecting platelet-rich plasma; a study undertaken in Saudi German hospital K.S.A

Dr. Hassan El Motawkel Ala Allah HASSAN SOLIMAN✉

HOD & Consultant Obstetrics & Gynecology, Saudi German Hospital, Aseer, KSA.

✉Corresponding author's Email: obgyn1.asr@sghgroup.net

## ABSTRACT

**Aim.** The research was based on the objective of vaginal recovery after vaginal delivery of women. PRP was used to determine whether the effects of the injecting PRP on vagina made any difference on vaginal prolapse repair or not. Therefore, the primary goal was to find the application of the PRP on the case of vaginal tear recovery of the mothers. **Methods.** The observational approach was utilized to conduct the following research. We examined (p=210) participants, while study duration was 10 months from November 2017 to August 2018. **Results.** The outcomes were 100% positive in the researcher's cohort since all the participants responded well while recovered fast than the usual estimated time. **Conclusion.** Injecting PRP for repairing vaginal tear is considered to be optimizing for the general medical background patients whereas, for the long-term follow-up, the study requires to get the large numbers of participants in order to make the research generic.

## Original Article

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## Keywords

Post-Partum,  
Vaginal Tear,  
Vaginal Repair,  
Platelet-Rich Plasma,  
Gynecological Study

## INTRODUCTION

During the vaginal delivery, it is common to have perineal postpartum tear due to stretching of the vagina. It usually causes the tear of vaginal layers which eventually causes the temporary injury [1]. The degrees of vaginal tears are divided into 4 categories. While these degrees depend upon the severity of the tear, in the first degree tear, it includes the tear of vaginal mucosa and the connective tissue [2]. In the second degree tear, it involves the tear of vaginal mucosa and connective tissue along with the underlying muscles. For the third degree tear, it involves the complete transection of an anal sphincter [3-5]. And the last degree tear includes the tear of rectal mucosa [6]. A woman may suffer from any of these after delivery while just how there are several degrees of injury [7], there are different method for its recovery as well [8, 9].

The following research is based on the postpartum vaginal repair by injecting Platelet-rich plasma (PRP). The primary objective of the research study is to analyze and evaluate the use and benefits of PRP in order to know its significance and in the area of postpartum vaginal repair.

## MATERIAL AND METHODS

The observational study method was implied in the following research. The study was undertaken at tertiary referral unit in K.S.A. Saudi German Hospital, Aseer. Whereas, the participants were undergo observations for the research purposes. The participants for the research comprised of 210 laboring women between 22-46 years old.

### Ethical approval

The review board and ethics committee of Saudi German Hospital, Aseer approved the study protocol and informed consents were taken from all the participants.

### Limitations

The study includes some of the significant limitations which are significant to come in the observation. Those are given as follow: The observational study lacks in providing the conclusive results or the authentic

evidence as a result. Moreover, date limitations also play their role in making evidence weak. In order to overcome these limitations, it is essential to conduct a randomized controlled trial. The sample size of the participants limits the research to get appropriate conclusion and generalized outcome. For that reason, it is essential to carry the evidence-based research along with the large sample to make the outcomes generalized.

### Procedure and analysis

The following study was undertaken in the time period of 10 months in which 210 laboring women between the ages of 22 to 46 were the participants. These participants were critically observed in order to analyze the application of PRP in vaginal repair.

The infiltration was made by using 20ml of Lidocaine (2%) with 1 Amp Vasopressin 20 IU + 30 ml Normal Saline +/- Sedation Inj. Dormicum 15mg/3ml. the major factors that have the significant role in the observational study include The Surgical Technique including Vaginoplasty and Perinorrhaphy which depends upon pre-delivery evaluation of vaginal laxity, widening, distance between the vagina and anus, any varicosities and mass. Following the experimental procedure, the participants were provided the sedation and after that the vasoconstrictor and local Analgesia Solution in both vaginal wall and perineum. The re-evaluation after the delivery was performed which further included: Careful dissection of the vaginal wall equally starting from the apex till the mucocutaneous junction at the introitus, two to three stitches at the deep and superficial perineal muscles and levator ani muscles and removal of the all excess vaginal tissues. After that the procedure proceeded by suturing the vaginal wall starting from the apex until the hymen ring and the one deep as well as a high stitch to approximate the bulbospongiosus muscle on both sides. The suturing was completed until the mucocutaneous junction while two or three stitches were tied muscles and interrupted stitches including subcuticular stitches of the perineal area. After completion of the repair process, inject  $\pm$  4.5 – 5ml of PRP which was already prepared at the time of delivery after extraction of 8-9 ml blood from the patient and put in the tube and centrifuge for 5 minutes to separate the PRP from the whole blood. Afterwards the PRP is injected to subcutaneous and subvaginal for further experimental approach. In the last compression and assurance of the hemostasis by vaginal back after catheterization, analgesia (mainly non-steroidal anti-inflammatory supplements) was done.

Furthermore, the statistical measurements of the parity and the age of participants are elaborated in tables 1 and 2. Any participant with any medical disorders e.g. hypertensive, diabetic, hypothyroid was well controlled before implication of the treatment. Thirteen of the women were diagnosed with hypertensive but not pre-eclampsia symptoms. Seventeen of them were Anemic with the Hb below 10.5. 41 of the women were diagnosed diabetic while the experiment was obtained on total 210 numbers of women from 22 to 46 years of age. Weight of the participants was measured between 63 to 114 kg.

**Table 1.** Characteristics of the participants of the study

Characteristics	
Age	22-46 years
Weight	69-117 kg
<b>Medical disorder</b>	
Diabetic	14.76 %
Hypertensive	6.19 %
Hypothyroid	27.14 %
Epilepsy	0.95 %
<b>Multiple medical disorder</b>	
Diabetic and hypertensive	5.23 %
Diabetic and hypothyroid	1.42 %
Hypertensive and hypothyroid	3.33 %
<b>Parity</b>	
P1 – P5	66.19 %
P6 – P11	33.80 %



**Table 2.** Vaginal Prolapse of the Participant

Vaginal prolapse	Percentage
Minor degree (1 <sup>st</sup> degree tear)	19.52 %
Moderate degree (2 <sup>nd</sup> degree tear)	52.85 %
Severe degree (3 <sup>rd</sup> degree tear)	22.61 %

## RESULTS AND DISCUSSION

After deeply analyzing the outcomes and observations made on the participant in ten months' time period, the researcher concluded the approach towards vaginal repair immediately after delivery is effective and more feasible. Furthermore, it adverts that the addition of vasopressin and lidocaine infiltration helps to prevent heavy blood loss and leads to prolong the analgesic effect. There were multiple more advantages observed during the observation like more analgesics time, cosmetic appearance, less infection and less dehiscence of the wound. Therefore the participant of the study (p=210) along with mediocre medical background responded well to the experimental vaginal repair experiment. Hence, the study was proved to be 100% successful whereas, for long-term follow-up, there is a need for large sample of participants for further evaluation and comparison.

The average size of a baby's head is 11.4 centimeters in diameter. The average diameter of a woman's vagina (according to a study) is 2.1 to 3.5 centimeters [10]. This initiates the scenario of complication in delivery [9-12]. Perhaps, some of the women do not require vaginal tear to deliver a child but some of them experience different degrees of the vaginal tear [13]. The process of repairing vagina takes long while the sensitivity of area makes it critical to handle [14]. That is why different approaches are usually followed in order to speed up the repair of an organ [15]. Usually the initial steps for the tear include suturing and stitches after that different medicines are used to cure the stitches further [13, 15]. This particular research follows the idea of injecting PRP for speeding up the process of vaginal repair while the observational study was prioritized on the basis of its advantages defined as follow:

Through the PRP approach for vaginal repair, there is a significant decrease in blood loss as well as time of the repair [15, 16]. It provides more analgesics time while providing more cosmetic appearance later on [15]. There are also very fewer chances of infection as dehiscence of the wound as per the results advert. For the concept of PR, the Plasma is the portion of liquid which contains whole blood. It has the large of water and proteins, platelets to circulate within the body for healing purpose [14]. Platelet activation plays a key role in the body's natural healing process [15]. Its major application is to heal the tissues of the body and has been used for multiple medical purposes in history.

## CONCLUSION

The applications of Platelet-rich plasma (PRP) was proved to be significant for the vaginal repair after first, second and third-degree tear of women during vaginal delivery. The necessary measurements were made to check the medical condition of the study participants and the approach towards new treatment was applied to them in order to observe its outcomes. The researcher took the consent of the laboring women before the experiment and it was conducted with all security measures from healthcare perspective.

## DECLARATIONS

### Funding statement

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

### Conflict of interests

Authors do not have any conflict of interests.

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# Results of cytokine research of pregnant women with the risk of premature birth

Ruzieva Nodira KHAKIMOVNA ✉✉

Tashkent Pediatric Medical Institute, Tashkent, Uzbekistan

✉ Corresponding author's Email: n-ruzieva@mail.ru

## ABSTRACT

**Aim.** The aim of the research is to study the content of pro-inflammatory and anti-inflammatory cytokines of pregnant women with the risk of preterm birth (PB). **Methods.** Examined 42 women in the third trimester of gestation with the risk of preterm birth. Determination of the cytokine status of IL-1 $\beta$ , IL-4, IL-6, IL-8, IL-10 and TNF- $\alpha$  in the serum of peripheral blood was performed by Enzyme immunoassay. **Results.** The systemic cytokine status was studied in pregnant women with the risk of PB. An imbalance of cytokines has been established, characterized by an increase in the content of pro-inflammatory cytokines and a decrease in anti-inflammatory interleukins, indicating an increased inflammatory response of the organism in the genesis of premature birth. **Conclusion.** The study of cytokine balance is important to assess the direction of the immune response, as well as the outcome of pregnancy for the mother and fetus. Excessive stimulation of the systemic humoral immune response as a result of increased activity of peripheral pro-inflammatory cytokines and low secretion of anti-inflammatory cytokines are one of the fundamental mechanisms underlying the development of premature birth.

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## INTRODUCTION

The physiological course of pregnancy is accompanied by a certain restructuring of the immune system, which ensures the tolerance of the mother's body to the antigens of the ovum and gestation. It has now become apparent that the protection of the fetus from damaging maternal immune response is based on a complex mechanism and that communication between different steps in the cascade of events is carried out by means of cytokines [1].

In the last decade, active research on the role of cytokines in the development of preterm birth (PB) has been conducted. Being biologically active factors, cytokines, first of all, regulate the development of local defense reactions in tissues with the participation of various types of blood cells, endothelium, connective tissue and epithelium. Cytokines are responsible for all successive stages of development of an adequate response to the introduction of the pathogen, ensuring its localization and removal, and then restoring the damaged tissue structure, no matter where the inflammatory reaction develops [2].

The main role is assigned to the cytokine network, the functioning of which determines the direction of the immune response in inflammation. The importance of cytokines for the life of the body cannot be overestimated. The most studied is their participation in the regulation of immunogenesis, where they are necessary at all stages of the immune response. Cytokines determine differentiation

T-helpers in Th-1 and Th 2-types, which differ in the profile of the cytokines synthesized by them in response to various inducers [3]. Th-1 proinflammatory cytokines produce interleukins: IL-1, IL-3, IL-8; interferons (IFN  $\beta$  and  $\gamma$ ), tumor necrosis factor (TNF $\alpha$ ), which play an important role in regulating the inflammatory response in the endometrium, limit trophoblast invasion, disrupting its formation. Th-2 is produced by interleukins: IL-4, IL-5, IL-6, IL-10, colony-stimulating factor, etc. – anti-inflammatory cytokines, and IL-10 is also called “suppressor”. It is known that Th-1 determines the development of the immune response by cell type, and Th-2 - by humoral type. The physiologically proceeding pregnancy develops with the participation of the Th-2 type of immune response, while there is a certain balance of interaction between Th-1 and Th-2 [4-6].

Until now, the main reasons leading to pronounced shifts in the immune system have not been fully studied. At the same time, the study of the state of the immune system during pathological pregnancy can contribute to the pathogenetic substantiation of rational ways of the ante- and intra-natal protection of the fetus and the prevention of complications during childbirth. The aim of study was to investigate the content of pro-inflammatory and anti-inflammatory cytokines in pregnant women at risk of developing PB.

## MATERIALS AND METHODS

There were 42 women examined in the third trimester of gestation with the risk of premature birth: recurrent with burdened obstetric history (abortion, preterm birth), with dysbiosis of the vagina and intestines. The study did not include patients with isthmus cervical insufficiency, uterine malformations and myomas, as well as carriers of TORCH infection. All patients came to the clinic with complaints of lower abdominal pain, constipation, poor health, dysuric disorders, and the presence of abnormal discharge from the genital tract.

In 86% of women in the vaginal contents using polymerase chain reaction diagnostics revealed the presence of pathogenic microflora and mixed infections. The species composition of the microbiocenosis of the vagina and the cervical canal of female patients was characterized by the predominance of the share of coccobacillary flora and gardnerellas. The diagnosis of bacterial vaginosis was established on the basis of clinical and anamnestic indicators, and verified according to light microscopy of a smear from the posterior vaginal fornix and determining the reaction of vaginal secretions (pH-metry). To describe the microscopic picture of the vaginal biocenosis, light microscopy of smears stained by Gram was performed (Lyumam-P8 microscope, JIOMO, St. Petersburg). The degree of vaginal dysbiosis was determined microscopically by the criteria proposed by Mavzyutov et al. [7]. Later bacteriological cultures were carried out with a quantitative analysis of the microbiocenosis.

Determination of the cytokine status of IL-1 $\beta$ , IL-4, IL-6, IL-8, IL-10 and TNF- $\alpha$  in the serum of peripheral blood was performed by Enzyme immunoassay. The data obtained in 24 women with physiological pregnancy were used as controls.

### Statistical analysis

Statistical data processing included determining the arithmetic mean and arithmetic mean error. Reliability of differences was calculated by Student's t-test.

## RESULTS

It was established that by women of the control group the level of cytokine IL-1 $\beta$  in serum was  $2.35 \pm 0.18$  pg/ml, IL-4:  $5.76 \pm 0.44$  pg/ml. The serum content of IL-6 was  $2.25 \pm 0.17$  pg/ml, IL-8:  $6.36 \pm 0.58$  pg/ml, IL-10:  $23.14 \pm 1.57$  pg/ml, and TNF- $\alpha$  level was in the range of  $1.68 \pm 0.13$  pg/ml (Table 1).

Analysis of indicators of pregnant women of the main group revealed a significant increase in serum IL-1 $\beta$  production by 6.7 times ( $14.6 \pm 0.87$  pg/ml,  $P < 0.05$ ). IL-1 is an inducible protein, the synthesis of which is necessary for the acute phase response. The main producers of cells are monocytes, macrophages, endothelium and other cells. An excessively high level of IL-1 indicates the possibility of undesirable immunopathological processes. IL-1 is characterized by the ability to stimulate prostaglandin production. Keeping this cytokine low is one of the factors contributing to pregnancy.

By pregnant women with the risk of premature birth, the level of IL-8 was increased 1.6 times ( $9.98 \pm 0.63$  pg/ml) compared with the same indicator in the control group. A high level of spontaneous production of IL-8 may indicate a significant activation of mononuclear phagocyte-producing pro-inflammatory cytokines, which play an important role in the development of immunopathological processes [8].

The obtained data on the increase in IL-1 $\beta$  and IL-8 are a reflection of the activity of the inflammatory process. An increase in the concentration of pro-inflammatory cytokines suggests that the inflammatory response in a given cohort of pregnant women has systemic manifestations. At the same time, IL-1 stimulates the release of stab leukocytes from the bone marrow, increases the formation and release of collagenase, causes the expression of endothelial-leukocyte adhesive molecules on the surface of endothelial cells and leukocytes, contributes to marginal standing of leukocytes and stimulates the process of their emigration.

As its shown by the results of our studies, pregnant women at risk of premature birth have an increase in serum IL-6 content 2.1 times ( $4.83 \pm 0.39$  pg/ml) compared with the data of healthy pregnant women ( $P < 0.05$ ).

Due to a violation of the placental barrier, a large amount of antigenic material of fetal origin enters the mother's circulation. This leads to the induction of an inflammatory response from the maternal immune system with the production of a large amount of IL-6 and TNF-alpha, which causes a high level of apoptosis of the trophoblast. In addition, IL-6 stimulates prostaglandin production, which leads to cervical remodeling and the development of labor activity. IL-6 is used as a marker for predicting preterm labor activity [9].

**Table 1.** Results of two comparison groups

Indicator	Pregnant women with the physiological course of gestation, n = 24	Pregnant women with the risk of premature birth, n = 42
IL-1 B, pg/ml	2.35±0.18	14.6±0.87*
IL-2, pg/ml	11.14±0.91	7.54±0.64*
IL-4, pg/ml	5.76±0.44	3.15±0.23*
IL-6, pg/ml	2.25±0.17	4.83±0.39*
IL-8, pg/ml	6.36±0.58	9.98±0.63*
IL-10, pg/ml	23.14±1.57	7.36±0.62*
TNF-a, pg/ml	1.68±0.13	3.12±0.28*
IgA, g/l	1.27±0.13	1.18±0.12
IgG, g/l	12.74±0.87	16.7±1.43*
IgM, g/l	--	3.08±0.29
In comparison with the control group (P<0.05).		

According to our data, by pregnant women with the risk of premature birth, the serum level of TNF- $\alpha$  increases 1.9 times (3.12±0.28 pg/ml) compared with the control data (P<0.05). TNF- $\alpha$  is formed by tissue macrophages, monocytes and lymphocytes in the zone of acute inflammation, strengthens the main functions of leukocytes, stimulates the release of histamine by basophils and mast cells, causes activation of fibroblasts, smooth myocytes and vascular endothelium in the inflammation, and induces synthesis of proteins of the acute phase of inflammation. TNF- $\alpha$  hypersecretion leads to a significant increase in the number of apoptotic trophoblast cells, which can be one of the factors contributing to miscarriage [10].

The presence of a strong positive correlation between increased levels of TNF-alpha, IL-1, IL-6, IL-8 and the clinical condition of the examined pregnant women indicates significant impairments in which pro-inflammatory cytokines enter the systemic circulation, which contributes to pathogenesis of preterm birth. As can be seen from the presented research results, an increase in TNF- alpha and cytokines can serve as markers of inflammation of the vascular endothelium of the uterus, and also indicate a high permeability of the membranes of the fetal membranes, which, in our opinion, is one of the causes of the mechanisms of preterm and amniotic fluid.

Among the risk factors that are considered to cause preterm birth, one of the main ones is infectious. Increased levels of pro-inflammatory cytokines under the influence of infection in the second and third trimesters of pregnancy lead to an increase in the synthesis of prostaglandin by amniotic membranes, contributing to the premature development of labor [11]. It was established that in the normal course of pregnancy, the cytokine status shifts towards immunosuppressive cytokines (IL-2, IL-4, IL-10, TGF- $\beta$ ), which inhibit cellular immunity reactions and stimulate the production of blocking antibodies [12]. In our study, the anti-inflammatory cytokines were: IL-2: 7.54±0.64 pg/ml, IL-4: 3.15±0.23 pg/ml, IL-10: 7.36±0.62 pg/ml that is, respectively, significantly 1.5 times, 1.8 and 3.1 times lower than the corresponding indicators of the control group. The most informative is the level of IL-10, insufficient production of this anti-inflammatory cytokine can happen to be a marker of the risk of developing preterm birth.

## CONCLUSION

Our research results suggest that the study of cytokine balance is important to assess the direction of the immune response, as well as the outcome of pregnancy for the mother and fetus. Excessive stimulation of the systemic humoral immune response as a result of increased activity of peripheral pro-inflammatory cytokines and low secretion of anti-inflammatory cytokines are one of the fundamental mechanisms underlying the development of preterm birth.



## DECLARATIONS

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### Authors' contributions

All authors contributed equally to this work.

### Competing interests

The authors declare that they have no competing interests.

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# Assessment of antibacterial efficacy of Lugol's iodine compared with commercial hand sanitizers of Bangladesh

Md. Nafiur RAHMAN<sup>1</sup>, Mohammad ABDULLAH-AL-SHOEB<sup>1</sup>, Saaimatul HUQ<sup>2</sup> and Muhammad ABUL KALAM AZAD<sup>1\*</sup>✉

<sup>1</sup>Department of Biochemistry and Molecular Biology, Shahjalal University of Science and Technology, Sylhet-3114, Bangladesh

<sup>2</sup>Molecular Biotechnology division, National Institute of Biotechnology, Savar, Dhaka-1349, Bangladesh

\*Corresponding author's Email: makazad-bmb@sust.edu;  ORCID: 0000-0002-6423-8144

## ABSTRACT

**Introduction.** Hand disinfection is an essential step to prevent infection, reduce morbidity and minimize health care costs in a community. **Aim.** In this study, the Lugol's iodine (2%) solution was evaluated to use as an emergency hand sanitizer and compared with the three commercially available hand sanitizers (Hexisol, Sepsil and Handirub) of Bangladesh. **Methods.** These hand sanitizers were examined and analyzed by susceptibility test, minimum bactericidal concentration test and efficacy determination test. The agar diffusion test was used to assess the efficacy of the products against pathogenic *Escherichia coli*, *Shigella flexneri*, *Staphylococcus aureus*, *Salmonella typhi* and *Streptococcus pneumoniae*. **Results.** Handirub has inhibited all the test organisms with highest zones of inhibition ranging between 24.38 mm and 28.63 mm while Hexisol zone of inhibition was ranging from 13.3 mm to 15 mm. Unfortunately, Sepsil was inactive against *Salmonella typhi*, with very poor performance against other test organisms. All the three commercial hand sanitizers were only bacteriostatic at 100% concentration, while both 2% and 1% iodine were 100% bactericidal. The comparative study of the efficacy determination tests revealed that the Hexisol, Sepsil and Handirub are 93.05%, 85.99% and 96.57% effective against microorganism, respectively. Interestingly, both 2% and 1% of iodine solutions gave 100% reduction of viable bacteria during the efficacy determination test. **Conclusion.** It is concluded that 1% iodine showed better results against infection when compared to the other hand sanitizers used in this study. **Recommendation.** Lugol's iodine could be an effective alternative to hand washing to achieve asepsis for the health-care professional in emergency outreach program and water scarcity areas.

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## INTRODUCTION

A hand sanitizer or hand antiseptic is a supplement or alternative to hand washing with soap and water. Keeping hand clean is one of the most essential actions for the reduction of transmission of infectious diseases in the community and hospitals environment [1, 2]. Cold viruses, flu viruses, and pathogenic bacteria are easily spread through public meeting places such as hospital, school, bus, office, etc. [3]. One gram of human feces which is about the weight of a paper clip can comprises one trillion of microorganisms [4]. Once someone coughed or sneezed or touched by some other contaminated object, the germ can spread easily from hands to hands. When these contaminated hands are not washed off, they can be passed from person to person and makes people sick [5].

A decent hand hygiene practice have been shown to be effective in various situations such as the reduction of gastrointestinal infection and diarrhea [6–8], alleviate the outbreaks of the Ebola-Virus Disease [9], lowers the rate of the respiratory illnesses, like common colds [6, 10], and finally overcome the global morbidity and minimize health care cost [11]. In a health care setting hand washing is mandatory procedure according to Centers for Disease Control and Prevention (CDCP) and it may protect us from thousands of microbes [6]. The CDC guideline reported that, about two million people get hospitalized each year due to infections and that around ninety thousands of these patients die as a result of their infections [12]. Improved hand hygiene practice by health care workers and better cleaning of common hospital equipment could reduce the probability of patients becoming colonized and lead to subsequent reductions in infectious diseases. Thus it was calculated that, routine hand hygiene could save one million lives per year [13].

Hand hygiene can be performed by the removal of microbes with ordinary soap and water, and/or hand antiseptic using an antimicrobial soap or an alcohol-based hand rub. Considering the importance of hand hygiene, the CDC issued a guideline endorsing that, the hand rub can be regularly used for decontaminating hands. The hand sanitizers are composed of alcohol, ethanol, isopropanol or propanol with a suggested concentration [14, 15]. However, iodine-based hand sanitizers also used frequently and a povidone-iodine hand wash and hand rub products demonstrated efficacious virucidal products to help prevent infection and limit the spread of Ebola virus disease [16].

Some research already reported that, hand washing with soaps may result in cracked skin as soap can remove body's fatty acid from the skin, which then provides an entry portal for pathogens [17, 18]. On the other hand, eminent antiseptic has supplementary skincare product such as emollients, and recommended that the hand sanitizers are also well-suited by the skin [19]. Another great benefit of hand sanitizer is that it could play a vital role to prevent commonly transmissible pathogens in water lacking areas as it does not require water to wash hands. However, when use too frequently, the alcohol based hand sanitizers also can cause drying and cracking on skin. Moreover the alcohol-based hand sanitizers are classified as a fire hazard [14, 15]. Therefore, they should be stored out of child's reach and only should use with adult supervision. If ingested, alcohol toxicity can even lead to alcohol poisoning [15]. The iodine have persistent antimicrobial activity for a prolonged period and iodine-based hand sanitizers could be a good alternative for alcohol-based hand sanitizers.

This particular study was aimed to check out the efficacy of some alcohol-based hand sanitizers and a Lugol's iodine (2% iodine) formulation against bacteria of clinical importance using both dilution and diffusion susceptibility methods. This investigation serves to broaden the knowledge of the general public about the effect of hand sanitizers and also increases awareness on hand hygiene. Furthermore, this research might lead the manufacturers of these products to improve their products and make it more users friendly as well as a fetal tool for infectious microorganism.

## MATERIAL AND METHODS

### Test isolates

The clinical isolated used in this study were previously characterized and obtained from the Enteric Microbiology Laboratory of the International Central for Diarrheal Disease Research, Bangladesh. These isolates include the *S. flexneri*, *S. aureus*, *S. typhi*, *E. coli*, and *S. pneumoniae*. All isolates were stored in -70°C until when needed.

### Hand sanitizers and Lugol's iodine

Three brands of alcohol-based hand sanitizers were purchased from the local shop of Sylhet, Bangladesh. These are Hexisol, Sepnil, and Handirub (Table 1). Lugol's iodine solution (2% iodine) prepared in the general laboratory of the Department of Biochemistry and Molecular Biology, Shahjalal University of Science and Technology (SUST) according to FDA manual [20]. The following table 1 was developed for showing the ingredients used in hand sanitizers.

**Table 1.** Hand sanitizers used in this study and their fundamental ingredients

Product Name	Active ingredients	Manufacturer name
Hexisol	0.5% w/v chlorhexidinegluconate, 70% w/w isopropyl alcohol	Advanced Chemical Industries Limited
Sepnil	62% Ethanol	Square Toiletries Limited
Handirub	0.5 % w/v chlorhexidinegluconate, 70% w/w isopropyl alcohol	Eskayef Bangladesh Limited
Lugol's Iodine	Potassium iodide and iodine crystal	Laboratory formulation

### Agar diffusion test (well variant)

In this study, the agar diffusion method was used demonstrated by Valgas et al. [21]. This test was carried out as a preliminary screen to assess the antimicrobial activities of the various products. This involved the use of an inoculum corresponding to 0.5 [22]. The absorbance of the 0.5 McFarland standards was adjusted to 0.08-0.10 in 625 nm wavelengths. The prepared standard always keeps into a dark cabinet until needed [23]. Müller-Hinton agar (MHA) was prepared for antibiotic susceptibility testing [24]. The test inoculum was swab

inoculated to an MHA plate and allowed to stand at room temperature for 15 minutes. With the aid of a sterile 6 mm cork-borer, 4 equally spaced holes were bored in the agar plate with a fifth hole in the center of the plate. Fifty microliters (50 µL) of the hand sanitizer was then introduced into each of the 4 wells while the central well was filled with an equal volume of sterile water to serve as a control. This was done for all the test organisms and hand sanitizers. The plates were incubated for 24 hours at 37°C in an upright position. They were then examined for zones of inhibition. The test was carried out in duplicates and the average of two readings was taken as the zone of inhibition in each case. Inhibition zones were measured with the aid of a ruler and all the measurement was taken as millimeter [21].

#### **Determination of minimum inhibitory concentration (MIC)**

MIC was carried out to determine the lowest concentration of test substances needed to prevent the growth of a given organism *in vitro* [25]. Various concentrations of the sanitizers were prepared in ascending order (40%, 60%, 80%, and 100%). In case of iodine solution, a formulation of 0.5%, 1%, 1.5%, and 2% of iodine solutions were used. The tubes were incubated for 24 hours at 37°C and examined for visible growth or turbidity. The concentration of the sanitizer at which no visible growth was observed compared with the controls, was regarded as the MIC [26].

#### **Determination of minimum bactericidal concentration (MBC)**

MBC is the lowest concentration of a specific antimicrobial that kills 99.9% of cells of a given bacterial strain [25]. MBC was determined by assaying for live organisms in the tubes from the MIC tests which have shown no visible growth. A loop full of inoculums from the MIC tubes was streaked on fresh nutrient agar plates without the hand sanitizer incorporated into them. The plates were observed for growth after incubated at 37°C for 24 hours. Absence of growth indicated a bactericidal effect of the sanitizers at that concentration which is the MBC.

#### **Determination of efficacy of hand sanitizers in reducing viable counts of bacteria on the hands of subjects**

All the three commercial hand sanitizers and Lugol<sup>s</sup> iodine were further evaluated for their efficacy in reducing baseline bacterial counts of resident flora on the hands of subjects. Twenty individual volunteers were randomly selected for the study and verbal permission was obtained from all participating volunteers prior to the experiment. Before starting this procedure, the volunteers were well educated about correct hand disinfection procedure according to WHO [27]. The five randomly selected subjects hand were examined for baseline bacterial count reduction with each sample. Sterile nutrient agar plates were serially numbered and marked as with sanitizer and without sanitizer. At first, the test was carried out with unwashed hands of the subjects. Subjects' left hands were gently used to make a finger impression on the agar by pressing and rolling the finger on the agar in the plate marked as without sanitizer. After that, three milliliters of the sanitizer was applied to the hand and then rubbed thoroughly on the palm, hands, and fingernails until the hands became dry. Further the finger impression was repeated on the plate marked with sanitizer for all subjects. The plates were incubated for 24 hours at 37°C and after 24 hours the number of colonies was counted with a colony counter. The reduction in colony-forming unit (CFU) percentage was calculated to evaluate the efficacy of different hand sanitizers. The CFU percent reduction was determined by the following simple formula.

$$\text{CFU percent reduction} = \frac{(A-B) \times 100\%}{A}$$

Where A is the viable counts of microorganism before treatment

Where B is the viable counts of microorganism after treatment

## **RESULTS**

#### **Agar diffusion test**

In the susceptibility test, all the test products exhibited inhibitory activity against the test isolates (Table 2), except Sepnil against *S. typhi*. There was no inhibition zone for Sepnil against *S. typhi* (Figure 1), and also had lowest inhibition zone against *S. flexneri*, *S. aureus*, *E. coli*, and *S. pneumoniae*, which were 6.63 mm, 9.63 mm, 10.13 mm, and 8.30 mm respectively. Thus Sepnil was the least effective hand sanitizer to kill bacteria in agar diffusion test. Handirub gave better agar diffusion test result against *S. aureus*, *E. coli*, *S. flexneri*, and *S. typhi* by comparing with Hexisol and Sepnil. It showed the maximum diameter of the inhibition zone against *S. typhi* (27

mm) and lowest diameter of inhibition zone against *E.coli* (25.38 mm). The highest inhibition zones were observed by the 2% iodine and Handirub ranging from 24.38 mm to 28.63 mm.

**Table 2.** Summary of the susceptibility patterns of test organism against different hand sanitizers

Sanitizers name	Diameter of inhibition zones (mm) of hand sanitizers against test organisms				
	<i>S. flexneri</i>	<i>S. aureus</i>	<i>S. typhi</i>	<i>E. coli</i>	<i>S. pneumoniae</i>
Hexisol	15.00	13.13	14.50	14.50	16.50
Sepnil	06.63	09.63	0	10.13	8.30
Handirub	25.88	26.00	27.00	25.38	26.80
2% iodine	28.63	26.75	24.38	26.36	28.00



**Figure 1.** Sample MHA plate of Hexisol and Sepnil against *S. flexneri* and *S. typhi* respectively

#### Minimum inhibitory concentration (MIC)

All the commercially available hand sanitizers tested here had a MIC of 100% (Table 3). At 80% concentration, Handirub was effective against all the test organisms except *Salmonella typhi*, and Hexisol was effective against *S. flexneri* and *S. aureus* only (Table 3). Sepnil was not effective even at a concentration of 80% for any of the test organism. In the case of Lugol's iodine, inhibitions of all the test organisms were observed at 1%, 1.5%, and 2% concentrations (Table 3). Thus only 1% of iodine is highly effective to kill all the test organisms used in this study.

**Table 3.** Minimum inhibitory concentration determination (MIC) test results

Hand sanitizer	Concentration (%)	Test organism					MIC
		<i>S. flexneri</i>	<i>S. aureus</i>	<i>S. typhi</i>	<i>E. coli</i>	<i>S. pneumoniae</i>	
Hexisol	40	+	+	+	+	+	100%
	60	+	+	+	+	+	
	80	-	-	+	+	+	
	100	-	-	-	-	-	
Sepnil	40	+	+	N/A	+	+	
	60	+	+	N/A	+	+	
	80	+	+	N/A	+	+	
	100	-	-	N/A	-	-	
Handirub	40	+	+	+	+	+	
	60	+	+	+	+	+	
	80	-	-	+	-	-	
	100	-	-	-	-	-	
Iodine	0.25	+	+	+	+	+	
	0.50	+	+	+	+	+	
	1.0	-	-	-	-	-	
	1.5	-	-	-	-	-	
	2.0	-	-	-	-	-	1%

Key: + growth, - no growth, N/A – not applicable



### Minimum bactericidal concentration (MBC)

The contents of the 100% concentration tubes were further tested to determine the MBC. Unfortunately, the MBC test plates of commercial hand sanitizers showed the bacterial growth indicating that the products were only bacteriostatic against the organisms and not bactericidal. Interestingly, when the 2% iodine contents were plated on nutrient agar, there were no growths of test organisms. Similar results were also observed with the iodine concentration of 1.5% and 1%. Thus 2% iodine appeared to be the more effective hand sanitizer option as it is highly bactericidal.

### Efficacy determination test

The efficacy of hand sanitizers in reducing viable counts of bacteria on the hands of volunteers was determined after applying the hand sanitizers and 2% iodine individually. The internal ethics committee of SUST approved the study protocol and informed consent were taken from all the participants. There were no commercial hand sanitizers which can reduce the 100% viable bacterial count. The efficiency determination test revealed that Handirub had highest CFU reduction rate (96.57%) by comparing with Hexisol and Sepnil (93.05% and 85.99 %, respectively) (Table 4). However, 2% iodine formulation was highly effective for the reduction of viable bacterial count on volunteer's hand (100%). The performance of Sepnil was only 85.99%, which represent the lowest performance.

**Table 4.** Viable bacterial count reduction on Hands of volunteers

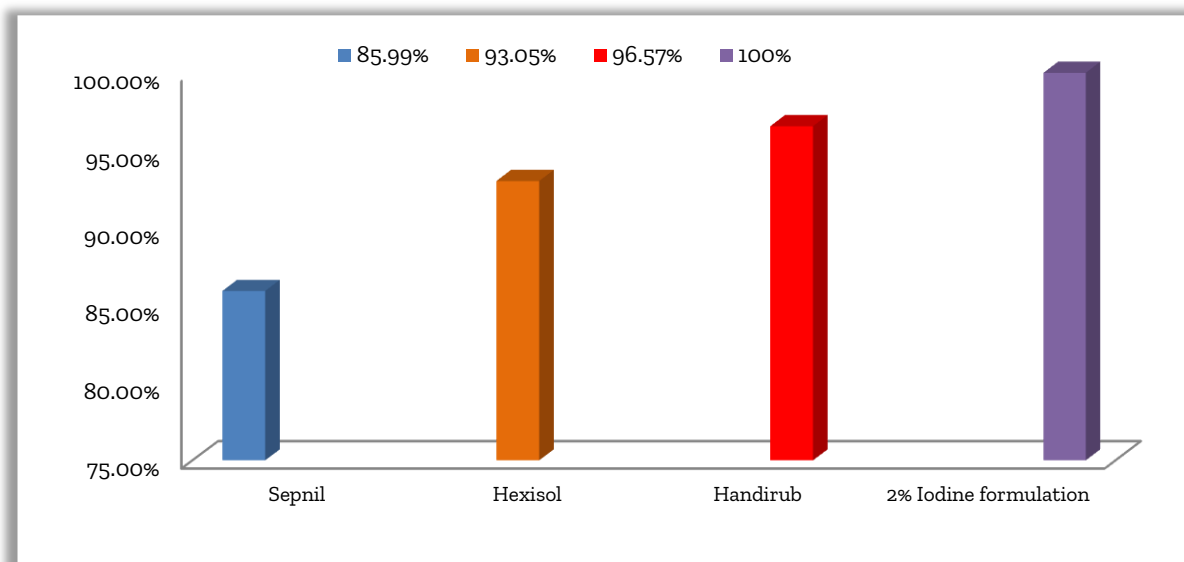
Volunteers no	CFU percentage reduction			
	Hexisol	Sepnil	Handirub	2% iodine
1	98.16	82.72	97.12	100
2	92.69	87.5	99.66	100
3	94.39	85.34	96.86	100
4	96.21	91.83	89.90	100
5	83.79	85.5	99.32	100
Average reduction	93.05	85.99	96.57	100

## DISCUSSION

Hand hygiene is one of the most important parts to control infections and prevent various diseases [28, 29]. The importance of efficacy in choosing the right-hand hygiene product is reflected in the CDC guideline on hand hygiene [30]. An eminent and prescribed method of hygiene is hand sanitizing especially in a healthcare setting and in areas lacking adequate water supply [28]. We have evaluated the antibacterial efficacy of the most popular and available brands of hand sanitizers sold in Bangladesh. Laboratory preparation of 2% iodine was also used as a hand sanitizer in this study, which can be considered as a homemade hand sanitizer.

In this study, the commercially available hand sanitizers showed a variable level of efficiency in the MIC test. Although Hexisol and Handirub have chlorohexidine and isopropyl alcohol as their active ingredient, Hexisol showed a lower diameter of inhibition zone for *S. aureus* and *S. typhi*. This could be occurring due to the poor or prolonged storage of the products which could lead to increased temperature causing evaporation of the active ingredient. In addition, the diluted hand sanitizers did not show antibacterial activity in the MIC test. Thus the antibacterial effect in MIC tests was only observed with 100% concentration of commercial hand sanitizers. On the other hand, the laboratory formulation of 2% iodine was effective in a diluted form such as 1% during MIC test.

This study revealed a poor performance in the agar diffusion test of Sepnil, as the highest diameter of inhibition zone was only 10.13 mm against *E. coli*. Moreover, there was no zone of inhibition for *S. typhi*, which represent that this bacterium was resistant against Sepnil. The Sepnil also gave the lowest CFU reduction value among the four hand-sanitizers (Graph 1). The poor activity of Sepnil is probably due to the negative interactive effects of the additional ingredients such fragrance, emollients, humectants, and thickening agents added to them. Besides, Sepnil is a gel type hand sanitizer whereas the other two sanitizers sold in liquid form. Therefore, the efficacy of hand sanitizers is also affected by the types of the sanitizers and liquid form is more suited and well distributed to the skin when it is applied to hand. The same type of finding also obtained by Kramer and his colleagues and they recommended that alcohol-based gels should not replace liquid hand disinfects in hospitals [31].



**Graph 1.** The overall efficiency of the used hand sanitizers to reduce the viable bacterial count

The CFU reduction rate for the commercial hand sanitizers was ranging from 85.99 to 96.57%, although the manufactures claim is 99.9% leveled on the bottle. A useful and effective hand antiseptic is still lacking in Bangladesh. Government and proper authorities should take care of this issue because the effect of hand hygiene interventions on rates of gastrointestinal and respiratory illnesses is well known. As the hand hygiene is the simplest and most effective measure to reduce hospital-acquired infections [32], government and proper authorities should take care of this issue to certify the effective hand sanitizers.

This study also focused on a laboratory-made iodine-based hand sanitizer, as they are reported as antimicrobial agents for many years [33]. However, some Muslim health care workers also refuse to use alcohol-based hand sanitizers [34]. Thus an iodine-based hand sanitizer could be a good alternative. Previously, a different form of iodine such as tincture of iodine was used as an antiseptic [35]. Interestingly, 2% iodine hand sanitizer was performed very accurately in the context of all kind of efficiency which represents it as strong hand sanitizers. Instead of all good antibacterial activity of iodine, there were some disadvantages of using it as hand sanitizer also. The iodine solution has an odd odor and a yellowish color, which might discourage to use of this iodine formulation. A further study is needed to establish this iodine formulation to use as a suitable hand sanitizer with good odor and color.

## CONCLUSION

Proper hand hygiene is an important first-line defense against the spread of numerous infectious diseases. The commercially available hand sanitizers are not effective in this study, although the manufacturers claim that their products could kill 99.9% germs in hands. Thus these hand sanitizers are not sufficient for our safety, and some hand sanitizer is proved for unfair claims. On the other hand, only 1% iodine is more effective than commercial hand sanitizers in preventing bacteria from the hands of individuals. Therefore there is a necessity to confirm the effectiveness of hand sanitizers sold in Bangladesh. Regulatory authorities and manufacturers should enforce stringent quality control measures and routine inspections during production to ensure the efficacy of these products and thus protect consumers from buying inferior products. Finally, in case of an emergency and water deficit areas of the world, only 1% iodine formulation can be used as a suitable and effective hand sanitizer verified in this study.

## DECLARATIONS

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### Authors' contributions

All authors contributed equally to this work.

### Competing interests

The authors declare that they have no competing interests.

### Consent to publish

Not applicable.

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# Esophagus extirpation in the surgical treatment of neglected stages of esophageal achalasia

Feruz Gafurovich NAZIROV, Zaynitdin Mahamatovich NIZAMKHODJAYEV, Ruslan Efimovich LIGAY, Aleksey Olegovich TSOI, Doniyor Bakhtiyarovich SHAGAZATOV, Elnar Ildarovich NIGMATULLIN✉ and Kudratbek Bahtiyarovich BABADJANOV

Republican Specialized Surgery Centre named after Academician V.Vakhidov, Tashkent city, Uzbekistan

✉Corresponding author's Email: rscs.elnar@gmail.com

## ABSTRACT

**Aim.** The surgical treatment experience of patients with neglected stages of esophageal achalasia has been presented in the article. **Methods.** The esophagus extirpation with simultaneous gastroesophagoplasty due to esophageal achalasia of stage III-IV was performed in 28 patients. **Results.** The results of the research, identifies indications for surgical intervention, features of intra- and postoperative complications, immediate and long-term results of esophageal extirpation. Cardiodilation remains the main treatment method for patients with esophageal achalasia, but its efficiency is significantly reduced in patients with neglected stages. **Conclusion.** Esophagus extirpation in patients with neglected stages of achalasia is pathogenetically reasonable surgical intervention when there is severe esophagoectasia and S-shaped deformity of the esophagus and cardio-esophageal junction. Further control randomized trials and multicentric studies should be performed.

## Original Article

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## Keywords

Achalasia,  
Neuromuscular diseases  
of the esophagus,  
Esophageal extirpation,  
gastroplasty.

## INTRODUCTION

Esophageal achalasia is one of the most common neuromuscular diseases of the esophagus at which the dystrophy of the Auerbach's plexus occurs. As a result, there is a disorder of the reflex of the cardia opening in response to a sip, the peristaltic activity of the esophagus is inhibited which leads to the development of severe esophagoectasia [1-4].

The etiopathogenesis of the disease still remains unclear. All treatment options are symptomatic and aimed at eliminating the main symptom - dysphagia. The main method of treatment is cardiodilation which is effective at any stages of the disease. However, in neglected cases, as well as in the recurrence of dysphagia, the effect of dilation is much less and surgical treatment is often necessary. There are more than 60 variants of surgical interventions for achalasia, most of which are numerous modifications of the Geller's operation. They are aimed to an extra-mucosal dissection of the distal esophagus and the stomach cardia muscles for reducing the gradient of the esophagogastric pressure, which facilitates the passage of the cardia [4-6]. However, in patients with achalasia the complete absence of the cardia opening in response to the sip and the complete absence of peristaltic activity of the esophagus wall, come to the fore. Therefore, in stage IV of the disease a good effect from cardioplastic operations cannot be expected.

The esophagus extirpation remains one of the most complicated operations in thoraco-abdominal surgery which is characterized by trauma, duration, high risk of intraoperative and postoperative complications. In most cases it is performed at esophageal cancer. The main advantage of esophagus extirpation is a complete removal of the pathologically changed organ – the esophagus. There are isolated reports in the world literature on the experience of using the extirpation of the esophagus in patients with achalasia of the cardia, which can be considered the only radical method of surgical treatment of this category of patients [1-4, 7].



This study aimed to investigate the esophagus extirpation results in the surgical treatment of neglected stages of esophageal achalasia.

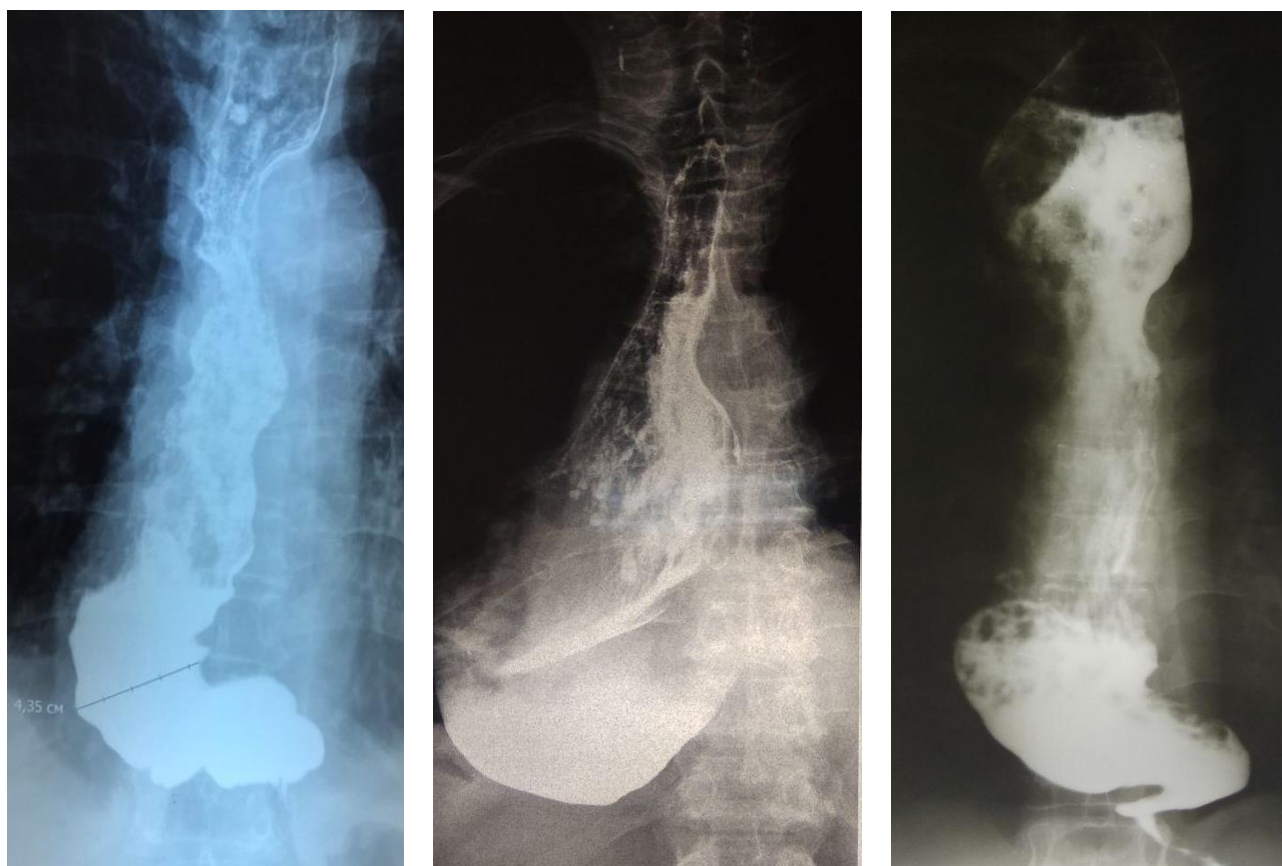
## MATERIALS AND METHODS

### Ethical approval

The review board and ethics committee of Republican Specialized Surgery Centre named after Academician V.Vakhidov approved the study protocol and informed consents were taken from all the participants.

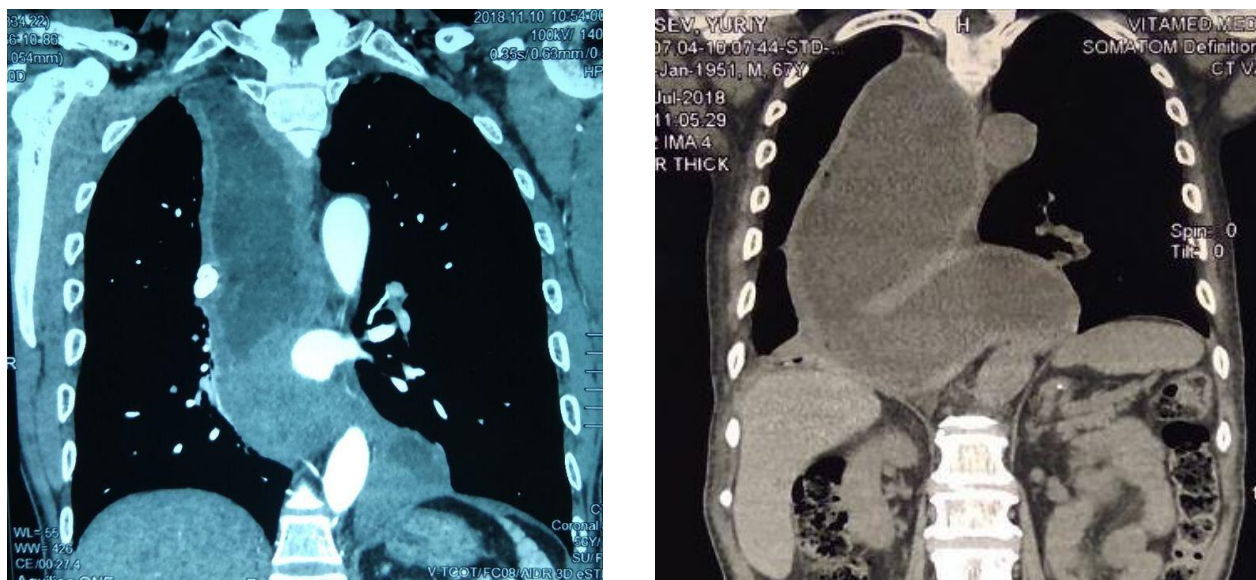
Total of 28 esophagus extirpations due to the neglected stages of achalasia were performed at the Department of Esophagus and Stomach Surgery of the Republican Specialized Scientific and Practical Medical Center of Surgery from 1998 to 2018. There were 18 males (64.2%) and 10 females (35.8%) participated in the study. The age of patients ranged from 11 to 62 years. Achalasia of stage III was in 4 patients (14.3%) and stage IV in 24 patients (85.7%). When collecting anamnestic data it was determined that 2 patients (7.1%) had previously undergone esophagocardiomy, and 1 patient (3.6%) had previously undergone esophago-cardiomyotomy. The rest of patients were performed repeated courses of cardiodilation. The disease duration in all patients was more than 5 years.

All patients were performed a comprehensive examination which included endoscopic, radiopaque investigations, as well as Modern methods of radiation diagnostics (MSCT). Characteristic features along with the clinical presentation were evident esophagoectasia, the absence of peristaltic activity of the esophagus muscular wall, S-shape deformity of esophagus and cardia. The X-ray pattern of patients with neglected stages of achalasia stage IV is presented in Figure 1.



**Figure 1.** X-ray pattern of the esophagus (achalasia of stage IV)

Modern methods of radiation diagnostics (MSCT) allow not only to make a diagnosis, but also to determine the features of topographic-anatomical ratio of the esophagus to the rest of the structures of the mediastinum and pleural cavities (Figure 2). This is important when mobilizing the esophagus from the mediastinum through abdomino-cervical approach which is limited for visualization.



**Figure 2.** MSCT pattern of the esophagus (achalasia of stage IV)

## RESULTS

The main methods of patients treatment with achalasia are various cardiodilation options (pneumatic, hydroballoon). However, in patients with neglected III-IV stages when there is S-shaped deformity, both of the esophagus and the stomach cardia, the possibilities of dilatation are sharply limited and the restoration of food patency is short. Such patients have to be performed surgical treatment. Indications for the esophagus extirpation in our patients were:

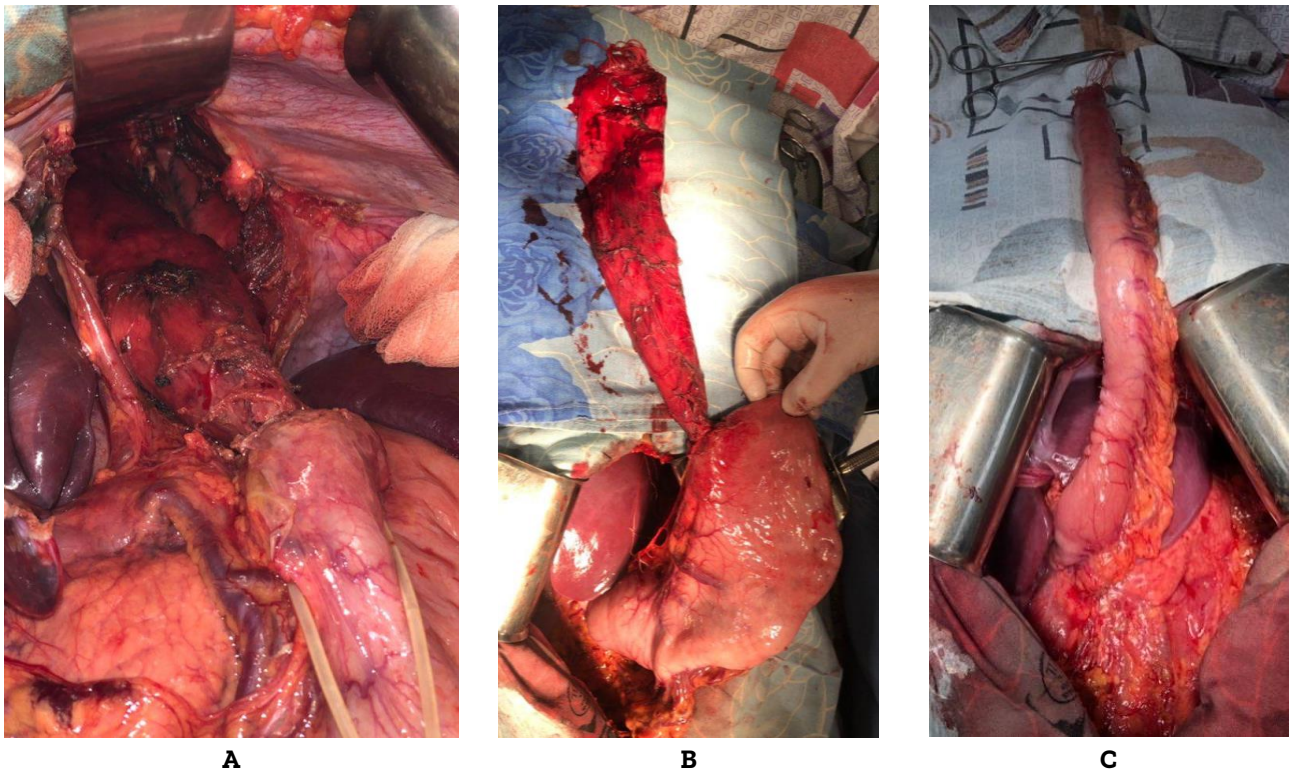
- Dilatation inefficiency, i.e. directly unsatisfactory result when after repeated (5-7) sessions patients did not have a clinical effect – in 8 cases (28.6%);
- The impossibility of holding the dilator in the stomach which was evaluated on the basis of a comprehensive examination and was confirmed when trying to hold the dilator, when the risk of the esophagus injury exceeded the expected clinical effect – in 17 cases (60.7%);
- Stenotic reflux esophagitis of the lower third of the thoracic esophagus against the background of previously performed esophagocardiomyotomy – in 3 cases (10.7%).

There are 5 main factors in solving the issue of using esophageal extirpation in patients with neglected stages of achalasia:

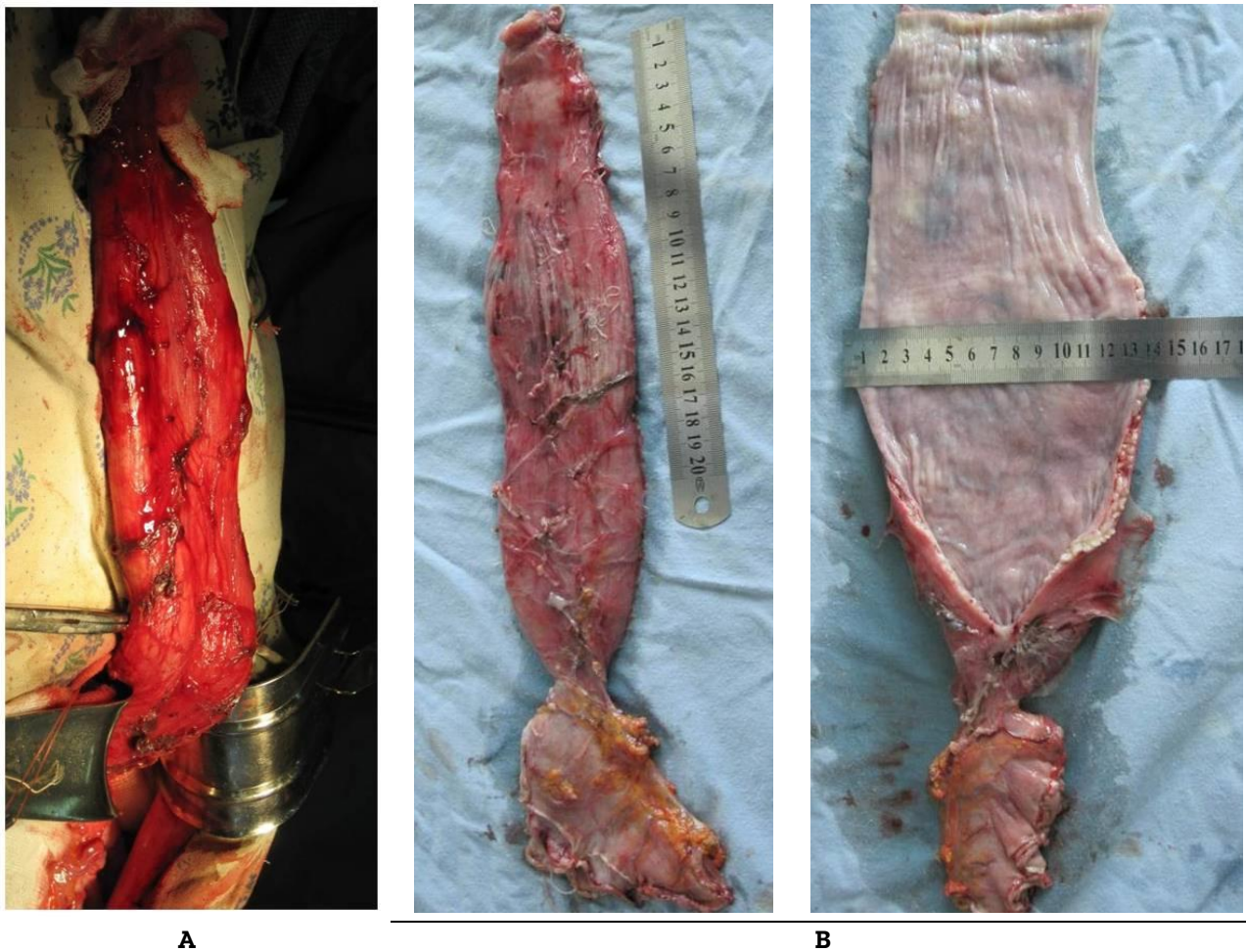
1. Simultaneous performance of esophagoplasty. In all 28 cases the resection and recovery stage (esophagoplasty) were performed in one stage.
2. The choice of surgical approach. Abdomino-cervical approach was used in 27 patients (96.4%) and thoraco-abdomino-cervical approach was performed in 1 case (3.6%) because of the presence of concomitant pathology (echinococcosis of the middle lobe of the right lung) a simultaneous echinococcectomy from the lung was performed. The choice of the surgical approach nature was based on the fact that achalasia is a benign disease and does not require extensive lymphadenectomy, as the esophageal cancer, and therefore it is not advisable to use traumatic thoracic approach.
3. Volume of the esophagus resection (extirpation or resection). In patients with neglected stages of achalasia, esophagoectasia of all parts of the esophagus is noted due to dystrophy of the Auerbach's plexus. In the presence of indications for radical surgery it is necessary to remove almost the entire esophagus. Therefore, in all cases we performed the extirpation of the esophagus while leaving only a part of the cervical esophagus (3-4 cm) which was enough to form an anastomosis on the neck.
4. Method of esophagoplasty. When choosing the method of esophagoplasty, we preferred the use of an isoperistaltic gastric tube from the greater curvature of the stomach which was used in 24 patients. Only in 4 patients we used the left half of the colon to create a transplant due to the impossibility of gastropasty.
5. Level of esophageal anastomosis application (intrapleural or extracavitary cervical). The solution of this issue is debatable only in patients with esophageal cancer. In all cases a cervical extracavitary esophageal anastomosis was formed in patients with achalasia.

The stages of the esophagus extirpation with gastropasty have been shown in [figure 3](#).





**Figure 3.** The stages of the esophagus extirpation with gastroplasty. A= Mobilization of the esophagus after diaphragmotomy. B= The extracted esophagus with mobilized stomach. C= The formed gastrotransplant



**Figure 4.** The extracted macro-preparation. A= The mobilized esophagus. B= The extracted macro-preparation.

Complications of the esophagus extirpation in patients with neglected stages of achalasia are divided into intraoperative, immediate and late postoperative complications. The difficulty of the esophagus mobilization through the abdomino-cervical approach which are caused by severe esophagectasia and periesophagitis. In this regard, we observed the following intraoperative complications: bleeding from the mediastinum in 5 (17.8%) which was stopped intraoperatively by a mediastinal plugging; injury of the mediastinal pleura in 14 (50%) which required additional drainage of the pleural cavities; injury of the left recurrent nerve in 4 (6.3%) which caused a temporary loss of voice and a disorder of the swallowing act and which was normalized during the first 6 months after the operation against the background of therapy in the ENT specialists.

The following complications were observed in the immediate postoperative period: bronchopulmonary complications in 5 patients (17.8%): pneumonia in 2 patients, exudative pleurisy in 3 patients and specific complications in 1 patient (3.6%) had the esophagogastric-anastomosis failure.

All complications were stopped by conservative measures. No lethal outcomes were observed. All 28 patients were examined in the long-term period, in terms from 6 months to 20 years. Only in 2 cases (7.2%) cicatricial narrowing of esophagogastric anastomosis was diagnosed which required repeated bougienage and dilatation courses with a good clinical effect.

## CONCLUSION

The main treatment method for the patients with achalasia remains cardiomyotomy which belongs to the minimally invasive methods and allows ensuring adequate restoration of food patency. However, in patients with neglected stages its efficiency is significantly reduced, and the frequency of recurrent dysphagia is increased. In patients with neglected stages of achalasia when the peristaltic activity of the esophagus is completely lost severe esophagectasia is developed, as well as S-shaped deformation of the esophagus and the cardia itself. The operation of choice for these patients is the esophagus extirpation with simultaneous gastroesophageal anastomosis and the formation of extracavitary esophagogastric anastomosis in the neck. Compliance with all principles of gastroesophageal anastomosis will minimize the risk of dangerous intraoperative and postoperative complications. Further control randomized trials and multicentric studies should be performed. Though the represented study is a single center results and control randomized trials and multicentric studies should be performed.

## DECLARATIONS

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### Authors' contributions

All authors contributed equally to this work.

### Competing interests

The authors declare that they have no competing interests.

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# Systematic review on avian immune systems

Mastewal BIRHAN<sup>1</sup>✉

College of Veterinary Medicine and Animal Science, Department Veterinary Paraclinical Studies, University of Gondar, Ethiopia

✉Corresponding author's Email: maste675@gmail.com ; ORCID: 0000-0002-0984-5582

## ABSTRACT

**Aim.** The aim of this review paper is too summarized and compares avian immune systems to the other domestic animals as comparative immunology type of review. Appreciation of the avian immune systems and their functions are very critical for disease diagnostics and new vaccine developments. Some of the avian immune systems are differ from mammalian immune systems, based on their production sources of immune cells like B-cells production site bursa of fabrics, but in mammalian is bone marrow. When we see the antibody type of birds; there are three principal classes of antibodies: IgM, IgG, IgY and IgA. Antibody diversity is achieved by gene re-arrangement. The other effector immune cell of birds is T cells. There are two distinct pathways that are  $\alpha/\beta$  and  $\gamma/\delta$ , avian T-cell diversity is probable made through combinatorial and junctional mechanisms. Recently, genes of several avian cytokines have been cloned and expressed. A number of naturally occurring viruses cause immunosuppression in chickens. **Conclusion.** There is much current interest in understanding the mechanisms of immunosuppression and developing strategies to enhance immune responsiveness in commercial poultry.

## Review Article

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## INTRODUCTION

One of the wonderful rules in the poultry industry is to hardly working on disease and predator control, good institutional linkage, and with good management from the healthy birds it is possible to increased high productive efficiency, capacity and with it, economic profitability" [1]. Scientific research on poultry immunology and the diseases affecting avian species is not a new concept [2]. But, more recently, the chicken was the first agricultural species as an income sources for which indicted by a genome sequence map [3]. Meaningful what specific immune molecules are encoded in the chicken genome delivers an outstanding background to form and magnify our information on the avian immune systems [2]. Comparable other avian immune systems, the immune system of chickens is made up of two types of mechanisms non-specific and specific [4]. The potential pathogen and other risks facing mechanisms are slight different from those come across by mammals. It is therefore essential that mechanisms be available to combat invading bacterial, viral and parasitic pathogens and to destroy neoplastic or other altered cells. It is also essential in birds, as in mammals, that the resulting immune response be regulated to ensure that it is adequate in quantity and quality [5].

We need to understand the chicken immune system, to familiarize you with those defense mechanisms. The bursa of Fabricius and the thymus organs are the central lymphoid organs in the chicken, essential to the development of adaptive immunity [6]. In bird's poor of all bursal lymphoid tissue, but still holding a normal thymus, no circulating antibody was detected after challenge with different antigens. Delayed hypersensitivity reactions to tuberculin or vaccinia virus (VACV) were nearly completely inhibited [7].

From the pronounced important avian organs, gut-associated lymphoid tissue is one of the organ that contains functionally immature T and B lymphocytes at hatch, and that function is achieved during the first 2 weeks of age as demonstrated by mRNA expression of both ChIL-2 and ChIFN $\gamma$  confirmed by Bar-Shira et al. [8]. The gut is a vital organ system which makes up two equally important functions, that are digestion systems and host defiance [9]. When we address the chickens immune systems, the innate immunity includes physical barriers (skin, mucus coat of the GI tract), specific molecules (agglutinins, precipiacute phase proteins, lysozyme), phagocytic function of phagocytes (macrophages and neutrophils), and lysing activity of a class of lymphocytes called natural killer (NK) cells [10].

In females birds, may improve their reproductive victory by mediating brotherly competition and growth of offspring by means of differential hormone transfer to the egg yolk [11-13]. For example, differential transfer

of steroids to eggs within the same grasp may alleviate or intensification the effect of hatching asynchrony as yolk steroids enhance nestling growth and competition [14] and [13]. Yolk testosterone was also present in the eggs of female canaries that were kept without a male, indicating that it is of maternal origin [11]. Birds are born with an imperfect immune system and young chicks have to rely on maternal antibodies and the innate immune defiance system to fight off pathogens [15].

While the avian system shares several similarities with mammalian systems, there are differences in the genes and molecules involved, the cells and organs involved, as well as the functional mechanisms. Chickens, for example, have a different assortment of Toll-like receptors, defensins, chemokines and antibodies. Birds do not have eosinophils though the functional corresponding to the mammalian neutrophil is the avian heterophil. Birds do not have lymph nodes, but do have a Bursa of Fabricius, which mammals do not. The mechanisms by which the different receptors are generated are also fundamentally different [16]. Therefore, the aim of this review paper are compering and analyzing of how the avian immune systems, structures organization, cells and organs differ from the other domestic animal immune systems.

## OVERVIEW OF THE AVIAN IMMUNE SYSTEMS

Studies that comprehensive study type, as a comparative method to the immunology with an gratefulness for physiological ecology and evolution are defining an important new field in biology-ecological immunology [17]. Though in wide-ranging terms the avian immune response is strangely similar to that of mammals, when one looks at specifics birds have a different repertoire of immune organs, cells and molecules compared to those characterized in mammals.

The unique structures of chickens are adversely distresses by heat stress, so, due to this impressions reeducations of productive performance, immune response, survival and profitability of fast growing chickens [18]. Beyond the beneficial features, the risk regarding the development of antimicrobial resistance and transference of antibiotic resistance genes from animal to human microbiota led the European Union to ban the application of antibiotics as growth promoters since<sup>st</sup> January 2006, which was followed by the other parts of the world including North America [19].

Avian are extremely vulnerable to varies infection by opportunistic pathogens during the first few days after hatching [20]. In avian species, adaptive immunity encompasses both humoral and cell-mediated immune (CMI) responses [21]. The avian embryo provides numerous compensations for studies on development of the immune system [22]. The bird egg is worthily adapted to house, feed, and protect the developing embryo. The outer lime-flavored shell and adherent shell membranes provide a physical barrier that excludes most microorganisms, but permits free exchange of respiratory gases [23]. Interior to the shell membranes is a thick zone of albumen that provides a sterile fluid medium for the free growth and morphogenesis of the embryo and the extra embryonic membranes. In the center of the egg is the yolk mass that will nourish the embryo through the incubation period [24].

Commonly, Birds are lack organized lymph nodes, yet have the Bursa of Fabricius. Birds lack neutrophils and functional eosinophils, yet have a distinct group of polymorph nuclear granulocytes known as heterophil. Birds also have a different repertoire of cytokines, chemokines, Toll-like receptors, defensins and integrin's [25].

## INNATE IMMUNE SYSTEMS

### Innate cells

The innate immune system develops in the bone marrow (BM) from common myeloid progenitors (CMPs). Due to the expression of AR in hematopoietic progenitors, there is reason to believe testosterone may play an important role in shaping the immune cell repertoire even prior to the cells leaving the BM [26].

### Macrophages

Macrophages instigate from bone marrow stem cells by differentiating into monoblasts, promonocytes, and monocytes. However monocytes establish foremost phagocytic cellular component in chicken blood, tissue macrophages are extensively dispersed and present in almost every organ. Monocyte cultures from peripheral blood leukocytes can be established by incubating the leukocyte fraction on a solid substrate such as Petri dishes or glass coverslips. The adherent blood monocyte cultures can then be established by incubation and washing off the non-adherent cell fractions [27]. The two most commonly used avian macrophages cell lines are

MQ-NCSU, and HD11, an avian myelocytomatosis virus (MC29) transformed chicken macrophage-like cell line [28]. The MQ-NCSU cell line was established from spleen of a broiler-type chicken experimentally challenged with the JM/102W strain of Marek's disease virus. The cultural, morphological and functional characteristics of the MQ-NCSU cell line imply that this is a malignant-transformed chicken cell line belonging to the mononuclear phagocyte lineage. Avian macrophages harvest chemotactic cytokines of both macrophage inflammatory protein (MIP) families. The chicken MIP-1 and MIP-2 chemokines have the identical amino acid motifs as mammalian chemokines: adjacent cysteine's (CC) in the MIP-1 chemokines and cysteine's separated by another amino acid (CXC) in the MIP-2 family. The chicken MIP-2 family chemokine is currently designated as 9E3/CEF4. It has high homology to mammalian interleukin (IL)-8 and is abundantly expressed by activated peripheral blood monocytes [29-31].

## TLR

Pattern recognition receptors (PRRs) are a serious component of pathogen recognition in both mammals and chickens [32]. Toll-like receptors (TLRs), a main family of PRRs, are expressed in chicken intestinal tissues and the local immune cells have been shown to respond to bacterial ligands [33]. Influxes of heterophil as well as increases in cytokines and chemokines are evident [34, 35] and are thought to contribute to the pathology detected. However, once chicks are more than a few days old, *S. Typhimurium* persistently colonizes their intestines in the absence of pathology [36], signifying that maturity of host defenses contribute to the deficiency of clinical signs

In chickens, it has been established that heterophil constitutively express TLR2A, TLR2B, TLR1/6/10 mRNA and that heterophil isolated from neonatal chicks and exposed to LTA undergo an oxidative burst [37]. There are also data to suggest that CD14 and TLR2 mediate LTA-stimulated oxidative burst in heterophil [37]. Chicken TLR3 expression pattern appears to be similar to what is observed in mammals [33]. For example, chicken heterophil express TLR3 and are approachable to poly I:C, demonstrated by an induced oxidative burst and degranulation of the stimulated heterophil, which may be mediated by a signalling pathway involving phospholipase C, phosphatidylinositol 3-kinase and intracellular  $Ca^{2+}$  [38]. In contrast, others have confirmed the poor ability of poly I:C to stimulate nitric oxide (NO) production in chicken monocytes, while HD11 cells, a chicken macrophage cell line, were readily stimulated to produce NO by poly I:C [34, 39].

The first groups of TLR are expressed on the cell surface and recognize primarily cell-surface PAMPs. They include TLR1, TLR2, TLR4-6 and TLR10 in human and TLR11 in mice. There are direct chicken orthologous of mammalian TLR4 and TLR5 [33, 40]. In mammals, there is a single TLR2 gene, and the genes encoding TLR1, 6 and 10 lie in a single locus. Mammalian TLR2 forms functional heterodimers with at least TLR1 and TLR6, allowing recognition of a wider panel of pathogen associated molecular patterns (PAMPs). At the equivalent locus to the mammalian TLR1, 6 and 10 locus, the chicken genome encodes only two genes, TLR1LA and TLR1LB [41, 42]. Avian TLR repertoire and the response to various agonists [43]. Toll-like receptors (TLRs) are important for eliciting innate immunity in animals by playing an essential role as pattern recognition receptors that detect infectious pathogens by recognizing the conserved molecular structures known as pathogen associated molecular patterns [44]. There are ten avian toll-like receptors and that five of these, TLR2a, 2b, 3, 4, 5 and 7, are clear orthologous to TLRs found in mammals [45]. The non-mammalian TLR21 exists in many species of birds, fishes, and frogs [46, 47]. As a homologue of mammalian TLR9, TLR21 can recognize synthetic oligo-deoxy-ribonucleotides (ODN) and DNA viruses that contain CpG motifs, which further trigger the innate immune response [46, 48]. The RLR family encompasses three members: RIG-I, melanoma differentiation-associated gene 5 (MDA5) and research laboratory of genetics and physiology 2 (LGP2), which are located in the cytoplasm

## AVIAN ADAPTIVE IMMUNITY

### Cell mediated immunity and humeral immunity

Chicken  $\alpha\beta$  T cells express either CD4 or CD8 accessory molecules, whereas most of the  $\gamma\delta$  T cells do not [49]. The cytotoxic T lymphocyte response can decrease viral shedding in mildly pathogenic avian influenza viruses, but provides doubtful protection against HPAI. Influenza viruses can directly affect the immune response of infected birds, and the role of the Mx gene, interferon's, and other cytokines in protection from disease remains unknown [50]. Avian T cell progress has emerged with the use of monoclonal and functional antibodies to elucidate T cell differentiation antigens and molecular and functional explanations of mammalian

T cell receptors (TCRs) [51]. Avian T cells bearing a  $\gamma\delta$  TCR are the first to be generated during ontogeny and they comprise up to 50% of the recirculating T-cell pool in mature birds [52].

Progress of B cells in chickens proceeds via a series of disconnected developmental phases that includes the maturation of committed B cell progenitors in the specialized microenvironment of the bursa of Fabricius [53]. Three classes of chicken immuno globulins have been identified immunochemically [54] and genetically [55] as homologues to the mammalian IgM, IgA and IgG, and their organizational properties have been reviewed in more detail elsewhere [56]. The intestine is a complex tissue that includes a major immune constituent. Indeed, the numbers of immune cells found in intestinal tissues exceed the numbers found in the rest of the body [57, 58].

Expression of selected genes involved in pathogen detection and the innate immune response were profiled in caecal tissues by quantitative RT-PCR. TLR4 and TLR21 gene expression was transiently increased in response to both bacterial species [59, 60] and . Defense of the intestinal mucosal surface from enteric pathogens is initially mediated by secretory IgA (SIgA) [61].

Three classes of chicken immunoglobulin's have been identified immunochemically [62, 63] and genetically [64, 65] as homologues to the mammalian IgM, IgA and IgG and their structural properties have been reviewed in more detail elsewhere [66]. Chicken IgM is structurally and functionally homologous to its mammalian counterpart, being current in serum as a high molecular weight pentamer of m2L2 units and being the first antibody generated during a primary antibody response. IgM is also the major class of immunoglobulin expressed on the surface of chicken B lymphocytes [67].

### Chemokines and Cytokines

Interferon's (IFNs) are a family of multifunctional cytokines with significant roles in cellular resistance against viral infection [68]. In response to virus invasion, host pattern recognition receptors (PRRs) detect pathogen associated molecular patterns (PAMPs) and subsequent activation of innate immune system through retinoic acid inducible gene I (RIG-I) like receptors (RLRs)-MAVS-dependent IFN signaling or toll-like receptors (TLRs)-TRIF/MyD88-dependent IFN signaling [69], eventually, inducing the expression of type I IFNs. IFNs then bind their cognate receptors, triggering a signaling cascade that outcomes in the expression of abundant interferon-stimulated genes (ISGs) by the JAKSTAT signaling pathway, various of which possess antiviral properties [70, 71]. Interferon regulatory factors (IRFs), a family of transcription factors, play authoritative roles in the regulation of IFN expression during viral infection [72]. To date, 9 IRF genes (IRF1-9) have been described in mammals, a tenth (IRF10) is present in numerous avian species and a total of 11 IRFs (IRF1- 11) have been identified in fish [68].

## CONCLUSION AND RECOMMENDATIONS

The chicken, perhaps surprisingly, has made several influential contributions towards our understanding of immune responses as comparable way. Notwithstanding this, before the chicken genome sequence, our ability to study immune systems in detail in birds is appropriate and also in our thoughtful of the immune gene catalog. There are still gaps, both in the chicken immuno systems and their catalog. In comprehensive study is well important by comparing of birds immune systems with the other animals. Both innate and adaptive immune responses, with the latter including both cell-mediated and humoral immune responses, leading to address and increases our knowledge about chicken's immune activity. However, looking at the organs, cells, and molecules of the immune response in birds, it appears that mammals and birds accomplish the equivalent overall responses-often in quite different ways. Instead, we concentrate on the basic immune response, as well as a description of the major cell types and major areas where the cells and molecules of the immune response differ from those of mammals. Generally, the immune system of the chicken is very helpful in avoiding disease and helping to insure maximum productive potential is realized. We must learn how to take advantage of all parts of the system when designing health programs. Based on the above information's the following recommendation will be forwarded:

- Researcher should be focus on the avian immune systems and their role of contributions, and the delineation of the bursal and thymus-derived arms of the immune system.
- The genes of several avian cytokines have been cloned and expressed; so that scientists would be given an attention for new disease resistant gene formed.
- The researcher should be emphasis on current attentiveness in thoughtful the mechanisms of immunosuppression and developing approaches to advance immune responsiveness in commercial poultry.

## DECLARATIONS

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### Authors' contributions

Mastewal Birhan conceived the review, coordinated the overall activity, and write and submit the manuscript.

### Availability of data and materials

Data will be made available up on request of the primary author

### Consent to publish

Not applicable.

### Competing interests

The authors declare that they have no competing interests.

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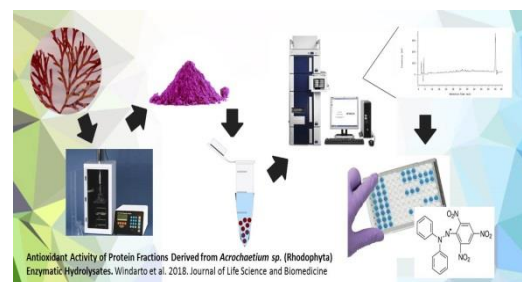
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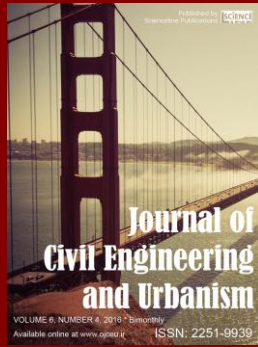
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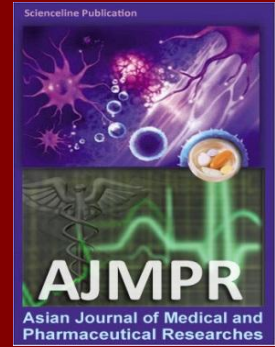
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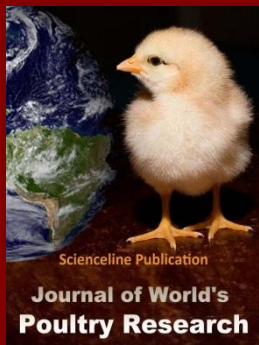
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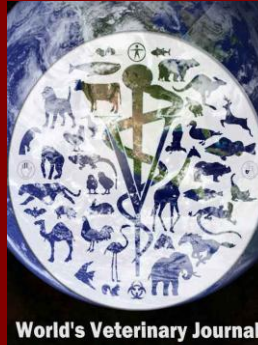
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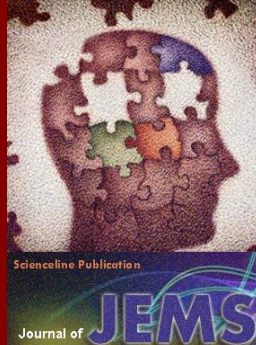
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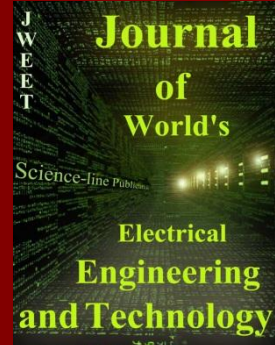
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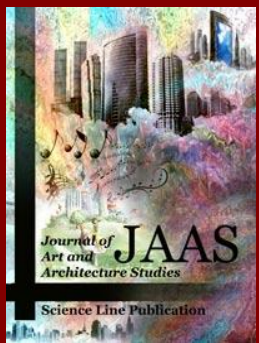
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