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# EFFECTIVENESS OF THE IMMUNOCORRECTION-DEWORMING-VACCINATION CHAIN BASED ON THE DOSTIM IMMUNOCORRECTOR IN THE PREVENTION OF INFECTIOUS DISEASES IN SERVICE DOGS

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**DOI: 10.67620/sai.58d0001**

**ABSTRACT**
*The effectiveness of organizing the prevention of infectious diseases in young service-dog puppies on the basis of an immunocorrection-deworming-vaccination sequence was evaluated. A total of 16 puppies were included in the study, and four groups were formed according to breed: Labrador, Belgian Shepherd, German Shepherd, and Cocker Spaniel. Each group contained 2 experimental and 2 control animals. In the experimental groups, Dostim was administered at a dose of 0.4-0.6 mL for 1-5 kg of live body weight, three times at 3-day intervals. Five days later, Adjipras and Azinox Plus were given at a dose of 1 tablet per 10 kg of live body weight, twice at 14-day intervals, after which Multican-5 vaccination was performed. Clinical observation was conducted for 21 days after vaccination. The same regimen was maintained in the control groups, except that Dostim was not administered. Various clinical signs were recorded in the control animals, whereas none were observed in the experimental animals treated with Dostim. The results indicate a positive clinical trend associated with the immunocorrection stage in this preventive chain.*

**ACCEPTED**

**25.08.26**

***Keywords:*** *service dogs, puppies, Dostim, immunocorrection, infectious diseases, deworming, vaccination, immunization, prevention.*

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## Introduction

Since the first days of our independence, great attention has been paid to national security both during the tenure of our First President I.A. Karimov and under our President Sh.M. Mirziyoyev. Therefore, special attention is also given to developing the structures that support these services. Cynology is one such field. In order to develop this field comprehensively, President Sh.M. Mirziyoyev signed a decree "On the Development of National Cynology." On the basis of this decree, it was stipulated that National Cynology Centers within security and law-enforcement structures should be further improved and that the activities of their kennels (service-dog training facilities) and schools for training canine inspectors should be brought to the level of developed countries. For the purpose of developing cynology and training qualified personnel for this field,

The dog is considered one of the animals most loyal to humans. According to J. Cuvier, dogs are among the most unique, useful, and highly developed discoveries of humankind. Humans recognized dogs' exceptional intelligence, acute sense of smell, good vision and hearing, speed, and endurance, and therefore brought them closer than other animals (Narziyev & Uzoqova, 2010).

Since ancient times, people have used dogs for hunting and for guarding homes. The use of dogs in the military sphere is also particularly effective. They are widely used to guard borders, locate and apprehend criminals, search for explosives and narcotic substances, and protect military facilities. Thus, dogs not only provide emotional support to people, but also make a significant contribution to economic development.

Veterinary medicine has become one of the important fields today. At present, veterinary work concerns not only the health of livestock, but also the health of companion animals, including service dogs widely used in the canine units of state special services, as well as their breeding and proper care. The prevention of infectious diseases plays an important role in maintaining the health and working ability of service dogs. In young puppies, while the immune system is still developing, factors such as parasitic infestations and subsequent vaccination may place an additional burden on the body. Therefore, organizing preventive measures as an interconnected sequence is of practical importance (Day, 2007; O‘lmasov, 2023).

The main idea of this study is to support the general resistance of the body by carrying out immunocorrection before deworming and to compare the clinical condition after subsequent vaccination with that of the control group.

The materials provided for Dostim indicate that, as an immunocorrector, the preparation is intended to activate cellular and humoral immunity, phagocytosis, and antibody production.

**Research Aim and Objectives**

Canine distemper is one of the serious diseases occurring in dogs. Puppies affected by this disease rarely survive. Adult dogs have a greater chance of recovery. Dogs that recover from distemper retain immunity to the disease for the rest of their lives. In dogs, the viruses that cause distemper spread through the digestive and respiratory systems. Once they enter the animal's body, the viruses affect all organs through the circulatory system. The initial stage of the disease remains latent for several days, during which time the virus spreads throughout the body. Distemper is not considered a seasonal disease because the virus can survive even at -24 °C. At the same time, cases of the disease in dogs are recorded more frequently in spring and autumn. Animals susceptible to the disease include poorly nourished dogs, puppies under one year of age, and stray dogs (Gaskell & Bennett, 2014; Martella et al., 2008; Ravilov, n.d.).

Affected dogs show weakness, loss of appetite, reddening around the eyes, and discharge from the nose and eyes. Photophobia develops in sick dogs, and they tend to hide in the shade. The body temperature of affected dogs rises to +40 °C and may remain elevated for 2-3 days. Adult dogs with strong immunity may overcome the disease on their own, but in weak dogs and young puppies the disease continues and the condition may rapidly worsen. Dogs that have recovered from distemper may experience deterioration in hearing, smell, and vision.

**Treatment and Prevention Measures for Affected Dogs**

The most appropriate way to identify the clinical signs of distemper is through examination by a veterinarian. Specific medicines that treat the viruses causing canine distemper have not yet been developed. After examining the affected dog, the veterinarian prescribes comprehensive treatment according to its condition. The use of preparations that enhance immunity is important in the treatment of dogs. It is important for the owner of an affected dog to provide appropriate supportive conditions to help it survive the disease. The dog's kennel should be dry, warm, and free from drafts. Exposure to light should be reduced because photophobia becomes pronounced in affected dogs. Discharge from the nose and eyes should be removed, and wounds on the body should be cleaned with disinfectant solutions. The food provided should be easily digestible. Liquid soups containing finely chopped meat and porridges can help dogs recover more quickly.

The only means of preventing canine distemper is vaccination. The first vaccination is administered when puppies are 2-3 months old. Dogs are usually vaccinated after deworming. Current canine


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vaccination guidelines emphasize age-appropriate core vaccination schedules and the influence of maternally derived antibodies on puppy immunization (Day et al., 2016; Ellis et al., 2024). Although vaccination performed in this order has generally produced good results in dogs receiving their first vaccination, cases in which clinical signs of adenovirus, parvovirus, and gastroenteritis appear in puppies within 7-14 days after vaccination have been observed. Large-scale clinical surveillance has also documented vaccine-associated adverse events in dogs within the first several days after vaccination (Moore et al., 2005). For canine parvovirus, persistent disease burden and immunisation failures, including those associated with maternally derived antibodies, are well recognized (Decaro & Buonavoglia, 2012; Decaro et al., 2020). Therefore, our scientific research is aimed at preventing the development of viral pathogens in the body after vaccination by strengthening the immune system before the vaccination procedure. Earlier regional conference literature has also examined factors influencing immunity during vaccination against canine distemper (Sagdiev, n.d.).

The main aim of the study is to determine the effectiveness of a preventive chain based on the sequential implementation of immunocorrection, deworming, and vaccination in young service-dog puppies, and to evaluate the practical significance of the Dostim immunocorrector within this chain.

- grouping puppies by breed and age
- carrying out immunocorrection with Dostim before deworming
- applying the same deworming and vaccination regimen in the experimental and control groups
- monitoring the clinical condition for 21 days after vaccination
- comparatively evaluating the results

**Materials and Research Methods**

A total of 16 puppies were included in the study. Four 2.5-month-old Labradors, four Belgian Shepherds aged 2 months and 10 days, four 2-month-old German Shepherds, and four 3-month-old Cocker Spaniels were selected. Each breed group included 2 experimental and 2 control animals; in total, 8 animals formed the experimental group and 8 animals formed the control group (Table 1).

**Table 1**

*Study Group Composition by Breed and Age*

| Group | Breed | Age | Total | Experimental | Control |
|---|---|---|---|---|---|
| I | Labrador | 2.5 months | 4 | 2 | 2 |
| II | Belgian Shepherd | 2 months 10 days | 4 | 2 | 2 |
| III | German Shepherd | 2 months | 4 | 2 | 2 |
| IV | Cocker Spaniel | 3 months | 4 | 2 | 2 |
| Total | — | — | 16 | 8 | 8 |

In the experimental groups, Dostim was administered at a dose of 0.4-0.6 mL for 1-5 kg of live body weight, three times at 3-day intervals. Five days after Dostim administration, Adjipras and Azinox Plus were given at a dose of 1 tablet per 10 kg of live body weight, twice at 14-day intervals. Subsequently, Multican-5 vaccination was performed, followed by 21 days of clinical observation.

The same deworming and vaccination regimen was applied in the control groups, but Dostim was not administered. Thus, the principal distinguishing factor in the study was the immunocorrection stage before deworming.

**Research Results**

In Labrador puppies in the control group, deterioration of general condition, loss of appetite, recumbency, and an increase in body temperature to 40.5 °C were observed during the 2 days following vaccination. In the Belgian Shepherd group, diarrhea was recorded 1 day after vaccination (Figure 1).



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In the German Shepherd group, reduced activity, loss of appetite, and a decreased heart rate were observed. In the Cocker Spaniel group, vomiting, loss of appetite, an increase in body temperature to 41.5 °C, and diarrhea were recorded on the 14th day after vaccination (Figure 2).

None of the clinical signs listed above were observed in the 8 experimental animals that underwent immunocorrection with Dostim. This result indicates a positive clinical trend associated with the immunocorrection stage (Table 2).

**Figure 1**

*Number of Animals With Recorded Clinical Signs in the Control Groups*

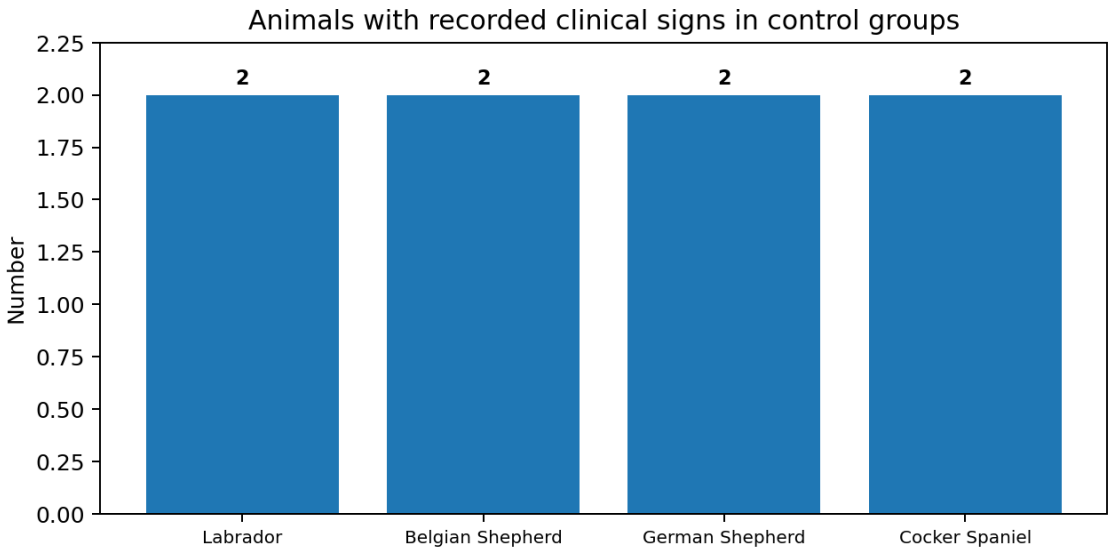
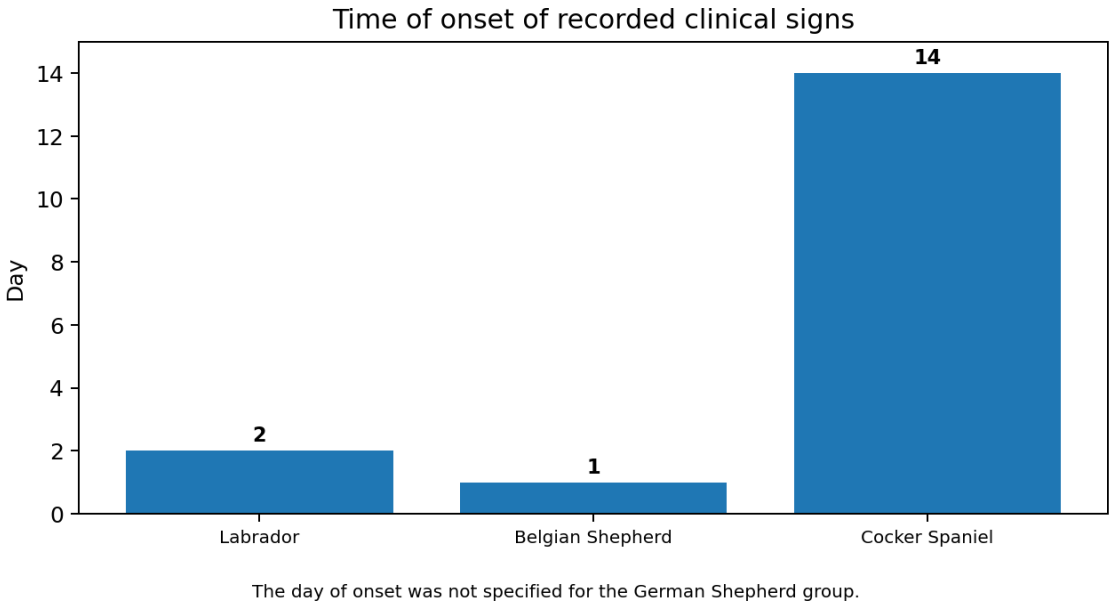



**Figure 2**

*Time of Onset of the Recorded Clinical Signs*




*Note.* The day of onset was not specified for the German Shepherd group.



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**Table 2**

*Post-Vaccination Clinical Observations*

| Group | Breed | Signs recorded in the control group | Time | Experimental group |
|---|---|---|---|---|
| I | Labrador | Deterioration of general condition; loss of appetite; recumbency; T=40.5 °C | 2 days | Not observed |
| II | Belgian Shepherd | Diarrhea | 1 day | Not observed |
| III | German Shepherd | Reduced activity and appetite; decreased heart rate | Not specified | Not observed |
| IV | Cocker Spaniel | Vomiting; loss of appetite; T=41.5 °C; diarrhea | 14th day | Not observed |

Because the experimental and control groups underwent deworming and vaccination according to the same regimen, with the main difference being whether Dostim was administered, the observed clinical differences may be interpreted as a possible positive effect associated with the immunocorrection stage.

However, because each subgroup contained only 2 animals, statistical generalization of the results to a broader population is limited. Since immunological markers and antibody titers were not provided, the clinical results do not constitute direct evidence of the immunological mechanism and should be regarded as clinical observations.

In future studies, increasing the number of animals, performing a complete blood count and leukocyte differential, determining immunoglobulins and post-vaccination antibody titers, and conducting statistical analysis would increase the scientific reliability of the study.

**Conclusions and Practical Recommendations**

1. Of the 16 puppies, 8 were assigned to the experimental group and 8 to the control group.
2. In the experimental group, Dostim was administered at 0.4-0.6 mL for 1-5 kg of live body weight, three times at 3-day intervals.
3. Five days after Dostim administration, deworming was carried out, followed by Multican-5 vaccination and 21 days of clinical observation.
4. In the control group, the remainder of the preventive regimen was repeated without the administration of Dostim.
5. During the 21-day observation period, various clinical signs were recorded in the control groups, whereas none were observed in the experimental groups treated with Dostim.

The use of an immunocorrection-deworming-vaccination sequence in organizing the prevention of infectious diseases in young service-dog puppies may be regarded as a promising approach. Dostim should be administered under the supervision of a veterinarian and in accordance with the instructions for the preparation.

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# EFFECT OF DIFFERENT SUTURE MATERIALS AND TECHNIQUES ON GASTRIC WALL TISSUE HEALING IN GASTROTOMY SURGERY IN DOGS

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**ABSTRACT**
*The article investigates the effect of different suturing techniques and suture materials used to close surgical wounds of the gastric wall during gastrotomy on the wound-healing process. The study was conducted at the Veterinary Clinic of Tashkent State Agrarian University and involved gastrotomy procedures performed on six dogs of different breeds diagnosed with pathological conditions associated with gastric lesions or foreign body ingestion. The animals were divided into two groups of three dogs each. In the first group, the gastric wound was closed using a two-layer suture technique consisting of Schmieden and Lambert sutures with synthetic lavsan suture material. In the second group, the wound was closed using a single-layer seromuscular Lambert suture with silk suture material. During the postoperative period, the general condition, appetite, behavior, defecation, and local condition of the surgical wound were monitored. The wound condition was assessed on days 5 and 10 after surgery. According to the observations, the group in which the two-layer Schmieden–Lambert suture technique and synthetic lavsan material were used developed a relatively smooth and firm scar. In contrast, the group treated with a single-layer Lambert suture and silk material showed a relatively coarse scar with localized areas of prominence. The practical findings of the study were also supported by clinical cases observed in veterinary clinics in Kibray, Tashkent District, and Chirchiq.*

**ACCEPTED**

**25.08.26**

***Keywords:*** *dog, gastrotomy, stomach, foreign body, Schmieden suture, Lambert suture, Lavsan, silk, wound healing, ultrasonography, veterinary surgery.*

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## Introduction

In recent years, canine-service programs in Uzbekistan have highlighted the importance of maintaining the health and working capacity of service dogs, while the growing population of privately owned dogs has increased the clinical importance of digestive disorders and gastrointestinal foreign-body ingestion. Surgical intervention is often required when a foreign body cannot be managed conservatively or endoscopically (Abdurahimov & Ulmassov, 2025; Hayes, 2009; Hobday et al., 2014; Ulmasov et al., 2026).

Modern veterinary surgery emphasizes prevention of postoperative infection and careful selection of suture materials. Suture composition and structure can influence local tissue reaction, inflammation, and wound healing, and the biological behavior of the material should be considered when closing gastrointestinal incisions (Ellison, 2011; Gazivoda et al., 2015; Regier, 2022).

Standard veterinary surgical literature describes a range of suturing patterns used in abdominal surgery, including interrupted, mattress, circular, Schmieden, Lambert, Cushing, Connell, and related techniques. Selection of a pattern should account for tissue apposition, luminal diameter, vascular preservation, and the expected healing characteristics of the organ (Ellison et al., 2019; Narziev, 2023).

The use of synthetic surgical suture materials with low tissue reactivity remains an important consideration in gastrointestinal surgery. Experimental and clinical evidence indicates that both suture material and closure technique can affect tissue reaction and healing, while increasing the number of suture layers does not necessarily improve clinical outcomes. Contemporary studies also support safe alternatives to traditional double-layer hand-sewn closure, including single-layer gastric closure and stapled gastrointestinal closure in selected patients (Hastings et al., 1975; Schwartz & Coolman, 2018; Velay et al., 2024).

Accurate diagnostic evaluation is important in diseases of the digestive organs because early recognition of general and local changes can support timely treatment and reduce complications. In dogs with suspected gastrointestinal foreign bodies, diagnostic imaging contributes to determining the location and clinical significance of the obstruction (Abdurahimov & Ulmassov, 2025; Hayes, 2009).

The examinations were performed using an ultrasound unit. The dog's abdominal cavity was examined with a transducer adapted for external imaging of the internal organs at a frequency of 4.5 MHz. During the examination, the hair over the abdominal region was clipped, the skin was treated with antiseptic, and the internal organs were evaluated by imaging with the aid of a special gel (Abdurahimov & Ulmassov, 2025).

Diseases of the digestive system in dogs, including gastric and intestinal foreign bodies, are important problems in veterinary surgical practice. Foreign bodies can be associated with obstruction, tissue injury, perforation, and the need for surgical intervention; prompt diagnosis and appropriate treatment are therefore important to outcome (Hayes, 2009; Hobday et al., 2014). Gastrotomy is an abdominal procedure used to remove foreign bodies from the stomach and to address selected gastric lesions when less invasive treatment is insufficient.

The final outcome of gastrotomy is not limited to removal of the pathological lesion. The gastric wall incision must also be closed with adequate strength, preservation of tissue perfusion, and minimal adverse effects on healing. Suture material, closure pattern, and the number of layers may influence tissue reaction and postoperative integrity (Ellison, 2011; Regier, 2022; Velay et al., 2024).

The preliminary materials of the study described Schmieden, Lambert, and other sutures used in abdominal surgery and identified the use of synthetic suture materials as a relevant area of investigation. These techniques remain part of veterinary surgical teaching and have also been discussed in recent work on gastrotomy closure in dogs (Narziev, 2023; Ulmasov et al., 2026).

Accordingly, the aim of the study was to comparatively evaluate the effects of different suturing techniques and materials on wound healing when closing gastric wall wounds during gastrotomy surgery in dogs.

**Materials and Methods**

The experiments were conducted at the veterinary clinic of the Department of General Animal Husbandry and Veterinary Medicine, Faculty of Zooengineering, Tashkent State Agrarian University. The study material consisted of dogs from the kennel of the Tashkent Regional Department of Internal Affairs canine service and privately owned dogs in which conditions associated with gastric injury or foreign-body ingestion had been identified.

Gastrotomy surgery was performed on a total of six dogs of different breeds, which were divided into two experimental groups of three animals each. In Group I, the gastric wound was sutured using a two-layer Schmieden-Lambert technique with synthetic Lavsan material. In Group II, a single-layer seromuscular Lambert suture with silk thread was used (see Figure 1).


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During surgery, the animals were placed and restrained in dorsal recumbency (Figure 2). The abdominal cavity was entered through a median laparotomy, the stomach was identified and exteriorized into the operative field. After removal of the foreign body or pathological lesion, the area around the wound was cleansed with 0.9% sodium chloride solution and closed using the appropriate suture technique.

After surgery, the animals' general condition, behavior, appetite, defecation, and the local condition of the surgical wound were monitored. In some animals, the wound condition was examined by diagnostic laparotomy on day 5, and the healing process was reassessed on day 10.

The practical validation materials also included clinical cases treated in Kibray District, Tashkent District, and the city of Chirchiq. In these cases, synthetic Vicryl/Vicryl Rapide-based suture materials and different suturing techniques were used, and wound healing was monitored by ultrasonography (see Table 3).

**Figure 1**

*Experimental Group Design and Suture Techniques*

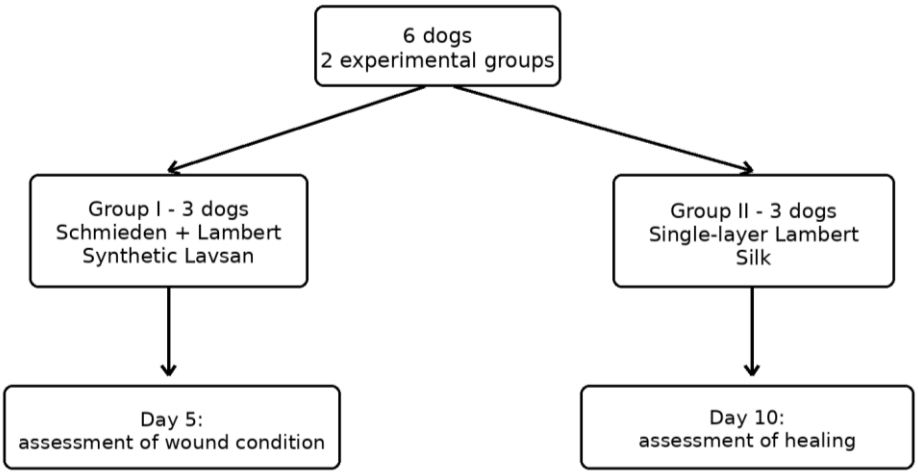



**Table 1**

*Breed Distribution Across Experimental Groups*

| No. | Dog breed | Group I | Group II | Total |
|---|---|---|---|---|
| 1 | German Shepherd | + | | 1 |
| 2 | Central Asian Shepherd | | + | 1 |
| 3 | Belgian Shepherd | + | | 1 |
| 4 | Cocker Spaniel | + | | 1 |
| 5 | East European Shepherd | | + | 1 |
| 6 | Local-breed dog | | + | 1 |
| Total | | 3 | 3 | 6 |

According to the grouping reported in the source, Group I included a German Shepherd, a Belgian Shepherd, and a Cocker Spaniel; Group II included a Central Asian Shepherd, an East European Shepherd, and a local-breed dog.


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**Figure 2**
*Gastrotomy Surgery: Tissue Dissection*



**Figure 3**
*Continuous Suturing of the Soft Tissues of the Gastric Wall*

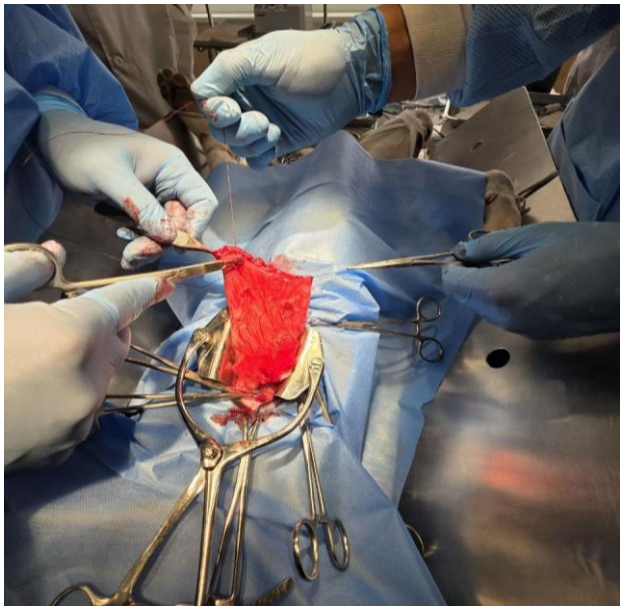


**Figure 4**
*Schmieden Suturing of the Gastric Wall*

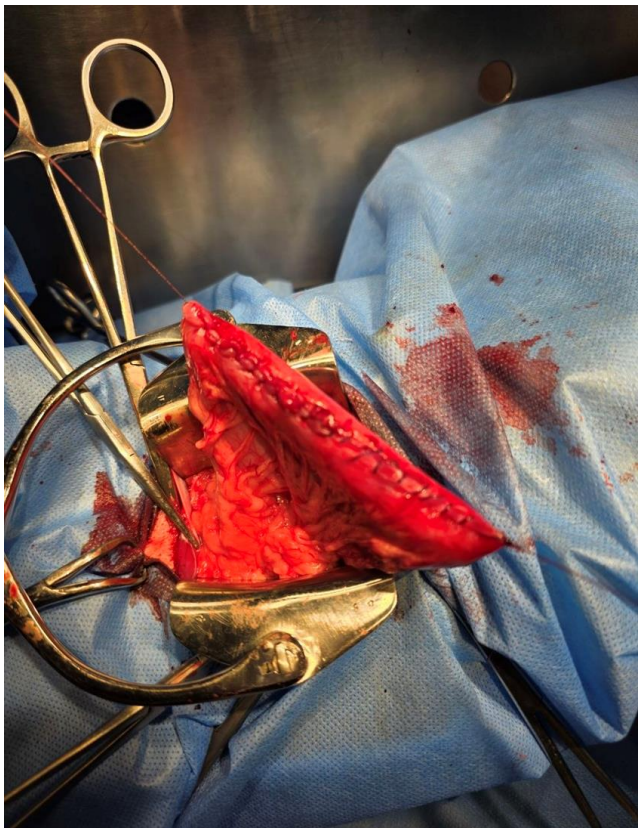
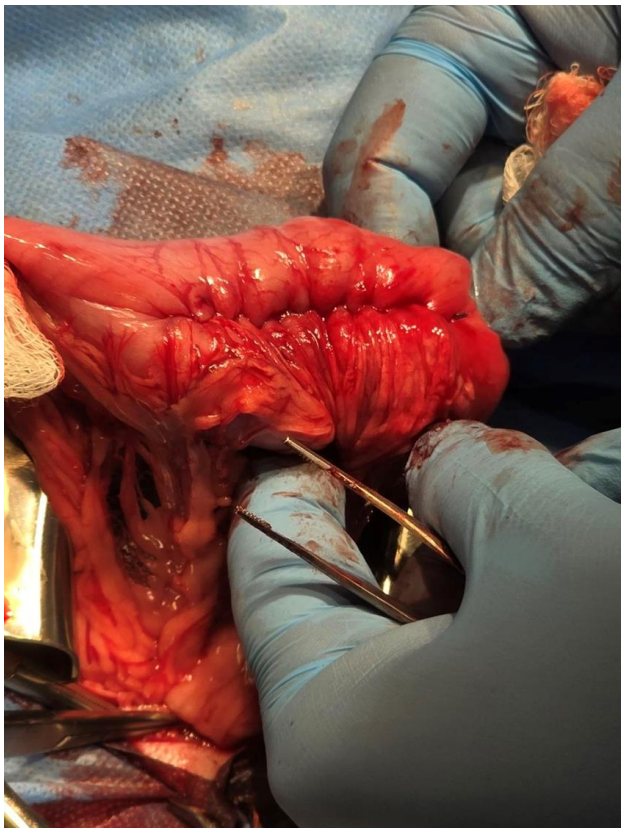


**Figure 5**
*Lambert Suturing of the Gastric Wall*



## Results

During the main stages of the gastrotomy procedure, the gastric wall wound was handled carefully, with attention to controlling bleeding, cleaning the area around the wound, and anatomically approximating the wound edges (Figure 3).

In experimental Group I, use of the two-layer Schmieden-Lambert suture combination with synthetic Lavsan thread resulted in satisfactory wound healing during the 10-day observation period. A smooth scar formed at the wound site, and the animals' general condition was satisfactory (Figure 4).

In Group II, a single-layer seromuscular Lambert suture with silk thread was used. Wound healing


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was also observed in this group; however, at the day-10 assessment the scar appeared relatively coarse and protruded in some areas (Figure 5).

During the early postoperative period, inflammatory reactions such as local redness and swelling were observed in both groups. The source material reported redness and swelling in Group I and redness with marked swelling in Group II (Table 2).

These observations indicate that the suturing technique and material influence the morphology of wound healing. However, because the study included only six experimental animals, caution is required when statistically generalizing these results to a broader population.

**Table 2**

*Postoperative Wound Appearance by Experimental Group*

| Indicator | Group I<br>Schmieden + Lambert / Lavsan | Group II<br>Lambert / silk |
|---|---|---|
| Wound healing | Observed | Observed |
| Scar appearance | Smooth | Relatively coarse,<br>with localized bulging |
| General condition | Satisfactory | Satisfactory |
| Local reaction | Redness and swelling<br>recorded | Redness and marked swelling<br>recorded |

**Results of Practical Validation**

The practical significance of the study results was also evaluated in individual clinical cases. In Kibray District, gastrotomy was performed on a 6-month-old German Shepherd and a foreign body was removed from the stomach. The gastric wound was sutured using the Schmieden-Lambert technique with synthetic Vicryl material, and wound healing was monitored by ultrasonography.

In Tashkent District, gastrotomy was performed on a 4-month-old dog and a foreign body was removed. The gastric wound was closed using the Connell-Lambert technique with synthetic Vicryl Rapide material. Wound healing and suture absorption were monitored dynamically by ultrasonography.

In the city of Chirchiq, gastrotomy was performed on a 3-month-old Drahthaar. After removal of the foreign body, the gastric wound was sutured using the Cushing-Lambert technique with synthetic Vicryl suture material. The wound surface was treated for 10 days, and healing of the muscle and gastric wounds was monitored by ultrasonography.

These practical cases do not directly replace the results from the experimental groups; however, they demonstrate the feasibility of using synthetic absorbable suture materials and layered suturing techniques in routine veterinary practice (Table 3).

**Table 3**

*Clinical Validation Cases and Suturing Approaches*

| Location | Animal | Procedure | Suture method/material | Monitoring |
|---|---|---|---|---|
| Kibray District | 6-month-old German Shepherd | Gastrotomy | Schmieden-Lambert / Vicryl | Ultrasound |
| Tashkent District | 4-month-old dog | Gastrotomy | Connell-Lambert / Vicryl Rapide | Ultrasound |
| Chirchiq City | 3-month-old Drahthaar | Gastrotomy | Cushing-Lambert / Vicryl | Ultrasound |



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**Discussion**

The observations obtained indicate the importance of selecting the suturing technique and material together when closing a gastric wall wound. This interpretation is consistent with evidence that gastrointestinal tissue response and healing can vary with closure pattern and suture material (Ellison, 2011; Hastings et al., 1975; Regier, 2022). In the two-layer Schmieden-Lambert combination used in the present study, the inner layer approximated the wound edges and the outer layer brought the serosal surfaces together; the day-10 scar appeared smoother in this group.

Although wound healing occurred in the group in which a single-layer Lambert suture with silk was used, the scar was reported to be coarser and to protrude in some areas. This finding should not be attributed solely to the suture material because the suture technique also differed between groups. Recent clinical evidence indicates that single-layer gastric closure can be safe in dogs, emphasizing the need to separate the effects of closure pattern from those of suture material in future controlled studies (Velay et al., 2024).

The practical validation cases included synthetic Vicryl and Vicryl Rapide materials, and wound healing was monitored by ultrasonography. Experimental evidence indicates that absorbable synthetic materials can differ in the degree of local tissue reaction they produce, supporting deliberate material selection rather than treating all absorbable sutures as equivalent (Gazivoda et al., 2015).

Future studies should increase the number of animals, randomize group allocation, separate suture-material effects from suture-technique effects, assess wound healing with standardized clinical and histological scoring criteria, and calculate statistical significance. Larger, controlled clinical studies of gastric closure techniques provide an appropriate model for such comparisons (Velay et al., 2024).

**Conclusions and Practical Recommendations**

Gastrotomy is one of the effective surgical methods for removing foreign bodies that have entered the stomach in dogs. In the group in which the two-layer Schmieden-Lambert suture combination and synthetic Lavsan material were used, the scar on day 10 appeared relatively smooth and firm.

In the group in which a single-layer Lambert suture and silk material were used, wound healing was observed; however, the scar was relatively coarse and protruded in some areas.

In practical clinical cases in Kibray District, Tashkent District, and the city of Chirchiq, synthetic Vicryl/Vicryl Rapide-based suture materials were used, and wound healing was monitored by ultrasonography.

The study results indicate that, when closing gastrotomy wounds, the suturing technique and material should be selected with consideration of the animal's age, the characteristics of the wound, and the anatomical and physiological condition of the stomach.

The use of a two-layer Schmieden-Lambert suture combination is considered appropriate for closing a gastric wall wound during gastrotomy. When selecting suture material, its biological compatibility with tissues, mechanical strength, and absorbability should be taken into account. During the postoperative period, regular monitoring of the animal's general condition and local wound signs is recommended, with dynamic ultrasonographic monitoring when necessary.

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# EFFECT OF DIFFERENT SUTURE MATERIALS AND TECHNIQUES ON GASTRIC WALL TISSUE HEALING IN GASTROTOMY SURGERY IN DOGS

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## ABSTRACT

*Trematode infections of small ruminants cause substantial production losses in Uzbekistan, and their control depends on a narrow set of flukicides against which resistance is increasingly reported. Oleo-gum-resins of the genus Ferula L. have demonstrated in vitro activity against liver and rumen flukes, but the published evidence concerns Ferula assa-foetida L. almost exclusively. Ferula kuhistanica Korovin, abundant in the foothills of southern Uzbekistan, has not been evaluated, and no documented procedure exists for obtaining its oleo-gum-resin as a defined veterinary raw material. This study documents a field-to-laboratory protocol for tapping F. kuhistanica oleo-gum-resin and converting it into a dried powder. Natural stands were surveyed in Dehqonobod District, Qashqadaryo Region. Latex was obtained by serial excision of the upper root crown, with the cut surface shielded from direct sunlight by cardboard and cellophane; exudate was harvested at 4- to 5-day intervals and the surface thinly re-trimmed to restore flow. Collected resin was shade-dried under gauze, milled to a powder, and stored in opaque containers under refrigeration. Ferula kuhistanica was the predominant Ferula species at the site. Tapping was practicable from early July to the first half of October and could be repeated up to 20 to 25 times per plant, depending on root size. The dried product milled to a free-flowing, whitish powder with a faint garlic-like odor considerably less intense than that of F. assa-foetida resin. The protocol yields a reproducible raw material from a locally abundant species and is transferable to other foothill districts of southern Uzbekistan. Anthelmintic efficacy was not assessed in this work; an evaluation protocol is set out in Appendix A.*

**ACCEPTED**

**04.09.26**

***Keywords:*** *Ferula kuhistanica, oleo-gum-resin, asafoetida, anthelmintic, trematodosis, small ruminants, Uzbekistan.*

CC BY

## Introduction

Trematode infections are among the most economically damaging parasitoses of ruminants worldwide. In sheep and goats the principal agents are the liver flukes *Fasciola hepatica* L. and *Fasciola gigantica* Cobbold, the lancet fluke *Dicrocoelium dendriticum* (Rudolphi), and the rumen flukes *Calicophoron calicophorum* (Fischoeder), *Gastrothylax crumenifer* (Creplin), and *Liorchis scotiae* (Willmott). Their effects are largely chronic — depressed growth rate, reduced milk and wool yield, and liver condemnation at slaughter — which makes them easy to underestimate and costly to tolerate (Kahl et al., 2021; Rojo-Vázquez et al., 2012).

Control rests almost entirely on chemotherapy, and the available pharmacological repertoire is narrow. Triclabendazole is the only compound active against both immature and adult *Fasciola* and has consequently been used heavily enough that resistant fluke populations are now reported from many countries (Fairweather et al., 2020; Kelley et al., 2016). The remaining agents — closantel, nitroxynil, clorsulon, oxyclozanide, and albendazole at elevated doses — act principally on mature flukes (Fairweather et al., 2020). It is worth noting that macrocyclic lactones such as ivermectin, although widely used against nematodes and ectoparasites, have no efficacy against trematodes and do not constitute an alternative. Beyond resistance, repeated administration raises the familiar problems of residues in edible tissues and the withdrawal periods these impose.

These constraints have renewed interest in plant-derived anthelmintics, and the genus *Ferula* L. (Apiaceae) is a credible candidate. Its oleo-gum-resins are rich in sesquiterpene coumarins, ferulic acid, umbelliferone, and sulfur-containing volatiles (Amalraj & Gopi, 2017; Mahendra & Bisht, 2012), several of which have documented antiparasitic activity. In vitro, an ethanolic extract of *Ferula assa-foetida* L. root latex is lethal to *Fasciola gigantica* at concentrations in the low milligram-per-milliliter range (Kumar & Singh, 2014). A hydroalcoholic extract of the same species kills adult *Dicrocoelium dendriticum* and *Fasciola hepatica*, producing extensive tegumental damage visible by scanning electron microscopy, including loss of sensory papillae and destruction of tegumental vesicles (Arbabi et al., 2023). Crude aqueous-methanolic extracts and ethyl acetate fractions of *F. assa-foetida* latex are also active against *Haemonchus contortus* in egg hatch, adult motility, and fecal egg count reduction assays (Badar et al., 2021), and against *Strongylus* spp. larvae (Tavassoli et al., 2018). The proposed mechanisms — uncoupling of oxidative phosphorylation and binding of polyphenolic constituents to cuticular glycoproteins (Arbabi et al., 2023; Gundamaraju, 2013) — are distinct from those of the benzimidazoles, which is precisely what makes the group interesting where benzimidazole resistance is established.

This evidence, however, concerns *F. assa-foetida* almost exclusively. Uzbekistan possesses a rich *Ferula* flora, and *Ferula kuhistanica* Korovin is abundant in the foothill and mountain zones of Qashqadaryo Region, where it is already tapped locally for its resin (Bussmann et al., 2020; Pimenov, 1983). It has not been evaluated against helminths of any kind. National policy is favorable to such work: Resolution No. PQ-4670 (2020) addresses the protection, cultivation, processing, and rational use of wild-growing medicinal plants; Decree No. PF-139 (2022) concerns value-chain creation from medicinal plant raw materials; and Resolution No. PQ-251 (2022) provides for cultivation, processing, and therapeutic use, and specifically for the allocation of quotas for collecting wild-growing *kovrak* (*Ferula*) raw material.

There is a prior obstacle, however, and it is the one addressed here. Anthelmintic screening of a crude botanical is meaningful only if the material tested is defined and reproducible. Tapping season, cut interval, drying regime, and storage conditions all affect the composition of an oleo-gum-resin, and no documented protocol exists for obtaining *F. kuhistanica* resin as a veterinary raw material. Without such a protocol, efficacy results cannot be compared between laboratories or between seasons.

The purpose of the present study was therefore to document and standardize a field-to-laboratory procedure for tapping *F. kuhistanica* oleo-gum-resin and converting it into a dried powder suitable for pharmacological evaluation. Three objectives were pursued: to characterize the occurrence of *F. kuhistanica* at a representative site in Dehqonobod District; to define a workable tapping regime in terms of season, cut interval, and number of cuts; and to define drying, milling, and storage conditions and describe the resulting product. Anthelmintic activity was not assessed in this study, and no claim of efficacy is made.

**Method Study Site and Period**

The study was carried out in naturally occurring *Ferula* stands in Dehqonobod District, Qashqadaryo Region, in the southern foothill zone of the Republic of Uzbekistan. The district lies on the northwestern slopes of the Hisar range, where *Ferula* species occupy dry stony slopes and loess foothill


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plains. Fieldwork covered a full tapping season, from the first survey of stands in late spring to the cessation of exudate flow in autumn.

**Plant Material and Identification**

Plants were identified as *Ferula kuhistanica* Korovin (Apiaceae) using the standard regional determination key for Central Asia (Pimenov, 1983), on the basis of habit, leaf division and pubescence, umbel architecture, and fruit morphology. Nomenclature follows Plants of the World Online (POWO, n.d.), under which *F. kuhistanica* Korovin is the accepted name for the taxon, native to Uzbekistan, Tajikistan, and Kyrgyzstan. Stands were surveyed before tapping to establish which *Ferula* species were present, and only individuals with a well-developed root crown were selected for tapping.

**Regulatory Compliance**

Collection of wild-growing *Ferula* raw material in Uzbekistan is a regulated activity, subject to quota under Resolution No. PQ-251 (2022). Material for this study was collected in accordance with that instrument. The study involved no animal or human participants and therefore required no ethics committee approval.

**Tapping Procedure**

Tapping followed the practice established for oleo-gum-resin-yielding *Ferula* species, with the modifications described below. For each selected plant, soil was cleared from around the root crown and a thin slice of its upper part was excised transversely with a clean knife, exposing the central core. The exposed surface was immediately shielded from direct sunlight with a cardboard cover overlaid with cellophane, both secured against wind and rain. Exudate released from the cut surface solidified under ambient conditions into a thick resinous mass.

Cuts were revisited at intervals of 4 to 5 days. At each visit the accumulated resin was lifted from the cut surface with a purpose-made knife or spatula and transferred to labeled polyethylene containers; the surface was then re-trimmed thinly to restore exudate flow. On completion of the season the exposed root crown was covered with soil.

**Drying and Powder Preparation**

Collected resin was transferred to Petri dishes and dried in a shaded, well-ventilated area, covered with gauze to exclude insects and dust while permitting airflow, and protected from direct sunlight. Drying was continued until the mass had hardened and no further change in consistency was observed.

Dried resin was separated from the Petri dishes with a spatula, transferred through a porcelain funnel into a porcelain mortar, and reduced to a powder using a laboratory micro-mill (DEEPAS). The finished powder was transferred to opaque, airtight containers and stored under refrigeration until use.

**Results Species Composition at the Study Site**

*Ferula kuhistanica* was the predominant *Ferula* species in the surveyed stands of Dehqonobod District. Plants occurred in dense natural aggregations without cultivation, growing and regenerating spontaneously across the foothill terrain, and were sufficiently abundant to permit selective tapping without exhausting any one stand.

**Tapping Season and Pattern of Exudation**

Exudate accumulation was consistently visible at the cut surface 4 to 5 days after each excision, appearing first as a milky latex that solidified into a resinous mass on exposure to air. Tapping was practicable from the beginning of July to the first half of October. Within this window, thin re-trimming of the cut surface reliably restored flow, and the procedure could be repeated up to 20 to 25 times per plant over the course of the season, the number achievable depending on the size and vigor of the root.

Protecting the cut surface proved essential rather than optional. Where the cardboard and cellophane cover was displaced, the exposed surface dried and crusted, and exudation at the next visit was visibly reduced until the surface was re-trimmed. The operating parameters established over the season are summarized in Table 1.


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**Table 1**

*Operating Parameters for Serial Tapping of Ferula kuhistanica in Dehqonobod District, Qashqadaryo Region*

| Parameter | Specification |
|---|---|
| Tapping season | Early July to first half of October |
| Site of excision | Upper part of root crown, transverse cut exposing central core |
| Surface protection | Cardboard cover overlaid with cellophane, secured |
| Interval between collections | 4–5 days |
| Surface renewal | Thin re-trimming after each collection |
| Cuts per plant per season | Up to 20–25, depending on root size and vigor |
| Collection implements | Knife or spatula; polyethylene containers |
| Post-season treatment | Exposed root crown covered with soil |

*Note.* Parameters reflect the regime found workable across a full tapping season. Resin yield was not quantified gravimetrically in the present study (see Limitations).

**Characteristics of the Dried Powder**

Shade drying under gauze produced a brittle resinous solid that separated cleanly from the Petri dishes with a spatula and milled without difficulty. The finished product was a free-flowing powder, whitish in color, with a faint garlic-like odor markedly less intense than that of *F. assa-foetida* oleo-gum-resin. No caking or discoloration was observed in opaque containers under refrigeration. Organoleptic characteristics are given in Table 2.

**Table 2**

*Organoleptic Characteristics of Ferula kuhistanica Oleo-Gum-Resin Powder*

| Characteristic | Observation |
|---|---|
| Color | Whitish |
| Odor | Faint, garlic-like; considerably weaker than *F. assa-foetida* |
| Texture | Free-flowing powder |
| Behavior on milling | Brittle; reduces readily without caking |
| Storage container | Opaque, airtight |
| Storage condition | Refrigerated |
| Stability observed | No caking or discoloration under the above conditions |

*Note.* Characteristics were assessed organoleptically. Physicochemical parameters such as loss on drying and total ash were not determined (see Limitations).

**Discussion**

The contribution of this work lies less in novelty of technique than in specification. Tapping of *Ferula* for oleo-gum-resin is an old practice in Central Asia and Iran, but it is transmitted largely as craft



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knowledge, and craft knowledge does not transfer into a pharmacological literature that requires defined materials. By fixing the season, the cut interval, the surface protection, the number of cuts, and the drying and storage conditions, the procedure described here converts a local practice into a raw material that another laboratory can reproduce.

**Relation to Work on *Ferula assa-foetida***

Published anthelmintic work on the genus concerns *F. assa-foetida*, and the extracts tested are typically described in terms of solvent and concentration but rarely in terms of how the starting resin was obtained (Arbabi et al., 2023; Badar et al., 2021; Kumar & Singh, 2014). Because exudate composition in Apiaceae varies with phenological stage, tapping intensity, and post-harvest handling, two studies nominally using asafoetida may not be working with comparable material. Anchoring *F. kuhistanica* work to a documented protocol from the outset avoids importing that ambiguity into a new species.

The powder obtained here differs organoleptically from *F. assa-foetida* resin, whose odor is notoriously persistent and is attributed to its sulfur-containing volatiles (Mahendra & Bisht, 2012). The much fainter odor of the *F. kuhistanica* product suggests a lower content of these constituents. This is an observation rather than an analysis, and it cuts both ways: a weaker odor would be a practical advantage in a veterinary formulation, but if sulfur compounds contribute materially to antiparasitic activity, as has been suggested for related species (Amalraj & Gopi, 2017; Arbabi et al., 2023), it may equally indicate lower potency. Only chemical characterization and direct comparative testing can resolve this, and both are required before *F. kuhistanica* is assumed equivalent to *F. assa-foetida*.

**Sustainability of Serial Tapping**

*Ferula kuhistanica* is a monocarpic perennial: it accumulates root reserves over several years, flowers once, and dies. Removing 20 to 25 successive slices from the root crown within a single season is therefore a substantial intervention on a plant that has one reproductive opportunity. Covering the crown with soil at the end of the season is a sensible precaution, but it is not evidence that the plant recovers. Tapped individuals were not followed into the subsequent season in this study, and no survival or regrowth rate can be stated. Given that *Ferula* harvesting in Uzbekistan is quota-regulated under Resolution No. PQ-251 (2022), establishing that rate is a precondition for recommending the practice at scale.

**Limitations**

This study is descriptive and single-site, and three limitations should be borne in mind. First, resin yield was not quantified gravimetrically; the tapping regime is characterized by its operating parameters rather than by output per plant, and yield quantification across plants, cuts, and dates remains to be done. Second, the powder was not chemically characterized, so batch-to-batch consistency cannot be demonstrated. Third, and most importantly, no biological activity of any kind was measured: nothing in these results speaks to anthelmintic efficacy, dose, or safety.

**Directions for Further Research**

Three lines follow directly. Gravimetric quantification of yield per plant, per cut, and per season would convert the present protocol into a resource assessment capable of supporting quota decisions. Chromatographic fingerprinting, with quantification of ferulic acid and umbelliferone as marker compounds, would give any subsequent efficacy result a compositional anchor. Finally, revisiting marked plants in the following spring would settle the sustainability question raised above at minimal cost. The in vitro activity reported for *F. assa-foetida* against *F. hepatica* and *D. dendriticum* (Arbabi et al., 2023) and against *F. gigantica* (Kumar & Singh, 2014) provides a reasonable basis for expecting activity in a congener, but that expectation is a hypothesis and must be tested. Appendix A sets out an evaluation protocol for that purpose.

**Conclusion**

*Ferula kuhistanica* Korovin occurs abundantly in natural stands in Dehqonobod District, Qashqadaryo Region, and was the predominant *Ferula* species at the site surveyed. Under the conditions


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of the region, oleo-gum-resin can be tapped from this species from early July to the first half of October by serial excision of the root crown at 4- to 5-day intervals, for up to 20 to 25 cuts per plant, provided the cut surface is protected from direct sunlight and thinly renewed at each collection. Shade drying under gauze followed by milling yields a free-flowing whitish powder with a faint garlic-like odor that remains stable under refrigerated storage in opaque containers and is suitable as a raw material for pharmacological evaluation. Whether that material is active against trematodes of small ruminants remains an open question, and the present study does not answer it.

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# EFFECT OF DIFFERENT SUTURE MATERIALS AND TECHNIQUES ON GASTRIC WALL TISSUE HEALING IN GASTROTOMY SURGERY IN DOGS

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**ABSTRACT**
*Background: Helminth infections remain a relevant health problem among preschool children, particularly in the Khorezm region. Objective: To assess the clinical and biochemical profile associated with parasitological findings in preschool-aged boys. Methods: The study included 45 boys aged 1–7 years. Questionnaire data, anthropometric parameters, hematological and biochemical tests, coagulation indicators, and parasitological records were analyzed. Results: Parasitological agents were recorded in 91.1% of children, most commonly Enterobius vermicularis and Ascaris lumbricoides. Most source-reported severity classifications were mild, and mixed parasitological findings were frequent. Hemoglobin, total protein, and calcium values below the thresholds used in the source tables were also observed. Conclusion: Parasitological findings were frequent in this local cohort and were accompanied by hematological and metabolic abnormalities. Because the analysis was based on a small boys-only sample and on source records with incomplete agent-specific diagnostic documentation, the findings should be interpreted as preliminary and should not be generalized as regional prevalence estimates.*

**ACCEPTED**

**04.09.26**

***Keywords:*** *helminth infections, parasitic diseases, preschool children, Khorezm region, Enterobius vermicularis, Ascaris lumbricoides, mixed parasitic infections, hemoglobin, biochemical markers, parasitological screening.*

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## Introduction

Helminth infections and intestinal parasitic diseases remain among the most widespread infectious conditions affecting children in many regions of the world. Soil-transmitted helminth infections are acquired through exposure to infective stages associated with contaminated soil, food, or water, whereas enterobiasis is efficiently maintained by close contact and contaminated hands, bedding, toys, and household surfaces. Children in organized preschool settings may be particularly vulnerable because of close contact, shared objects, and incompletely developed personal hygiene habits (Centers for Disease Control and Prevention, 2024a, 2024b; Hotez et al., 2008; Wendt et al., 2019; World Health Organization, 2023).

The clinical significance of helminth infection extends beyond identification of the causative agent. Helminth infections may adversely influence nutritional status through iron and protein loss, impaired nutrient absorption, reduced appetite, intestinal inflammation, and lower physical activity. These mechanisms are particularly important in childhood, when growth and neurodevelopment depend on

adequate nutrition and metabolic stability (Bethony et al., 2006; Jourdan et al., 2018; World Health Organization, 2023).

Environmental and household conditions can influence the persistence and transmission of intestinal parasites. Sanitation, safe water access, hygiene behavior, and repeated exposure are important determinants of fecal–oral transmission and reinfection. Evidence from systematic reviews supports the relevance of water, sanitation, and hygiene measures in reducing soil-transmitted helminth exposure, although local epidemiological patterns can differ by setting (Freeman et al., 2017; Strunz et al., 2014; UNICEF & World Health Organization, 2025).

Laboratory findings in parasitic diseases require cautious interpretation. Eosinophilia may be absent in chronic or predominantly intestinal infection, while reduced hemoglobin, total protein, or altered mineral values may reflect nutrition, inflammation, dietary factors, concomitant disease, or parasitic infection. Laboratory markers therefore should be interpreted as components of an integrated clinical and parasitological assessment rather than as stand-alone diagnostic criteria (Bethony et al., 2006; Else et al., 2020; Wendt et al., 2019).

The scientific and practical value of the present study lies in the description of a local cohort of preschool boys, with emphasis on parasitological findings and the accompanying hematological, biochemical, and coagulation profile. Given the study design and available source documentation, the results are interpreted as descriptive and hypothesis-generating.

**Aim of the Study**

The aim of the study was to investigate the clinical and biochemical characteristics associated with helminth infections and other intestinal parasitic findings in preschool-aged boys living in the Khorezm region and to identify laboratory markers that may have additional diagnostic and monitoring value.

**Materials and Methods**

**Study design and setting**

This observational analytical study was based on secondary analysis of a fragment of the examination database collected at Preschool Educational Institution No. 39 in Urgench, Khorezm region. The study focused on medical, sanitary, clinical, anthropometric, parasitological, hematological, biochemical, and coagulation characteristics recorded in the source database.

**Study population**

The sample consisted of 45 boys aged 1–7 years. Within this manuscript, the term “preschool-aged” is used operationally for the boys represented in the participating preschool institution and does not imply use of a separate international age classification. The final analysis included children whose records contained the key examination components required for the study: questionnaire data, anthropometric measurements, complete blood count, biochemical blood analysis, and parasitological examination. Because the sample was limited and included only boys, the results are considered preliminary and descriptive rather than estimates for the entire preschool population of the Khorezm region.

**Clinical and anthropometric assessment**

The examination program included collection of demographic and questionnaire information, assessment of place of residence, and anthropometric measurements. Body weight, height, and body mass index were analyzed descriptively as indicators of physical development. Anthropometric z-scores were not available in the source database and were not retrospectively generated; therefore, no standardized nutritional-status categories were assigned. Future age-standardized analyses should use the WHO Child Growth Standards for children up to 5 years and the WHO growth reference for children older than 5 years (de Onis et al., 2007; World Health Organization, 2006).

**Laboratory assessment**

Hematological, biochemical, and coagulation tests were performed at the private clinic “Elizavita.” The assessed indicators included hemoglobin concentration, erythrocyte count, hematocrit, platelet count,


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leukocyte count, leukocyte differential, erythrocyte sedimentation rate, total protein, glucose, urea, creatinine, total bilirubin and its fractions, alanine aminotransferase, aspartate aminotransferase, calcium, and selected hemostasis indicators. Frequencies of abnormal values were retained exactly as classified in the original source tables; no age-specific reclassification was performed. Accordingly, these frequencies should be interpreted as source-threshold classifications rather than standardized clinical prevalence estimates. This is particularly important for hemoglobin, for which age-specific interpretation is recommended in current WHO guidance (World Health Organization, 2024).

**Parasitological assessment and source-data constraints**

The source database recorded parasitological examination performed at the regional Sanitary and Epidemiological Service and contained the presence or absence of parasitic agents, the named agent, the number of agents recorded in each child, and source-reported severity categories. The database fragment available for this secondary analysis did not preserve the specimen-specific or agent-specific diagnostic protocol for every reported organism, and no independent re-identification was possible. Therefore, all parasitological labels and severity categories are reproduced as recorded in the source dataset without reclassification. This limitation is relevant because standard diagnostic approaches differ by organism: the perianal tape test is the most common diagnostic method for *Enterobius vermicularis*, whereas *Toxocara* eggs are not expected in human stool and suspected human toxocariasis is evaluated primarily by clinical and serologic criteria (Centers for Disease Control and Prevention, 2024c; Centers for Disease Control and Prevention, n.d.). For dataset classification, mixed parasitological findings were defined as simultaneous recording of two or more agents in one child.

**Statistical analysis**

Descriptive statistics included absolute and relative frequencies, mean values with standard deviation (M ± SD), and median with interquartile range Me (Q1–Q3). Spearman's rank correlation coefficient was used to assess relationships between the number of recorded parasitic agents and selected laboratory parameters. The source analysis used $p < .05$ as the nominal significance threshold. Because the study was exploratory, the sample was small, and no adjustment for multiple comparisons was applied, p values are interpreted cautiously and alongside effect size and clinical relevance (Wasserstein et al., 2019).

**Results**

**General characteristics of the examined group**

The examined children were residents of the Khorezm region. In the analyzed dataset, the largest proportions of participants came from Urgench city and from the Urgench, Khanka, Khiva, and Koshkupyr districts. The mean age of the participants was 4.3 ± 1.7 years, and the median age was 4.0 years (3.0–6.0). The mean body weight was 19.6 ± 5.9 kg, the mean height was 106.8 ± 20.5 cm, and the mean body mass index was 17.1 ± 3.4 kg/m² (Table 1).

**Table 1. Characteristics of the examined group**

| Indicator | Value |
|---|---|
| Number of children | 45 |
| Sex | Boys - 45 (100%) |
| Age, years | 4.3 ± 1.7; Me 4.0 (3.0-6.0) |
| Body weight, kg | 19.6 ± 5.9; Me 19.0 (15.0-25.0) |
| Height, cm | 106.8 ± 20.5; Me 107.0 (95.0-127.0) |
| Body mass index, kg/m² | 17.1 ± 3.4; Me 16.2 (15.0-18.8) |

**Parasitological findings**

Parasitological agents were recorded in 41 of 45 children, corresponding to 91.1% of the examined group. In 4 children (8.9%), no parasitic agents were identified in the submitted samples. A total of 76


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parasitological findings were recorded because some children had mixed findings. *Enterobius vermicularis* was recorded in 28 cases (62.2%), *Ascaris lumbricoides* in 24 children (53.3%), *Hymenolepis spp.* in 11 children (24.4%), *Giardia/Lamblia intestinalis* in 9 children (20.0%), and *Toxocara spp.* in 4 children (8.9%) (Table 2, Figure 1).

**Table 2. Distribution of parasitic agents and source-reported severity classification**

| Parasitic agent | n | % of 45 | Mild | Moderate | Severe |
|---|---|---|---|---|---|
| *Enterobius vermicularis* | 28 | 62.2 | 26 | 2 | 0 |
| *Ascaris lumbricoides* | 24 | 53.3 | 19 | 5 | 0 |
| *Hymenolepis spp.* | 11 | 24.4 | 11 | 0 | 0 |
| *Giardia/Lamblia intestinalis* | 9 | 20.0 | 8 | 1 | 0 |
| *Toxocara spp.*, total | 4 | 8.9 | 4 | 0 | 0 |

*Note.* Agent names, counts, percentages, and Mild/Moderate/Severe categories are reproduced from the author-provided source data. Parasite-specific quantitative egg counts and the criteria used to assign severity categories were not available for independent verification.

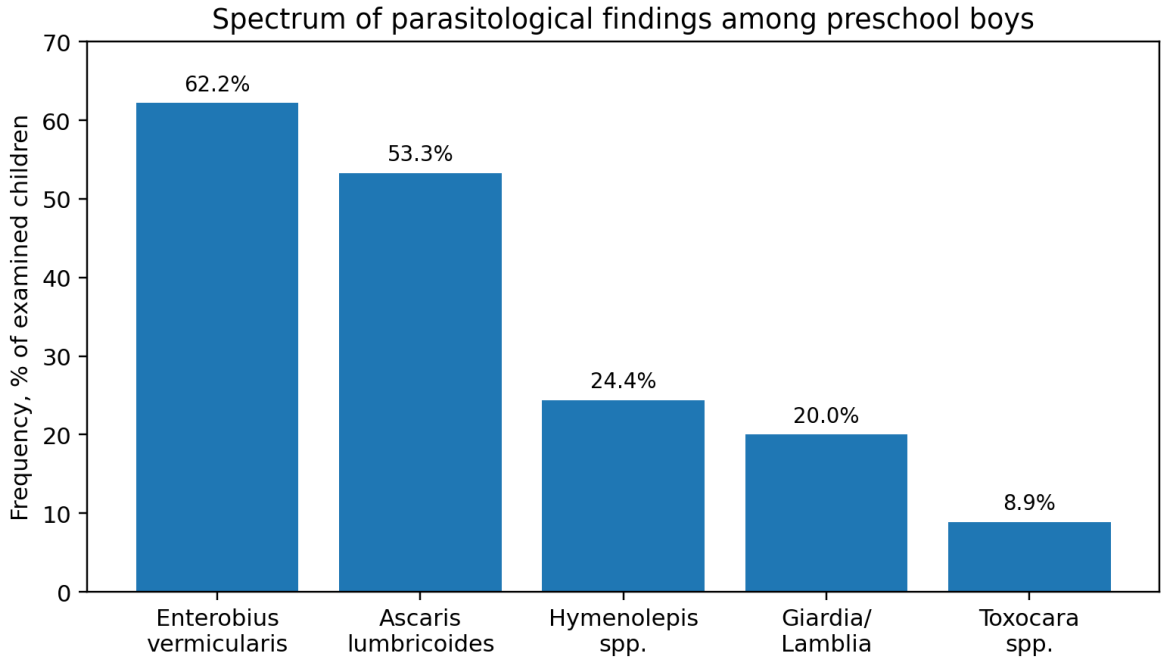



*Figure 1. Spectrum of parasitological findings among the examined children*

**Source-reported intensity and mixed parasitological findings**

In the source dataset, most recorded findings were classified as mild. Mild classification accounted for 68 of 76 parasitological findings (89.5%). Moderate classification was recorded in 8 cases (10.5%), including 2 cases of enterobiasis, 5 cases of ascariasis, and 1 case of giardiasis. No severe cases were recorded. Two agents were recorded in 29 children (64.4%), and three agents were recorded simultaneously in 3 children (6.7%) (Table 3). Because quantitative egg counts and classification criteria were not available, these categories are reported descriptively and should not be interpreted as independently verified infection-intensity grades.


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**Table 3. Distribution of parasitological findings by number of agents**

| Parasitological result category | n | % |
|---|---|---|
| No parasitic agents detected | 4 | 8.9 |
| One parasitic agent detected | 9 | 20.0 |
| Two parasitic agents detected | 29 | 64.4 |
| Three parasitic agents detected | 3 | 6.7 |

**Hematological profile**

The mean hemoglobin concentration was 98.2 ± 10.6 g/L, and the median was 100.0 g/L (90.0–105.0). Hemoglobin was classified as reduced in 37 children (82.2%) according to the source-table threshold. The mean platelet count was 237.6 ± 80.0 ×10⁹/L; values below 180 ×10⁹/L were recorded in 7 children (15.6%), while values above 320 ×10⁹/L were recorded in 9 children (20.0%). The mean leukocyte count was 5.6 ± 1.8 ×10⁹/L; values below 4.0 ×10⁹/L and above 9.0 ×10⁹/L were each found in 2 children (4.4%). The mean eosinophil percentage was 1.7 ± 2.0%, and values above 5% were found in 4 children (8.9%). ESR values above 10 mm/h were recorded in 16 children (35.6%) (Table 4).

**Table 4. Hematological parameters**

| Parameter | M ± SD | Me (Q1-Q3) | Frequency of abnormalities, n (%) |
|---|---|---|---|
| Hemoglobin, g/L | 98.2 ± 10.6 | 100.0 (90.0-105.0) | 37 (82.2) |
| Platelets, ×10⁹/L | 237.6 ± 80.0 | 193.0 (184.0-310.0) | <180: 7 (15.6); >320: 9 (20.0) |
| Leukocytes, ×10⁹/L | 5.6 ± 1.8 | 4.7 (4.1-7.0) | <4.0: 2 (4.4); >9.0: 2 (4.4) |
| Eosinophils, % | 1.7 ± 2.0 | 0.9 (0.6-1.4) | >5%: 4 (8.9) |
| ESR, mm/h | 21.7 ± 32.0 | 2.5 (2.1-14.2) | >10 mm/h: 16 (35.6) |

*Note.* Abnormality frequencies are reproduced from the thresholds used in the source tables and were not reclassified by age.

**Biochemical profile**

The mean total protein level was 63.6 ± 7.4 g/L, with a median of 64.2 g/L (60.2–67.4). A total protein level below 60 g/L was recorded in 11 children (24.4%). The mean glucose level was 4.8 ± 1.0 mmol/L; values below 3.3 mmol/L were recorded in 2 children (4.4%), while values above 5.5 mmol/L were recorded in 9 children (20.0%). Total bilirubin averaged 17.0 ± 3.9 µmol/L, and values above 20.5 µmol/L were found in 7 children (15.6%). ALT values above 35 U/L were recorded in 6 children (13.3%), while AST values above 35 U/L were recorded in 1 child (2.2%). Calcium levels below 2.0 mmol/L were found in 17 children (37.8%) (Table 5).

**Table 5. Biochemical characteristics**

| Parameter | M ± SD | Me (Q1-Q3) | Frequency of abnormalities, n (%) |
|---|---|---|---|
| Total protein, g/L | 63.6 ± 7.4 | 64.2 (60.2-67.4) | <60 g/L: 11 (24.4) |
| Glucose, mmol/L | 4.8 ± 1.0 | 4.6 (4.1-5.4) | <3.3: 2 (4.4); >5.5: 9 (20.0) |
| Urea, mmol/L | 4.8 ± 4.1 | 3.2 (2.5-6.3) | Variability of values |
| Creatinine, µmol/L | 52.2 ± 17.7 | 53.2 (38.0-68.0) | No group-level interpretation |
| Total bilirubin, µmol/L | 17.0 ± 3.9 | 16.2 (14.2-19.8) | >20.5: 7 (15.6) |
| ALT, U/L | 25.8 ± 8.0 | 24.0 (21.0-30.0) | >35: 6 (13.3) |
| AST, U/L | 19.3 ± 5.5 | 19.0 (15.6-22.0) | >35: 1 (2.2) |
| Calcium, mmol/L | 2.1 ± 0.2 | 2.0 (2.0-2.2) | <2.0: 17 (37.8) |

*Note.* Threshold-based frequencies are reproduced from the source tables. Fasting status and age-specific biochemical reference intervals were not available for reclassification.



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### Coagulation profile

The coagulation profile included activated partial thromboplastin time, prothrombin time, prothrombin index, international normalized ratio, thrombin time, fibrinogen, and D-dimer. The results showed considerable interindividual variability. The source data contained heterogeneous measurement documentation; therefore, these parameters are presented descriptively and were not used for diagnostic classification or inferential analysis (Table 6).

**Table 6. Coagulation parameters**

| Parameter | M ± SD | Me (Q1-Q3) |
|---|---|---|
| Activated partial thromboplastin time (APTT), s | 23.7 ± 4.8 | 24.0 (20.0-26.0) |
| Prothrombin time (PT), s | 10.0 ± 2.6 | 9.2 (8.2-11.3) |
| Prothrombin index (PTI), % | 131.9 ± 25.4 | 130.0 (110.0-150.0) |
| International normalized ratio (INR) | 0.8 ± 0.1 | 0.8 (0.7-0.9) |
| Thrombin time, s | 14.6 ± 4.0 | 14.0 (12.0-16.0) |
| Fibrinogen | 5.9 ± 1.3 | 5.7 (4.8-6.4) |
| D-dimer, μg/mL | 1.0 ± 0.2 | 0.9 (0.8-1.1) |

*Note.* Values are reproduced unchanged from the source data. The fibrinogen unit was not specified in the available source table and has not been inferred or added.

### Correlation analysis

The number of parasitic agents recorded in an individual child showed a weak positive correlation with total bilirubin level (rho = 0.31; p = .040). The association with hemoglobin level was weak and statistically insignificant (rho = -0.06; p = .678), and the correlation with eosinophil percentage was also weak and statistically insignificant (rho = 0.15; p = .324) (Table 7). Because three correlations were examined and no multiplicity adjustment was applied, the p = .040 result is interpreted as exploratory rather than confirmatory.

**Table 7. Correlation between parasitic burden and selected laboratory indicators**

| Compared variables | Spearman rho | p value | Interpretation |
|---|---|---|---|
| Number of parasitic agents and total bilirubin | 0.31 | .040 | Weak positive association |
| Number of parasitic agents and hemoglobin | -0.06 | .678 | Weak, statistically insignificant |
| Number of parasitic agents and eosinophils | 0.15 | .324 | Weak, statistically insignificant |

*Note.* p values are unadjusted for multiple comparisons. The reported rho values and p values are author-provided data and are reproduced unchanged.

### Discussion

The present study showed a high frequency of parasitological findings in this local cohort of preschool boys. *Enterobius vermicularis* and *Ascaris lumbricoides* were the most frequently recorded agents. Their prominence is epidemiologically plausible because enterobiasis is readily maintained in close-contact groups, whereas ascariasis and other soil-transmitted helminth infections are associated with fecal–oral exposure to contaminated soil, food, or water (Centers for Disease Control and Prevention, 2024a, 2024b; Wendt et al., 2019; World Health Organization, 2023).


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The parasitological results must nevertheless be interpreted in light of the source-record limitations. The available database did not retain the agent-specific diagnostic technique for every entry. This is particularly important for the recorded *Enterobius vermicularis* and *Toxocara spp.* findings. Standard practice commonly uses a perianal tape test for *Enterobius vermicularis,* while human toxocariasis is not established by detection of *Toxocara* eggs in human stool because humans do not harbor egg-producing adult worms; clinical and serologic assessment is used instead (Centers for Disease Control and Prevention, 2024c; Centers for Disease Control and Prevention, n.d.). The present analysis therefore preserves the author-provided labels but treats them as laboratory-recorded findings rather than independently revalidated species diagnoses.

Mixed parasitological findings were common: two agents were recorded in almost two thirds of children and three agents in a smaller subgroup. Mixed findings may reflect repeated exposure to different transmission routes and can complicate interpretation of symptoms and laboratory abnormalities. The source dataset also classified most findings as mild, but quantitative egg counts and parasite-specific classification criteria were not available. Consequently, the mild and moderate categories should be regarded as source-reported descriptors rather than independently verified measures of infection intensity.

Anthropometric measurements provided useful descriptive context, but the absence of age-standardized z-scores limits nutritional interpretation. Because the sample spans ages 1–7 years, standardized future analyses should use the WHO Child Growth Standards for children up to age 5 and the WHO 5–19-year growth reference for older children (de Onis et al., 2007; World Health Organization, 2006).

The hematological profile was notable for the high proportion of children whose hemoglobin values fell below the threshold used in the source tables. However, this 82.2% frequency should not be interpreted as an age-standardized estimate of anaemia prevalence because the source analysis did not apply current age-specific WHO haemoglobin cutoffs. Helminth infections can contribute to anemia through nutritional loss, inflammation, reduced intake, and impaired absorption, but anemia in children is multifactorial and requires assessment of iron status, ferritin, inflammatory markers, diet, growth, and concomitant disease (Bethony et al., 2006; World Health Organization, 2024).

Eosinophilia above the source threshold was recorded in only 8.9% of children despite the high frequency of parasitological findings. This supports cautious use of eosinophil percentage as an auxiliary rather than stand-alone screening marker, because eosinophilia may be absent in chronic or predominantly intestinal helminth infection (Else et al., 2020; Wendt et al., 2019).

Biochemical findings included total protein below 60 g/L in 24.4% of children and calcium below 2.0 mmol/L in 37.8%. These abnormalities may reflect diet, nutritional status, malabsorption, inflammation, concomitant disease, or parasitic infection and therefore cannot be attributed to parasites alone. The weak positive correlation between number of recorded parasitic agents and total bilirubin (rho = 0.31; p = .040) should be considered exploratory, particularly because the analysis involved multiple correlations without multiplicity adjustment.

The coagulation data were descriptive only. Heterogeneous source documentation and the absence of a recorded fibrinogen unit limit clinical interpretation and preclude standardized comparison. These values should therefore be treated as descriptive source data rather than evidence of a specific coagulation disorder.

From a public-health perspective, the findings support continued attention to hygiene education, sanitation, safe water and food handling, appropriate case management, and locally appropriate parasitological surveillance. However, this single-institution, boys-only sample of 45 children does not establish regional prevalence and should not by itself be used to justify region-wide screening or treatment policy. Population-level control decisions should be informed by representative epidemiological surveys


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and established WHO criteria (Campbell et al., 2016; Montresor et al., 2020; World Health Organization, 2021, 2023).

**Limitations**

The study has several limitations. The sample was small, included boys only, and was drawn from one preschool organization. There was no control group. Information on nutritional status, recent antiparasitic treatment, repeated parasitological testing, iron metabolism, inflammatory markers, and vitamin D status was limited or unavailable. The database fragment did not preserve agent-specific parasitological protocols for every reported organism, and the source severity categories could not be independently verified by quantitative egg counts. Laboratory abnormalities were classified using source-table thresholds rather than age-standardized reference ranges. Coagulation documentation included heterogeneous measurement information, with no fibrinogen unit available in the source table. Finally, the correlation analysis was exploratory and did not adjust p values for multiple comparisons.

**Practical Implications and Future Directions**

For clinical practice within comparable preschool settings, parasitological findings should be interpreted together with symptoms, exposure history, anthropometric status, and laboratory findings rather than by any single marker. Hygiene education should emphasize handwashing, nail care, individual towels, clean bedding, and safe handling of food and water. Children with parasitological findings and abnormal hematological or biochemical values should receive appropriate clinical evaluation and nutritional assessment. Future regional studies should include larger mixed-sex cohorts from multiple institutions and districts, repeated and agent-appropriate parasitological testing, standardized anthropometric z-scores, age-specific laboratory interpretation, iron and mineral metabolism markers, inflammatory markers, and follow-up after intervention.

**Conclusion**

1. In the analyzed dataset, parasitological findings were recorded in 91.1% of the 45 examined boys.

2. The most frequently recorded agents were *Enterobius vermicularis* and *Ascaris lumbricoides*. Two agents were recorded in 64.4% of children and three agents in 6.7%.

3. According to the thresholds used in the source tables, reduced hemoglobin was recorded in 82.2% of children, total protein below 60 g/L in 24.4%, and calcium below 2.0 mmol/L in 37.8%.

4. Eosinophilia above 5% was recorded in 8.9% of children, indicating that eosinophil percentage alone was not a sensitive marker of parasitological findings in this cohort.

5. Correlation analysis showed a weak positive association between number of recorded parasitic agents and total bilirubin (rho = 0.31; p = .040), while correlations with hemoglobin and eosinophils were weak and statistically insignificant. Because no multiple-comparison adjustment was applied, the bilirubin finding should be considered exploratory.

6. The results support integrated clinical, parasitological, anthropometric, and laboratory assessment, while larger standardized studies are required before regional prevalence estimates or population-level policy recommendations can be made.

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# DIGITAL TECHNOLOGIES FOR TOOTH SHADE DETERMINATION IN MODERN ESTHETIC DENTISTRY: CAPABILITIES, ACCURACY, AND PROSPECTS FOR APPLICATION

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**ABSTRACT**

*Accurate determination of natural tooth color is a key prerequisite for predictable esthetic outcomes in direct and indirect restorations. Conventional visual assessment with standardized shade guides remains widely used, but it is subjective and sensitive to illumination, operator color perception, surface condition, and tooth hydration. The digitalization of dentistry has introduced spectrophotometers, colorimeters, digital photography, intraoral scanners, and dedicated color-analysis software, and recent attention has shifted toward automated image processing and artificial intelligence. This review examines contemporary digital methods of tooth shade determination, their operating principles, reported accuracy and reproducibility, and the factors that influence measurement outcomes. Literature indexed in PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar was analyzed, with priority given to systematic reviews, meta-analyses, and clinical studies published within the past five years. The evidence indicates that spectrophotometry remains the most defensible instrumental reference method, that the clinical accuracy of digital photography depends primarily on standardization of capture and color calibration rather than on camera resolution, and that intraoral scanners achieve high repeatability but variable trueness. Artificial intelligence offers the greatest automation potential, although its evidence base remains constrained by heterogeneous algorithms and limited external validation.*

**ACCEPTED**

**07.09.26**

***Keywords:*** *tooth color, esthetic dentistry, digital dentistry, shade matching, spectrophotometry, digital photography, intraoral scanner, CIELAB, CIEDE2000, artificial intelligence.*

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## Introduction

Patients' esthetic expectations of dental treatment have risen considerably in recent years. When teeth are restored with composite materials, ceramic veneers, crowns, or other esthetic constructions, the clinical result is determined not only by the form and functional characteristics of the restoration but also by the degree of its optical correspondence to the natural dental tissues. Even when a restoration is fabricated with high precision, a visible color mismatch may adversely affect the patient's perception of the final result.

The color of a natural tooth is a complex optical characteristic arising from the interaction of light with enamel and dentin. The tooth is not a chromatically homogeneous object: the cervical, middle, and incisal thirds may differ in lightness, chroma, hue, and degree of translucency. Determining a single nominal shade value for the entire tooth surface therefore does not always convey its true optical characteristics.

The most common clinical approach to shade determination remains visual comparison of the natural tooth with tabs from standardized shade guides. This approach is associated with a number of limitations. The result may be influenced by the spectral characteristics of the light source, the color of surrounding objects, the duration of observation, the clinician's visual status, operator experience, fatigue of the visual analyzer, moisture on the tooth surface, and other factors (Chen et al., 2012; Tabatabaian et al., 2021).

The digitalization of dentistry has created the conditions for a transition from subjective shade selection to quantitative color assessment. Spectrophotometers and colorimeters, digital cameras, smartphones, intraoral scanners, and dedicated software are used for this purpose. Contemporary systems make it possible not only to relate tooth color to a specific position on a standard shade guide, but also to obtain quantitative color coordinates, store this information, and transmit it to the dental laboratory (Chen et al., 2012; Ebeid et al., 2022; Hina et al., 2024; Rashid et al., 2023).

Software-based analysis of digital images is of particular interest. With appropriate photographic standardization, a digital image can be used to determine the color coordinates of individual tooth regions, evaluate chromatic heterogeneity, and subsequently compare the resulting data with reference values (Hina et al., 2024; Rashid et al., 2023). The development of machine learning and artificial intelligence further opens the possibility of automating tooth image segmentation, correcting capture conditions, and classifying shade (Shetty et al., 2024).

**Aim of the review.** The aim of this review was to analyze contemporary digital technologies of tooth shade determination in esthetic dentistry; to evaluate their capabilities, accuracy, reproducibility, and limitations; and to identify promising directions for the development of software-based methods of color analysis.

**Materials and Methods**

An analysis of the national and international scientific literature devoted to visual and digital methods for determining the color of natural teeth was carried out. The search for publications was conducted primarily in the electronic databases PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar.

The following keywords and their combinations were used: *tooth color, tooth shade, shade matching, digital shade matching, digital dentistry, dental photography, spectrophotometer, colorimeter, intraoral scanner, CIELAB, CIEDE2000, artificial intelligence, machine learning*, and *dental shade selection*.

Priority was given to publications from the past five years and to systematic reviews, meta-analyses, and clinical studies addressing the accuracy and reproducibility of digital methods. Earlier publications were considered when addressing the fundamental principles of dental colorimetry and the threshold values of color difference.

**Fundamental Principles of Tooth Color Assessment**

Objective digital color assessment requires color information to be expressed in a standardized coordinate system. The CIE L*a*b* color space is widely used in dental research: the L* coordinate characterizes the lightness of the object, a* reflects the position of the color on the red–green axis, and b* its position on the yellow–blue axis (Hina et al., 2024; Rashid et al., 2023).

CIELAB allows color to be expressed not only qualitatively but also quantitatively, which is the fundamental advantage of instrumental and software-based methods. The difference between two measured colors can be expressed by the ΔE metric.

Alongside the classical ΔE*ab, contemporary dental research increasingly employs the CIEDE2000 formula (ΔE00), which accounts for the unequal sensitivity of human vision to changes in lightness, chroma, and hue. The use of ΔE00 permits a more appropriate comparison of an instrumentally recorded difference with its visual perceptibility (Paravina et al., 2015).


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When interpreting the resulting data, a distinction must be drawn between the perceptibility threshold, which is the color difference a person is able to detect, and the acceptability threshold, which is a difference that may be noticeable yet remains clinically tolerable. In a prospective multicenter psychophysical study, the 50:50% perceptibility and acceptability thresholds for dentistry were ΔEab = 1.2 and ΔEab = 2.7, corresponding to ΔE00 = 0.8 and ΔE00 = 1.8, respectively (Paravina et al., 2015). Current data nevertheless indicate that no universal absolute threshold exists for all clinical situations: the threshold may depend on the lightness and chroma of the object under examination and on the characteristics of the observer. Tejada-Casado et al. (2024) demonstrated that the 50:50% acceptability threshold varied from ΔE00 = 2.84 for low-chroma sample pairs to ΔE00 = 2.31 and ΔE00 = 1.80 for medium- and high-chroma pairs, respectively, with observers proving more tolerant of differences in more achromatic samples.

**Visual Shade Determination and Its Limitations**

The visual method is based on direct comparison of the natural tooth with tabs from standardized shade guides, of which VITA Classical and VITA 3D-Master are the most widespread.

The advantages of the method are its simplicity, its availability, and the absence of any requirement for expensive equipment. At the same time, visual assessment remains subjective. Even a single operator may select different shades for the same tooth when illumination or observation conditions change, and inter-operator variability may be greater still (Chen et al., 2012; Tabatabaian et al., 2021).

The color temperature of the light source, the intensity of illumination, bright items of clothing or make-up worn by the patient, and the color of the walls and surrounding objects are all capable of altering visual perception. Enamel dehydration is a further important factor: with prolonged drying the tooth becomes visually lighter and more opaque, and shade selection is therefore recommended before lengthy dental procedures.

In addition, the natural tooth exhibits pronounced spatial heterogeneity of color. Studies in which color is determined separately in the cervical, middle, and incisal thirds demonstrate differences between individual regions of the same tooth (Rashid et al., 2023; Tabatabaian et al., 2021). Consequently, determining a single shade for the entire crown may result in the loss of esthetically significant information.

**Digital Technologies for Shade Determination**

**Spectrophotometry**

The spectrophotometric method is based on recording the quantity of light reflected by the object under examination across different regions of the visible spectrum. The resulting spectral information is converted into color coordinates and, depending on the software of the device, may be related to the shades of standard dental guides.

Clinical dental spectrophotometers are characterized by high measurement reproducibility and by markedly lower dependence on the subjective perception of the operator than the visual method. For this reason, spectrophotometry is widely used in research as the reference method when evaluating new approaches to shade determination (Chen et al., 2012; Ebeid et al., 2022; Vitai et al., 2025).

Spectrophotometric measurement cannot, however, be regarded as entirely independent of the conditions of recording. The result may be affected by the position of the measuring tip, the curvature of the tooth surface, the translucency of the tissues, ambient illumination, and the condition and hydration of the enamel. In addition, the cost of specialized equipment restricts its universal use.

**Colorimetry**

Colorimeters determine color by measuring light intensity within several spectral bands using appropriate filters. Compared with spectrophotometers, they are of simpler construction and generate color coordinates directly.

Colorimetric devices make it possible to objectify the recording of shade, but their diagnostic capabilities depend on the characteristics of the sensor, the measurement geometry, and the signal


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conversion algorithms. In contemporary dentistry, dedicated spectrophotometers have found wider application in research on the accuracy of color determination.

**Digital Photography and Software-Based Image Analysis**

Digital photography is one of the most promising means of recording information about tooth color, owing to its accessibility, the possibility of documenting the entire tooth surface, and the potential for subsequent software analysis.

Unlike the point measurement obtained with a spectrophotometer, a photograph contains spatial information about the distribution of color. This makes it possible to analyze the cervical, middle, and incisal regions separately, to evaluate gradients of lightness and chroma, and to convey to the dental technician additional information about the morphology, texture, and optical features of the tooth.

The RGB values recorded by a digital camera are not, however, absolute characteristics of the color of an object. They depend on the camera sensor, the lens, exposure, white balance, the light source, the file format, and internal image-processing algorithms.

The most important condition for using photography for quantitative analysis is therefore standardization. This may include a fixed distance and camera position, constant exposure parameters, the use of a macro lens and flash, color or gray reference targets, control of white balance, and the exclusion of automatic software processing.

A comparative clinical study by Hina et al. (2024) showed agreement between standardized digital photography and spectrophotometric color determination in the majority of observations: agreement ($\Delta E \leq 2$) was found in 42 of 50 cases (84.0%), and the L*, a*, and b* values did not differ significantly between the two methods. The findings of different studies are nevertheless heterogeneous, which points to the substantial influence of the specific protocol of image capture and processing. Lazar et al. (2019), for example, reported that color differences between spectrophotometric measurements and polarized photography lay at or below the 50:50% acceptability threshold in only 23% of cases. Rondón et al. (2022) compared standardized photographic shade analysis with visual shade matching in a panel of 50 observers assessing a light and a dark maxillary central incisor, evaluating both approaches with two different color difference formulas.

This circumstance is of fundamental importance: digital photography is not in itself a method of objective color measurement. Objectivity is achieved only when standardized image acquisition, color calibration, and a validated processing algorithm are combined. Rashid et al. (2023) observed that manual white balance calibration was preferred by the majority of investigators precisely because it significantly improves digital color accuracy compared with automatic correction.

Software analysis may include selection of the tooth region of interest, exclusion of specular highlights, conversion of the original RGB values into a device-independent color space, derivation of the L*, a*, and b* coordinates, and calculation of the color difference relative to a reference.

Such an approach potentially allows a transition from subjective shade selection on a photograph to quantitative evaluation of individual tooth regions.

**Intraoral Scanners**

Contemporary intraoral scanners are used predominantly to acquire the digital geometry of the dental arches, but a number of models simultaneously record texture and color information. This creates the possibility of determining shade directly during digital scanning, without a separate clinical stage.

The principal advantage of this approach is the integration of color determination into the digital CAD/CAM protocol. The data obtained can be stored together with the digital impression and transmitted to the dental laboratory.

Systematic reviews demonstrate reasonably high repeatability of shade determination by intraoral scanners, but indicators of trueness differ substantially between devices and between studies (Akl et al., 2023; Vitai et al., 2025).



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The meta-analysis by Vitai et al. (2025) showed that intraoral scanners are characterized by high reproducibility, with pooled repeatability between 0.81 and 0.85, but that pooled trueness ranged only from 0.28 to 0.38 relative to spectrophotometry. High repeatability of a result should not therefore be interpreted automatically as high accuracy in determining the true color.

Clinical data reported by Baqleh and Alhouri (2026) likewise showed that the Medit i700 scanner determined the value (lightness) parameter with clinically acceptable agreement, but that its accuracy in full shade determination was insufficient for use as a stand-alone method. Agreement was also higher for molars and canines than for incisors, which is consistent with the greater translucency and more complex optical behavior of maxillary incisors.

At the present stage, therefore, the shade-determination function of an intraoral scanner is more appropriately regarded as a supplementary source of information, particularly where esthetic demands are high.

**Factors Affecting the Accuracy of Digital Shade Determination**

The digital nature of a method does not preclude the occurrence of error. On the contrary, the final result is formed by a sequence of stages, from the interaction of light with the tooth surface to the software interpretation of the data obtained. The most significant factors include the following:

- the spectral characteristics and intensity of illumination;
- the presence of direct or diffuse light;
- reflections and specular highlights on the enamel surface;
- the degree of tooth hydration;
- the distance and angle of recording;
- the characteristics of the camera or scanner sensor;
- exposure and white balance;
- the presence or absence of polarization;
- internal image-processing algorithms;
- color calibration;
- the choice of tooth surface region for analysis.

Specular highlights are of particular importance. Specularly reflected light may lead to the recording of regions with artificially high lightness that do not reflect the true optical characteristics of the tissues. Cross-polarized photography reduces surface reflections and yields a more informative image of the internal color characteristics of the tooth (Lazar et al., 2019).

Accordingly, a reproducible software-based method of color determination requires not only an analytical algorithm but also a standardized protocol for acquiring the source data.

**Artificial Intelligence in Tooth Shade Determination**

The development of artificial intelligence and computer vision is forming a new direction within digital dental colorimetry. Machine learning algorithms are potentially able to perform automatic recognition of the tooth in a photograph, segmentation of individual regions, exclusion of highlights and background objects, correction of color distortion, and classification of shade.

The systematic review by Shetty et al. (2024) demonstrated the promise of applying artificial intelligence to dental shade-matching tasks, although the authors noted the need for further standardization of methods, larger training samples, and external validation of algorithms.

A fundamental advantage of the artificial intelligence approach is the capacity to analyze a large number of image features simultaneously. Unlike an algorithm based solely on the mean RGB or L*a*b* values of a defined region, a machine learning model can take into account the spatial distribution of color, brightness, texture, and other characteristics.

Algorithms capable of operating with images obtained by different devices and under varying illumination represent a particularly promising direction. This is important for the possible use of


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smartphones and standard digital cameras outside a strictly controlled photographic studio. Tao et al. (2026) developed such a framework, which incorporates specular highlight suppression and brightness-first perceptual reasoning and requires neither polarizing filters nor device calibration; it achieved 79.12% top-1 accuracy on routine intraoral photographs captured with a range of smartphones and cameras, and 76.0% top-1 accuracy in an independent 50-case observer study.

High algorithm accuracy on its own training sample does not, however, guarantee comparable effectiveness when a different camera, a different light source, or a different patient population is used. Multicenter studies and external verification on independent data are therefore necessary for the clinical implementation of artificial intelligence systems.

**Comparative Characteristics of Digital Methods**

Spectrophotometry possesses high objectivity and reproducibility and currently remains the best-substantiated instrumental reference approach. Its drawbacks are the cost of the equipment and the predominantly localized nature of the measurement.

Digital photography provides a large volume of spatial information and is convenient for communication with the dental laboratory. Its potential advantages are accessibility and the possibility of software processing. The principal limitation remains the pronounced dependence of the result on standardization of capture and on color calibration. The meta-analysis by Hardan et al. (2022) is instructive in this respect: among the shade selection methods analyzed, only the use of digital photographs produced a statistically significant reduction in color difference relative to conventional shade tabs ($p < .0001$), whereas spectrophotometry showed no advantage over visual guides in the pooled clinical data ($p = .57$).

Intraoral scanning provides convenient integration with CAD/CAM and permits color data to be obtained simultaneously with the digital geometry. The accuracy of shade matching nevertheless depends on the device model, the software, and clinical conditions, and high repeatability is not always accompanied by adequate trueness.

Artificial intelligence systems possess the greatest potential for automation, but the evidence base remains limited by the heterogeneity of the algorithms and datasets employed.

The difficulty of drawing a single conclusion about the superiority of any one method is illustrated by the meta-analysis of Borse and Chaware (2020), which pooled 21 studies of visual shade methods, instrumental shade methods, and the factors affecting shade selection, and reported statistically significant heterogeneity across the included data ($Q = 1038.15$, $df = 20$, $p < .0001$).

Table 1 summarizes the operating principles, reported performance, and principal limitations of the visual and digital methods discussed above. Considered together, these data indicate that none of the existing methods can be regarded as a universal solution for all clinical situations. The choice of technology should be determined by the nature of the restoration, the esthetic requirements, the equipment available, and the accuracy required.



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**Table 1**

*Comparative Characteristics of Visual and Digital Methods of Tooth Shade Determination*

| Method | Operating principle | Reported performance | Principal limitations |
|---|---|---|---|
| Visual shade guides | Direct comparison of the tooth with tabs of a standardized guide (VITA Classical, VITA 3D-Master) | Lowest agreement with instrumental references; kappa agreement with spectrophotometry as low as 0.2 in one clinical comparison; visual and instrumental thresholds differ significantly | Subjectivity; dependence on illumination, observer experience and fatigue, surround, and tooth hydration |
| Spectrophotometry | Recording of spectral reflectance across the visible spectrum, converted into color coordinates | Serves as the reference standard in most comparative studies; highest reported precision and accuracy among instrumental methods | Cost of equipment; localized (point) measurement; edge-loss effect; sensitivity to probe positioning, surface curvature, and translucency |
| Colorimetry | Filtered measurement of light intensity within several spectral bands, generating color coordinates directly | Objectifies shade recording, but has been validated less frequently than spectrophotometry in recent accuracy research | Dependence on sensor characteristics, measurement geometry, and signal conversion algorithms |
| Digital photography with software analysis | Image-based extraction of RGB values, converted to device-independent CIE L*a*b* after color calibration | Agreement with spectrophotometry ($\Delta E \leq 2$) in 84.0% of cases under a standardized protocol; only 23% of cases within the acceptability threshold when cross-polarization was used without full calibration; significant reduction in $\Delta E$ versus conventional tabs in pooled analysis ($p < .0001$) | RGB values are not absolute; strong dependence on sensor, lens, exposure, white balance, light source, file format, and internal processing |
| Intraoral scanning | Color capture concurrent with acquisition of three-dimensional surface geometry | Pooled repeatability 0.81–0.85 but pooled trueness only 0.28–0.38 relative to spectrophotometry; acceptable agreement for value (lightness) but insufficient for full shade selection | Marked device-to-device variability; high repeatability does not imply trueness; lower agreement for translucent anterior teeth |
| Artificial intelligence–based image analysis | Learned mapping from image features (spatial color distribution, brightness, texture) to shade classes | 79.12% top-1 accuracy across smartphones and cameras without calibration; 76.0% top-1 accuracy in an independent 50-case observer study | Heterogeneous algorithms and datasets; small training samples; limited external validation across devices, illuminants, and populations |

*Note.* $\Delta E$ = color difference in the CIELAB color space; RGB = red, green, blue. Reported performance values are drawn from Baqleh and Alhouri (2026), Chen et al. (2012), Hardan et al. (2022), Hina et al. (2024), Lazar et al. (2019), Rashid et al. (2023), Shetty et al. (2024), Tao et al. (2026), and Vitai et al. (2025). Trueness and repeatability figures for intraoral scanning are pooled proportions.



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**Discussion**

Analysis of the contemporary literature reveals a consistent trend toward objectifying the process of tooth shade determination. The transition from visual shade selection to digital measurement makes it possible to describe color quantitatively and increases the reproducibility of results.

At the same time, the term digital is not synonymous with the term accurate. The results of a digital system are determined by the characteristics of the recording device, the conditions under which the data are obtained, and the algorithm by which those data are interpreted.

The heterogeneity of findings in studies of digital photography is particularly instructive. Under strict standardization, some authors obtain a high degree of correspondence with spectrophotometric data (Hina et al., 2024), whereas other studies demonstrate clinically significant discrepancies (Lazar et al., 2019). Such variability indicates that the further development of the method should be directed not so much toward the use of higher-resolution cameras as toward standardization of the entire chain of color recording and processing. This conclusion is supported by the systematic review of Rashid et al. (2023), which found that under controlled conditions non-proximity digital instruments produced clinical outcomes comparable to those of contact devices, while also reporting that a substantial proportion of the included studies failed to describe the camera apparatus adequately or to control for variation in ambient light.

A similar situation is observed with intraoral scanners. Contemporary devices demonstrate high measurement repeatability, but meta-analytic data do not permit them to be considered a full replacement for the spectrophotometer under all clinical conditions (Akl et al., 2023; Baqleh & Alhouri, 2026; Vitai et al., 2025).

The most promising approach appears to be a combined one, in which digital recording is supplemented by software analysis and the results are compared with objective color coordinates. In such a system the clinician receives not only the designation of a shade from a standard guide but also quantitative information about lightness, color coordinates, and the spatial heterogeneity of tooth color.

**Future Perspectives**

The further development of digital methods of color determination is likely to be associated with the integration of several technologies into a single clinical workflow.

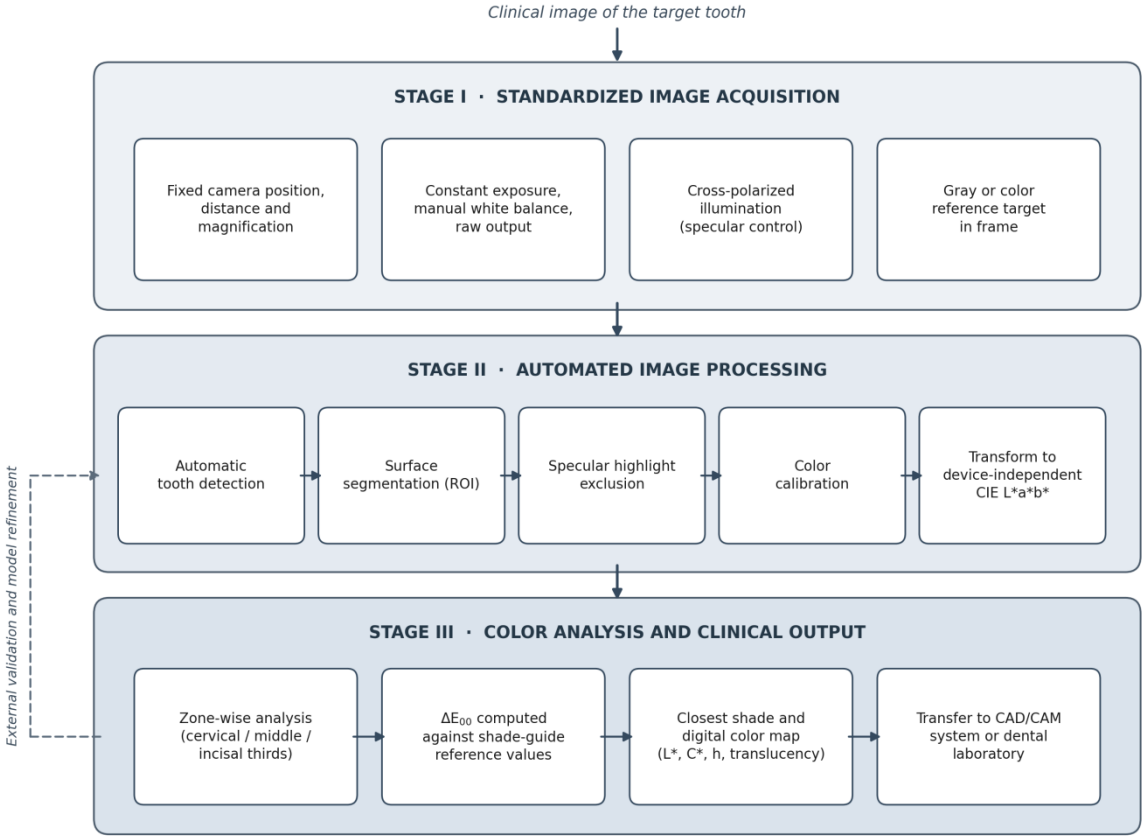
A prospective software system may comprise the sequential stages presented in Figure 1: acquisition of a standardized image, automatic recognition of the tooth, segmentation of the surface, exclusion of specular highlights, color calibration, transformation of color coordinates, analysis of individual tooth regions, determination of the closest shade, generation of a digital color map, and transfer of the data to a CAD/CAM system or dental laboratory.



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**Figure 1**

*Proposed Integrated Workflow for Digital Tooth Shade Determination*




*Note.* ROI = region of interest; ΔE00 = color difference calculated with the CIEDE2000 formula; L* = lightness; C* = chroma; h = hue angle; CAD/CAM = computer-aided design and computer-aided manufacturing. Solid arrows indicate the sequential processing pathway; the dashed pathway indicates external validation of algorithm output on independent clinical data and subsequent model refinement. The workflow synthesizes the standardization requirements described by Hina et al. (2024), Lazar et al. (2019), and Rashid et al. (2023) with the automated processing stages reported by Shetty et al. (2024) and Tao et al. (2026).

The application of artificial intelligence may reduce operator involvement at individual stages and potentially increase the reproducibility of results.

The development of software solutions that do not require a separate, costly device is of particular interest. The use of a standard digital camera or a smartphone camera together with a calibration reference and validated software could potentially make objectified color determination more accessible; the results reported by Tao et al. (2026) for device-agnostic algorithms support the feasibility of this direction.

A further promising direction is the transition from the determination of a single tooth shade to the construction of a digital color map. Such a map may contain data on the lightness, chroma, hue, and translucency of different regions of the crown, which is considerably more informative than a single designation from a standard shade guide.

The introduction of such systems requires standardized capture protocols, unified requirements for color calibration, the creation of large clinical image databases, and independent external validation of the algorithms developed.

**Conclusions**

1. Digital technologies allow a considerable increase in the objectivity and reproducibility of tooth shade determination compared with purely visual assessment; the accuracy of different digital methods is, however, not uniform.


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2. Spectrophotometry remains the best-substantiated instrumental reference method for determining the color of natural teeth and is widely used to evaluate the accuracy of other digital technologies.
3. Digital photography possesses considerable potential owing to the possibility of analyzing the entire tooth surface, documenting the result, and processing the image by software. Its clinical accuracy depends directly on the standardization of capture and on color calibration.
4. Intraoral scanners provide convenient integration of shade determination into the digital CAD/CAM protocol and are characterized by high repeatability; their trueness in determining color nevertheless depends on the particular system and does not always correspond to spectrophotometric data.
5. A promising direction is the development of software systems that combine standardized image acquisition, automated color calibration, analysis of individual tooth regions, and artificial intelligence algorithms.
6. The introduction of artificial intelligence systems for shade determination into broad clinical practice requires standardized datasets, external validation of algorithms, and studies of their effectiveness under real clinical conditions.

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# EARLY DETECTION OF CHRONIC KIDNEY DISEASE IN CHILDREN: RISK FACTORS AND CONTEMPORARY DIAGNOSTIC STRATEGIES: A NARRATIVE REVIEW

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**ABSTRACT**
*Pediatric chronic kidney disease (CKD) may remain minimally symptomatic while structural or tubular injury progresses, making early recognition essential. To synthesize risk factors, limitations of conventional detection, and emerging strategies for earlier pediatric CKD identification and risk stratification. This narrative review critically reorganizes the 46 publications in the source manuscript (2010-2025), including cohort, population-based, biomarker, imaging, review, and prediction-model studies. Because the source did not document a reproducible search strategy, formal eligibility criteria, or risk-of-bias assessment, no systematic-review claim is made. CAKUT, prior acute kidney injury, low birth weight, obesity, hypertension, nephrotoxic exposure, and reduced nephron reserve define important risk contexts. Creatinine-based eGFR remains essential but is complemented by urine protein or albumin quantification, cystatin C, tubular biomarkers, ultrasound and Doppler assessment, elastography, quantitative MRI, genomic testing, metabolomics, artificial intelligence, and prognostic models. The most defensible early-detection strategy is longitudinal and risk-oriented, integrating clinical history, kidney function, urine findings, blood pressure, and structural imaging. Emerging biomarkers and digital tools are promising but require further pediatric standardization and validation.*

**ACCEPTED**

**07.09.26**

***Keywords:*** *chronic kidney disease; children; early diagnosis; biomarkers; estimated glomerular filtration rate; pediatric nephrology.*

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## Introduction

Chronic kidney disease (CKD) in childhood comprises a heterogeneous group of persistent structural and functional kidney abnormalities whose clinical consequences can extend across the life course. Unlike adult CKD, which is frequently driven by diabetes and long-standing vascular disease, pediatric CKD more often arises from congenital, hereditary, and developmental disorders. Its importance is amplified by the fact that kidney dysfunction occurs during periods of somatic growth, neurodevelopment, and maturation of multiple organ systems. Even moderate loss of kidney function may be accompanied by impaired growth and nutritional status, disordered mineral and bone metabolism, hypertension, and cardiovascular morbidity (Baiko, 2020; Karimdzhanov et al., 2019; Panzarino et al., 2022; Warady et al., 2023).

The epidemiology of pediatric CKD remains less precisely characterized than that of adult disease. Severe CKD is uncommon, early stages may be clinically silent, diagnostic criteria and estimated

glomerular filtration rate (eGFR) equations vary by age and setting, and population-based screening is inconsistent. Consequently, registry data tend to overrepresent children with advanced disease or kidney replacement therapy and underrepresent subclinical or early-stage CKD (Amanullah et al., 2022; Baiko, 2020; Panzarino et al., 2022). Access to prenatal diagnosis, laboratory testing, pediatric nephrology services, and long-term follow-up also influences when CKD is recognized, particularly in low- and middle-income settings (Amanullah et al., 2022; Çetinkaya et al., 2020).

Congenital anomalies of the kidneys and urinary tract (CAKUT) are a leading cause of pediatric CKD, but the etiologic spectrum also includes hereditary nephropathies, chronic glomerular disease, obstructive uropathy, consequences of acute kidney injury (AKI), nephrotoxic exposure, and increasingly recognized metabolic stressors such as obesity and hypertension (Çetinkaya et al., 2020; Geylis et al., 2023; Panzarino et al., 2022; Sawyer et al., 2023). The early clinical problem is that preserved nephron compensation can maintain filtration within an apparently acceptable range after structural or tubular injury has begun. Serum creatinine may therefore rise after the pathological process is already established, especially in children with low muscle mass or abnormal growth (den Bakker et al., 2022; Skidmore et al., 2024).

This review examines the major risk contexts for pediatric CKD, the limitations of conventional early detection, and the emerging role of biomarkers, advanced imaging, genomics, metabolomics, artificial intelligence, and clinical prediction tools. The central premise is that early diagnosis is most likely to improve when clinicians integrate longitudinal risk information rather than waiting for an isolated abnormal filtration marker.

## Methods

### Review Design and Evidence Base

This article is a narrative review developed from the evidence base contained in the source manuscript. Forty-six cited publications, published between 2010 and 2025, were organized into thematic domains: epidemiology and etiology; clinical risk factors for CKD development or progression; conventional laboratory assessment; emerging biomarkers; imaging; and genomic, metabolomic, artificial-intelligence, and prognostic approaches. The source literature includes narrative reviews, cohort and population-based studies, biomarker studies, imaging studies, and prediction-model research.

The source manuscript did not report a reproducible bibliographic search strategy, search dates, database coverage, formal inclusion or exclusion criteria, duplicate screening, risk-of-bias assessment, or evidence-grading framework. Accordingly, the present paper is explicitly framed as a narrative review rather than a systematic review or meta-analysis. No pooled effect estimates were calculated. Findings were synthesized qualitatively according to clinical relevance for early detection and risk stratification.

## Results

### Epidemiology, Etiology, and High-Risk Clinical Contexts

The available evidence supports a risk-first approach to case finding. CAKUT, including renal hypoplasia or dysplasia, obstructive uropathy, posterior urethral valves, multicystic dysplastic kidney, and a solitary functioning kidney, may initially coexist with apparently adequate filtration because of compensatory hyperfiltration. Reduced nephron mass, however, creates a biological substrate for later proteinuria, hypertension, and progressive nephrosclerosis (Çetinkaya et al., 2020; Groen In 't Woud et al., 2023; Viteri et al., 2021; Weaver et al., 2023; Yavuz et al., 2024).

AKI is another important pathway to chronic dysfunction. Pediatric data indicate that kidney injury may not be fully reversible even when serum creatinine returns toward baseline. Recurrent AKI, persistent acute kidney disease after AKI, and nephrotoxic medication exposure are associated with subsequent CKD risk or faster loss of kidney function (Ameta et al., 2023; Melhem et al., 2021; Patel et al., 2023; Sigurjonsdottir et al., 2018). Children with pre-existing CKD are particularly vulnerable to accelerated decline after additional AKI episodes (Melhem et al., 2021).


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Perinatal and metabolic factors also contribute to risk. Low birth weight is associated with reduced kidney function and hypertension during adolescence, consistent with the concept of limited nephron reserve (Brathwaite et al., 2023). Obesity may promote glomerular hyperfiltration, metabolic and inflammatory stress, and albuminuria or proteinuria; it also complicates interpretation of kidney-function estimates because body composition can influence creatinine-based assessment (Barlabà et al., 2024; Carullo et al., 2023; Sawyer et al., 2023; van Dam et al., 2024). Hypertension is both a consequence of kidney disease and a mechanism of further injury. Ambulatory blood-pressure abnormalities, including nocturnal hypertension, may identify clinically important cardiovascular risk that is not captured by routine daytime measurements (Düzova et al., 2019; Karimdzhanov et al., 2019, 2024; Savenkova, 2017).

**Table 1**

*Risk-oriented framework for early detection of pediatric chronic kidney disease*

| Risk context | Rationale for surveillance | Priority assessments | Representative evidence |
|---|---|---|---|
| CAKUT / reduced nephron mass | Structural abnormalities may precede functional decline; compensatory hyperfiltration can mask early loss of nephron reserve. | Longitudinal eGFR, urine protein/albumin, blood pressure, renal ultrasound; phenotype-specific follow-up. | Çetinkaya et al., 2020; Groen In 't Woud et al., 2023; Viteri et al., 2021 |
| Prior AKI / nephrotoxic exposure | Incomplete recovery and recurrent injury can accelerate CKD development or progression. | Repeat kidney function after AKI, urine testing, blood pressure, medication review. | Ameta et al., 2023; Melhem et al., 2021; Patel et al., 2023 |
| Low birth weight | Lower nephron endowment may reduce renal reserve and increase later hypertension risk. | Blood pressure, eGFR, urinalysis when additional risk factors are present. | Brathwaite et al., 2023 |
| Obesity | Hyperfiltration and metabolic-inflammatory stress may produce albuminuria and complicate eGFR interpretation. | Blood pressure, urine albumin/protein, kidney-function assessment with attention to body composition. | Barlabà et al., 2024; Carullo et al., 2023; van Dam et al., 2024 |
| Hypertension | May reflect kidney injury and independently accelerate progression; nocturnal abnormalities can be missed in clinic. | Repeated standardized blood pressure; ambulatory monitoring when indicated. | Düzova et al., 2019; Karimdzhanov et al., 2024 |
| Persistent urinary abnormalities | Proteinuria/albuminuria can be an early marker and a progression factor; hematuria may indicate glomerular or genetic disease. | Confirm persistence; quantify protein/creatinine or albumin/creatinine; evaluate eGFR and blood pressure. | Kajiwara et al., 2020; Shanks et al., 2023 |

*Note.* The framework summarizes themes in the reviewed literature and is not a substitute for disease-specific pediatric nephrology guidelines.

**Conventional Laboratory Assessment and Its Limitations**

Routine urinalysis remains one of the most accessible routes to early detection. Proteinuria is both a marker of existing glomerular injury and a recognized risk factor for CKD progression. Quantification using a spot urine protein-to-creatinine ratio or albumin-to-creatinine ratio avoids the practical limitations of 24-hour urine collection and can support longitudinal monitoring (Baiko, 2020; Kajiwara et al., 2020; Vyalkova et al., 2013, 2019). School urine screening with quantitative protein-to-creatinine measurement has demonstrated the ability to identify a small number of children with clinically important, otherwise asymptomatic kidney disease (Kajiwara et al., 2020).

Proteinuria in children must be interpreted carefully because transient increases can occur during fever, exercise, or other physiologic stress. Persistent proteinuria, especially when accompanied by hematuria, hypertension, reduced eGFR, or structural kidney abnormalities, warrants more intensive evaluation. Conversely, CAKUT and tubulointerstitial disorders may produce important structural or



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tubular injury before substantial albuminuria becomes evident (Chesnokova & Vyalkova, 2021; McLeod et al., 2020; Musiał & Zwolińska, 2018).

Serum creatinine and creatinine-based eGFR remain central to CKD staging and follow-up, but creatinine is affected by age, sex, muscle mass, growth, and nutritional status. A value within a population reference range does not necessarily exclude early kidney injury in an individual child (Baiko, 2020; den Bakker et al., 2022; Komarova et al., 2010; Skidmore et al., 2024). Cystatin C is less dependent on muscle mass and may improve assessment when creatinine is an unreliable surrogate of filtration, including in children with low muscle mass or atypical body composition. The evidence supports cystatin C as a complementary rather than isolated measure (den Bakker et al., 2022; Komarova et al., 2010; Skidmore et al., 2024).

**Emerging Biomarkers and Molecular Phenotyping**

An important direction in pediatric nephrology is the identification of biomarkers that reflect active nephron injury before marked filtration loss occurs. Urinary markers of tubular health, tubular injury, and inflammation have been associated with CKD progression in children. In the CKiD cohort, biomarker patterns involving epidermal growth factor, alpha-1 microglobulin, kidney injury molecule-1, monocyte chemoattractant protein-1, and YKL-40 provided information beyond conventional clinical variables, supporting the concept that urine can capture biological processes not fully represented by serum creatinine or eGFR (Greenberg et al., 2021).

Tubular biomarkers may be particularly relevant in obstructive uropathy, where longitudinal trajectories can reflect ongoing injury despite relatively stable conventional kidney-function measures (McLeod et al., 2020). Other candidate approaches include fractional excretion measures as indicators of tubular dysfunction, markers of inflammation and fibrogenesis, and growth differentiation factor 15 (Chesnokova et al., 2025; Chesnokova & Vyalkova, 2021; Musiał & Zwolińska, 2018; Thorsteinsdottir et al., 2020). These tools are biologically attractive but are not yet replacements for established CKD criteria because pediatric reference intervals, assay standardization, reproducibility, and incremental prognostic value require further validation.

Metabolomics extends this approach from individual biomarkers to molecular signatures. Machine-learning analysis of metabolomic profiles has distinguished etiologic patterns within pediatric CKD, while D-asparagine and the D/L-serine ratio have shown associations with chronic impairment of kidney function that may be less dependent on physique than conventional markers (Lee et al., 2022; Morishita et al., 2024). Such findings support molecular phenotyping as a future adjunct to clinical classification rather than a current population-screening strategy.

**Imaging for Structural and Functional Characterization**

Ultrasound remains the foundational imaging modality because it is widely available, nonionizing, and suitable for serial pediatric assessment. Clinically relevant features include kidney size relative to age and height, parenchymal thickness and echogenicity, corticomedullary differentiation, cystic change, collecting-system dilatation, and congenital structural abnormalities. Quantitative measures such as renal parenchymal area may contribute additional prognostic information in infants with CAKUT (Çetinkaya et al., 2020; Viteri et al., 2021; Yavuz et al., 2024).

Doppler ultrasound can extend conventional sonography by assessing intrarenal vascular parameters that may correlate with renal function and histopathological injury, although these measures should be interpreted in conjunction with clinical and laboratory findings (Sawires et al., 2018). Shear-wave elastography offers a noninvasive estimate of tissue stiffness and may capture remodeling or fibrosis. Pediatric studies have demonstrated diagnostic potential, but age-specific normative ranges and protocol standardization remain important limitations (Liu & Wang, 2021; Tiwari et al., 2025).

Quantitative magnetic resonance imaging (MRI) provides multiparametric information on renal tissue without ionizing radiation. Differences between healthy children and young people with CKD have


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been demonstrated using quantitative MRI techniques, suggesting a role in noninvasive phenotyping and evaluation of selected patients with inconclusive conventional assessment (Dillman et al., 2022). Cost, scan duration, access, and the need for specialized expertise currently limit MRI as a broad screening modality.

### Genomics, Artificial Intelligence, and Prognostic Modeling

Genomic sequencing can identify inherited causes of pediatric kidney disease that may not be apparent from routine clinical evaluation. In children referred for microscopic hematuria, genomic assessment has shown clinically meaningful diagnostic yield, illustrating the potential value of phenotype-directed genetic testing where hereditary disease is suspected (Shanks et al., 2023).

Artificial intelligence and statistical learning are also being applied to standard clinical data and imaging. Deep-learning features extracted from kidney ultrasound images in children with posterior urethral valves have been used to predict CKD progression, and combined clinical-imaging models may outperform either modality alone (Weaver et al., 2023). Large electronic health-record cohorts have also been used to characterize trajectories of kidney-function decline and identify clinical progression factors such as lower baseline eGFR, proteinuria, hypertension, disease etiology, and medical complexity (Gluck et al., 2023).

Prediction tools developed from pediatric CKD cohorts can integrate age, diagnosis, laboratory measurements, and longitudinal change to estimate time to kidney replacement therapy. These models illustrate a broader transition from threshold-based diagnosis toward dynamic risk estimation (Ng et al., 2023). Their clinical value will depend on external validation, transportability across health systems and populations, calibration over time, and transparent integration into clinical decision making.

## Discussion

### Toward an Integrated Risk-Oriented Diagnostic Strategy

The reviewed evidence supports a conceptual shift in pediatric CKD detection. A model centered primarily on elevated serum creatinine or an advanced reduction in eGFR is inherently late for a disease in which structural, tubular, vascular, or molecular abnormalities may precede clear filtration failure. A more defensible strategy begins by identifying children with increased pretest probability of kidney injury and then applying longitudinal multimodal surveillance (Baiko, 2020; den Bakker et al., 2022; Warady et al., 2023).

At the clinical level, this means prioritizing children with CAKUT, a solitary functioning kidney, prior AKI, recurrent nephrotoxic exposure, low birth weight, obesity, hypertension, persistent urinary abnormalities, or suspected hereditary disease. Baseline and follow-up evaluation should integrate eGFR, quantitative proteinuria or albuminuria, blood pressure, and structural imaging rather than interpreting any of these measurements in isolation. The association of proteinuria and hypertension with more rapid CKD progression in real-world pediatric cohorts further supports attention to these markers as both diagnostic and prognostic variables (Gluck et al., 2023; Groen In 't Woud et al., 2023).

Advanced tests should be selected according to the clinical question. Cystatin C is most useful when creatinine-based filtration assessment is uncertain; tubular biomarkers may help characterize active injury; elastography and quantitative MRI may refine structural or fibrotic phenotyping; and genomic sequencing may be most informative when the phenotype suggests inherited disease. Metabolomic and artificial-intelligence tools remain promising for future risk stratification but should not yet be treated as universal screening tests (Lee et al., 2022; Shanks et al., 2023; Tiwari et al., 2025; Weaver et al., 2023).

### Clinical Implications

Three practical implications emerge. First, early detection should be longitudinal: repeated measurements are more informative than isolated normal values because pediatric CKD evolves over time and compensatory physiology may initially obscure loss of nephron reserve. Second, surveillance intensity should be proportional to risk. Children with structural anomalies, prior AKI, persistent proteinuria,


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hypertension, or multiple interacting risk factors warrant closer follow-up than children without these features. Third, emerging technologies should be used to answer specific diagnostic or prognostic uncertainties rather than added indiscriminately. This tiered approach may improve detection while limiting unnecessary testing and cost.

**Limitations of the Evidence Base**

This review has several limitations. Most importantly, it is a narrative synthesis of the literature contained in the source manuscript and not a systematic review. The absence of a documented comprehensive search strategy means that relevant studies may be missing and publication-selection bias cannot be excluded. The cited evidence is heterogeneous with respect to CKD etiology, age, disease severity, outcome definitions, biomarker assays, imaging protocols, and follow-up duration. Many emerging biomarkers and imaging methods have been evaluated in relatively small or selected pediatric cohorts, limiting generalizability. Finally, technological performance does not automatically establish clinical utility; future studies must show that new tests improve decisions and patient outcomes beyond established risk factors and conventional measurements.

**Future Research**

Future pediatric CKD research should prioritize prospective multicenter validation of integrated risk models; age- and development-specific reference ranges for cystatin C and emerging biomarkers; standardized protocols for elastography and quantitative MRI; evaluation of genomic and metabolomic testing in clearly defined clinical pathways; and external validation of artificial-intelligence models across diverse populations and health systems. Research should also address implementation in low-resource settings, where simple risk stratification, blood-pressure measurement, urine testing, and accessible ultrasound may have greater immediate population impact than high-cost technologies (Amanullah et al., 2022).

**Conclusion**

Pediatric CKD can remain clinically silent while structural and molecular kidney injury progresses. The most clinically useful early-detection strategy is therefore not a single novel test but an integrated, risk-oriented model that combines medical history, eGFR, proteinuria or albuminuria, blood pressure, and renal imaging over time. Cystatin C, tubular biomarkers, advanced imaging, genomics, metabolomics, artificial intelligence, and prognostic models can add value in selected contexts, but most require additional pediatric standardization and validation. Earlier identification of kidney injury creates an opportunity for timely nephroprotective management before substantial irreversible nephron loss occurs.

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# CLINICAL AND LABORATORY OUTCOMES OF COMBINED L-ARGININE AND N-ACETYLCYSTEINE THERAPY FOR COMMUNITY-ACQUIRED PNEUMONIA IN PATIENTS WITH A HISTORY OF ISCHEMIC STROKE

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## ABSTRACT

*Background: Community-acquired pneumonia (CAP) may be clinically more severe in patients with previous ischemic stroke because neurological impairment, dysphagia, inflammation, and vascular dysfunction can interact to worsen respiratory recovery. Objective: This study evaluated clinical and laboratory outcomes associated with adjunctive L-arginine and N-acetylcysteine (NAC) in patients with CAP and a history of ischemic stroke. Methods: The study included 150 patients with CAP. Patients with previous ischemic stroke received standard therapy alone or standard therapy supplemented with L-arginine, NAC, or both agents. Outcomes included C-reactive protein (CRP), procalcitonin (PCT), vascular endothelial growth factor (VEGF), nitric oxide (NO), endothelin-1 (ET-1), National Institutes of Health Stroke Scale (NIHSS), CURB-65, and hospitalization duration. Results: At baseline, the post-stroke CAP group had higher CRP, PCT, VEGF, and ET-1 and lower NO than the non-stroke comparison group. The combined-treatment subgroup showed the largest reported changes: CRP decreased 79.5%, PCT 80.7%, VEGF 42.5%, and ET-1 46.0%, while NO increased 59.2%. Post-treatment NIHSS and CURB-65 scores were 5.8 and 1.0, and mean hospitalization was 10.4 days. Conclusion: Combined L-arginine and NAC was associated with the most favorable biomarker and clinical profile, warranting prospective controlled confirmation before causal efficacy is inferred.*

## ACCEPTED

**08.09.26**

***Keywords:*** *community-acquired pneumonia; ischemic stroke; L-arginine; N-acetylcysteine; endothelial dysfunction; inflammation.*

CC BY

## Introduction

Community-acquired pneumonia (CAP) remains a major cause of acute respiratory morbidity and hospital utilization, especially among older adults and patients with substantial comorbidity. Contemporary CAP management requires prompt diagnosis, assessment of severity, appropriate antimicrobial therapy, and recognition of host factors that may alter prognosis (Metlay et al., 2019). In patients with a previous ischemic stroke, the clinical problem is more complex because persistent neurological deficits can impair airway protection, mobility, cough effectiveness, nutrition, and rehabilitation. These factors may increase vulnerability to respiratory infection even when pneumonia occurs outside the acute stroke period.

The association between stroke and pneumonia is well established. A systematic review and meta-analysis by Westendorp et al. (2011) estimated that pneumonia occurs in approximately 10% of patients after acute stroke and is strongly associated with mortality. More recent evidence continues to identify stroke severity, dysphagia, mechanical ventilation, nasogastric tube use, age, and selected cardiometabolic comorbidities as important predictors of pneumonia after stroke (Ahmad et al., 2024). Dysphagia is particularly relevant because impaired swallowing facilitates aspiration of oropharyngeal material. Chang et al. (2022) found a markedly increased odds of pneumonia among stroke patients with dysphagia, reinforcing the importance of airway protection and swallowing assessment in neurologically vulnerable populations.

Although the present investigation concerns CAP in patients with a history of ischemic stroke rather than pneumonia arising within the first seven days of an acute cerebrovascular event, the stroke-associated pneumonia literature remains clinically informative. The Pneumonia in Stroke Consensus Group recommended standardized diagnostic terminology for pneumonia occurring early after stroke and emphasized that inflammatory biomarkers alone are insufficient for diagnosis (Smith et al., 2015). This distinction is relevant because CRP and PCT should be interpreted as components of a broader clinical picture rather than as isolated diagnostic endpoints. PCT has demonstrated prognostic associations in pneumonia, but its performance varies by disease severity and timing; longitudinal change may be more informative than a single measurement (Liu et al., 2016).

A second pathophysiological dimension is endothelial dysfunction. Systemic infection and inflammation can disturb vascular tone, microcirculatory regulation, and endothelial signaling. Endothelin-1 (ET-1) is a potent vasoconstrictor implicated in vascular dysfunction, whereas nitric oxide (NO) has vasodilatory, antiplatelet, and endothelial-protective actions (Böhm & Pernow, 2007). Vascular endothelial growth factor (VEGF), although essential for angiogenic signaling and endothelial homeostasis, may increase in inflammatory and hypoxic states and can therefore serve as an indirect indicator of altered vascular biology. In patients who already have cerebrovascular disease, an infection-related shift toward vasoconstriction, oxidative stress, and impaired NO bioavailability may be clinically important.

L-arginine and N-acetylcysteine (NAC) offer a biologically plausible combination for addressing this inflammatory-endothelial interface. L-arginine is the physiological substrate for nitric oxide synthase and therefore contributes to endogenous NO formation (Böger, 2007). Meta-analytic evidence suggests that short-term L-arginine supplementation can improve flow-mediated dilation in selected patients with impaired baseline endothelial function, although effects are heterogeneous and not consistently demonstrated across cardiovascular and metabolic populations (Bai et al., 2009; Rodrigues-Krause et al., 2019). NAC, meanwhile, acts as a mucolytic agent and as a cysteine donor for glutathione synthesis. Its antioxidant effects depend substantially on cellular glutathione biology rather than on direct radical scavenging alone (Rushworth & Megson, 2014).

The potential complementarity of these agents is therefore clinically interesting: L-arginine may support NO-dependent vascular regulation, while NAC may improve mucus clearance and support intracellular antioxidant capacity. However, biological plausibility does not by itself establish therapeutic efficacy, and evidence for either agent as an adjunct specifically in post-stroke CAP is limited. The objective of the present study was to evaluate the clinical and laboratory outcomes associated with standard therapy, L-arginine, NAC, and combined L-arginine plus NAC in patients with CAP and a history of ischemic stroke. Particular attention was given to inflammatory markers, endothelial-regulatory markers, neurological status, pneumonia severity, and length of hospitalization.

**Method**

Study design and participants. The available study record describes a clinical and laboratory study of 150 patients diagnosed with CAP and treated in a hospital setting. The principal study population included patients with CAP who had a previous ischemic stroke and were in the late recovery or remote


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period after the cerebrovascular event. A comparison group consisted of patients with CAP without a history of stroke. CAP was established from clinical, laboratory, and instrumental findings consistent with accepted diagnostic approaches. The original record did not provide recruitment dates, a detailed sampling frame, or a participant flow diagram; consequently, these elements cannot be reconstructed without additional primary documentation.

Treatment groups. Patients with CAP and a history of ischemic stroke were divided into four therapeutic subgroups: IA, standard therapy; IB, standard therapy plus L-arginine; IC, standard therapy plus NAC; and ID, standard therapy plus both L-arginine and NAC. The source results table reports n = 25 for each treatment subgroup. The original study record does not specify the method of allocation, medication doses, routes, treatment duration, or the complete components of standard therapy. These details are important for reproducibility and should be added from the clinical protocol before journal submission. In this revised manuscript, treatment effects are therefore described as associations with the reported therapeutic regimens rather than as proof of randomized causal efficacy.

Laboratory outcomes. Systemic inflammation and infection-related activity were assessed using CRP and PCT. Endothelial and vascular-regulatory status was characterized using VEGF, NO, and ET-1. These markers were measured before treatment and after treatment. The source manuscript reports group means and standard deviations for the baseline comparison and percentage changes for selected treatment outcomes. Assay manufacturers, sampling times, specimen handling procedures, and analytic coefficients of variation were not available in the provided record and are not inferred here.

Clinical outcomes. Neurological status was assessed using the National Institutes of Health Stroke Scale (NIHSS), a standardized neurological deficit scale originally developed for acute cerebral infarction assessment (Brott et al., 1989). Pneumonia severity was assessed using CURB-65, which incorporates confusion, urea concentration, respiratory rate, blood pressure, and age of 65 years or older and is widely used to stratify mortality risk in CAP (Lim et al., 2003). Duration of hospitalization was also recorded as a pragmatic indicator of clinical recovery and resource use.

Statistical presentation. The revised analysis preserves the numerical values and significance statements reported in the source manuscript. Baseline values are presented as mean ± standard deviation. The source reports highly significant between-group differences for the baseline biomarkers ($p < .001$) and significant post-treatment differences for clinical outcomes ($p < .001$), but it does not identify the statistical tests, assumptions, multiplicity adjustments, or exact comparison model. No new inferential tests were generated because patient-level data were not available. Relative baseline differences discussed below were calculated descriptively from the reported means, and the figures reproduce reported percentages or means only. This approach strengthens transparency while avoiding unsupported statistical reconstruction.

**Results**

Baseline inflammatory profile. Patients with CAP and a history of ischemic stroke demonstrated a more pronounced inflammatory profile than patients with CAP without previous stroke (Table 1). Mean CRP was 82.6 ± 24.8 mg/L in the post-stroke group compared with 61.3 ± 19.5 mg/L in the comparison group, corresponding to an approximately 34.7% higher reported mean. PCT showed a similar pattern: 3.59 ± 1.38 ng/mL versus 2.67 ± 1.17 ng/mL, or approximately 34.5% higher in the post-stroke group. These findings indicate greater systemic inflammatory and infection-related activity in the neurologically vulnerable cohort at baseline.

Baseline endothelial-regulatory profile. The vascular markers showed an additional imbalance. VEGF was 486.5 ± 82.4 pg/mL in patients with previous ischemic stroke compared with 312.8 ± 64.7 pg/mL in the non-stroke CAP group, representing an approximately 55.5% higher mean. ET-1 was also higher (4.86 ± 0.82 vs. 3.74 ± 0.69 pg/mL; approximately 29.9% higher). In contrast, NO was lower in the post-stroke group (24.8 ± 4.9 vs. 29.7 ± 5.1 μmol/L), an approximately 16.5% reduction relative to the comparison mean. Considered together, increased ET-1 and reduced NO are consistent with an unfavorable



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vasoregulatory balance, while elevated VEGF may reflect inflammatory, hypoxic, or reparative endothelial signaling.

**Table 1**

*Baseline Indicators of Systemic Inflammation and Endothelial Regulation*

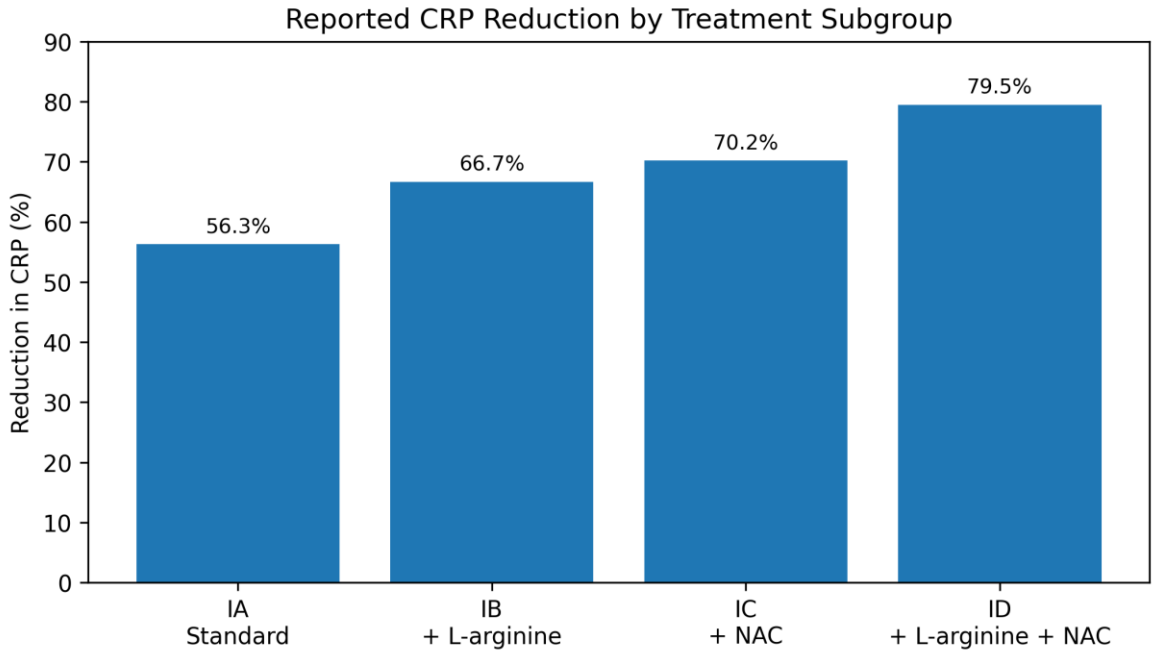
| Marker | CAP + previous ischemic stroke (n = 38) | CAP without stroke (n = 20) |
|---|---|---|
| CRP, mg/L | 82.6 ± 24.8* | 61.3 ± 19.5 |
| Procalcitonin, ng/mL | 3.59 ± 1.38* | 2.67 ± 1.17 |
| VEGF, pg/mL | 486.5 ± 82.4* | 312.8 ± 64.7 |
| NO, μmol/L | 24.8 ± 4.9 | 29.7 ± 5.1* |
| ET-1, pg/mL | 4.86 ± 0.82* | 3.74 ± 0.69 |

*Note.* Values are mean ± SD. *p < .001 as reported in the source manuscript. The relationship of these baseline denominators to the total sample of 150 requires clarification from the original study records.

Inflammatory response to treatment. All four therapeutic subgroups demonstrated reductions in CRP, but the magnitude differed across regimens. The reported decrease was 56.3% with standard therapy (IA), 66.7% with L-arginine added (IB), 70.2% with NAC added (IC), and 79.5% with the combined regimen (ID). Thus, the combined subgroup had the largest reported reduction in CRP (Figure 1). For PCT, the source manuscript provides the most detailed percentage for the combined group, in which PCT decreased by 80.7%. Because corresponding PCT percentages for all other subgroups were not provided, they are not estimated in this revision.

**Figure 1**

*Reported Percentage Reduction in C-Reactive Protein by Treatment Subgroup*




*Note.* Values reproduce the reported percentage decrease in CRP for subgroups IA–ID; no unreported values were estimated.

Endothelial response to treatment. The combined L-arginine plus NAC subgroup also showed the largest reported favorable change in endothelial markers. VEGF decreased by 42.5% and ET-1 decreased by 46.0%, while NO increased by 59.2%. The direction of these changes is biologically coherent with improved NO availability and reduced vasoconstrictor signaling. Nevertheless, the absence of complete post-treatment means and dispersion measures for every subgroup limits calculation of standardized effect sizes or confidence intervals. Table 2 therefore focuses on the clinical outcomes for which complete


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subgroup means are reported, while Table 3 summarizes the documented percentage changes without extrapolating missing values.

Clinical severity and hospitalization. Clinical improvement was observed in each subgroup, with the most favorable post-treatment values reported for subgroup ID. Mean NIHSS changed from 9.3 ± 2.0 before treatment to 5.8 ± 1.5 after treatment in ID. Corresponding post-treatment NIHSS values were 7.8 ± 1.9 in IA, 6.9 ± 1.7 in IB, and 6.6 ± 1.6 in IC. CURB-65 showed a parallel pattern: subgroup ID decreased from 2.7 ± 0.6 to 1.0 ± 0.3, compared with post-treatment values of 1.8 ± 0.5 in IA, 1.5 ± 0.4 in IB, and 1.4 ± 0.4 in IC (Table 2). The reported pre-treatment subgroup differences were not significant ($p > .05$), whereas post-treatment differences were reported as $p < .001$.

**Table 2**

*Neurological and Pneumonia Severity Before and After Treatment*

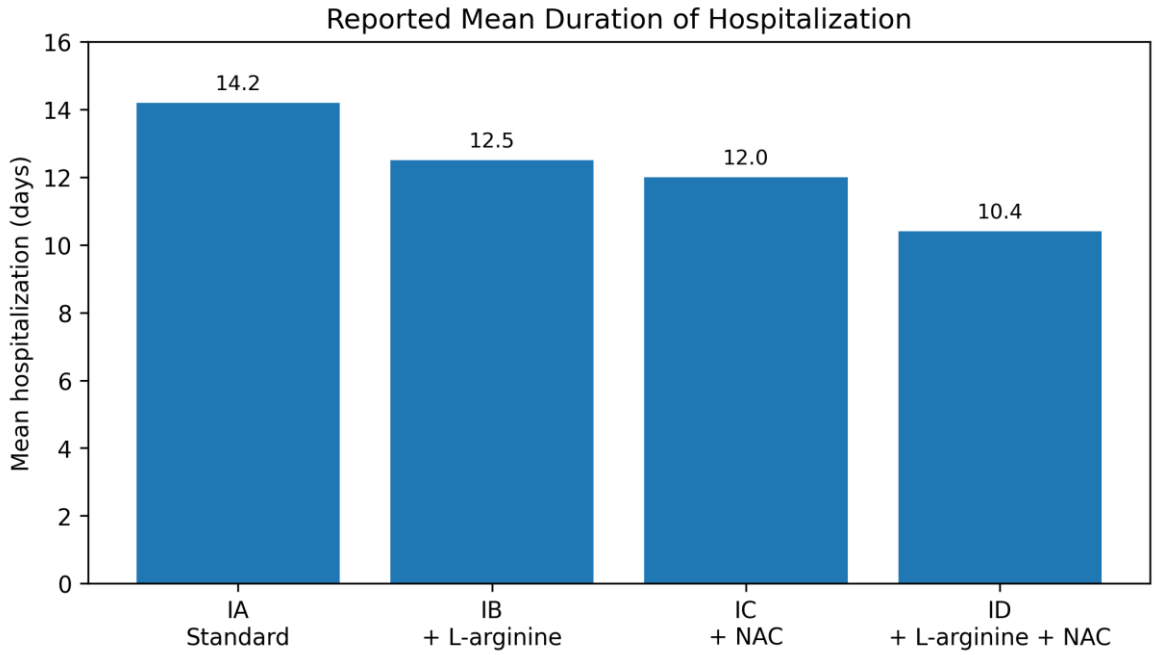
| Outcome | IA (n = 25) | IB (n = 25) | IC (n = 25) | ID (n = 25) |
|---|---|---|---|---|
| NIHSS, before | 9.4 ± 2.1 | 9.2 ± 2.3 | 9.5 ± 2.2 | 9.3 ± 2.0 |
| NIHSS, after | 7.8 ± 1.9 | 6.9 ± 1.7 | 6.6 ± 1.6 | 5.8 ± 1.5 |
| CURB-65, before | 2.8 ± 0.6 | 2.7 ± 0.5 | 2.8 ± 0.5 | 2.7 ± 0.6 |
| CURB-65, after | 1.8 ± 0.5 | 1.5 ± 0.4 | 1.4 ± 0.4 | 1.0 ± 0.3 |

*Note.* Values are mean ± SD. The source manuscript reports $p > .05$ for baseline subgroup comparisons and $p < .001$ for post-treatment subgroup comparisons; the specific statistical test was not provided.

Length of hospital stay was shortest in the combined-treatment subgroup. Mean hospitalization was 14.2 ± 2.1 days in IA, 12.5 ± 1.8 days in IB, 12.0 ± 1.7 days in IC, and 10.4 ± 1.5 days in ID (Figure 2). Relative to standard therapy, the combined regimen was associated with a mean stay that was 3.8 days shorter, or approximately 26.8% lower. This outcome is clinically relevant because length of stay integrates multiple domains of recovery, although it can also be influenced by discharge practices, rehabilitation access, social circumstances, and institutional policy.

**Figure 2**

*Reported Mean Duration of Hospitalization by Treatment Subgroup*




*Note.* Mean ± SD hospitalization values were IA 14.2 ± 2.1, IB 12.5 ± 1.8, IC 12.0 ± 1.7, and ID 10.4 ± 1.5 days; $p < .001$ was reported for the subgroup comparison.



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**Table 3**

*Summary of Reported Treatment-Associated Changes*

| Outcome | IA | IB | IC | ID |
|---|---|---|---|---|
| CRP reduction | 56.3% | 66.7% | 70.2% | 79.5% |
| PCT reduction | NR | NR | NR | 80.7% |
| VEGF reduction | NR | NR | NR | 42.5% |
| ET-1 reduction | NR | NR | NR | 46.0% |
| NO increase | NR | NR | NR | 59.2% |
| Hospitalization | 14.2 days | 12.5 days | 12.0 days | 10.4 days |

*Note.* NR = not reported in the supplied manuscript. This table intentionally leaves unavailable subgroup percentages blank rather than estimating them.

## Discussion

The principal finding of this study is that CAP in patients with a history of ischemic stroke was accompanied by a more adverse inflammatory and endothelial-regulatory profile than CAP in patients without previous stroke, and that the subgroup receiving both L-arginine and NAC had the most favorable reported laboratory and clinical changes. The results extend the clinical observation that stroke survivors remain vulnerable to respiratory complications by suggesting that vascular-regulatory disturbances may coexist with infection-related inflammation. This interpretation is consistent with the broader literature showing that pneumonia is a consequential complication of stroke and that neurological severity, dysphagia, and impaired airway protection contribute to risk (Ahmad et al., 2024; Chang et al., 2022; Westendorp et al., 2011).

The baseline CRP and PCT findings are clinically plausible. CRP is a nonspecific acute-phase reactant, while PCT can provide additional information regarding systemic bacterial inflammatory activity and prognosis. In a meta-analysis of pneumonia, elevated PCT was associated with increased mortality risk, although diagnostic and prognostic performance varied by clinical setting and threshold (Liu et al., 2016). The present study should therefore not be interpreted as establishing PCT as an independent diagnostic marker in post-stroke CAP. Rather, the higher PCT and CRP concentrations support the presence of a more intense systemic inflammatory response in the post-stroke cohort. This distinction is consistent with the PISCES consensus, which cautioned against overreliance on biomarkers for defining pneumonia after stroke (Smith et al., 2015).

The endothelial findings provide a mechanistic hypothesis for the observed treatment pattern. NO is central to vascular homeostasis, and reduced NO bioavailability is a common feature of endothelial dysfunction. ET-1 has opposing vasoconstrictor and proliferative effects and is implicated in vascular disease (Böhm & Pernow, 2007). The combination of lower NO and higher ET-1 at baseline can therefore be viewed as a marker pattern compatible with impaired endothelial regulation. Elevated VEGF is less specific: it may reflect endothelial activation, hypoxia, inflammation, or compensatory angiogenic signaling. Consequently, the reduction in VEGF after therapy should be interpreted as normalization of an altered signaling environment rather than as evidence that lower VEGF is universally beneficial.

L-arginine offers a plausible pathway through which NO signaling might be supported because it is a substrate for nitric oxide synthase (Böger, 2007). Earlier meta-analysis suggested that short-term supplementation improves flow-mediated dilation when baseline endothelial function is impaired (Bai et al., 2009). However, a later systematic review and meta-analysis found no consistent overall improvement in selected endothelial markers across heterogeneous cardiovascular and metabolic populations (Rodrigues-Krause et al., 2019). This mixed evidence is important for interpreting the present results. The 59.2% increase in NO in subgroup ID is noteworthy, but without placebo control, allocation details, treatment dose, complete post-treatment distributions, and individual-level data, it cannot establish a specific pharmacological effect of L-arginine.



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NAC may have contributed through different but potentially complementary mechanisms. It is a well-established mucolytic agent and provides cysteine for intracellular glutathione synthesis. Rushworth and Megson (2014) emphasized that NAC's antioxidant benefit depends on the cellular context and the capacity to restore glutathione, rather than representing a simple direct antioxidant effect. In CAP, improved mucus rheology could theoretically facilitate airway clearance, while glutathione support may help buffer oxidative stress associated with infection and inflammation. The stronger CRP reduction in the NAC subgroup than in standard therapy, and the still larger reduction in the combined subgroup, are consistent with complementarity, but the available data cannot separate pharmacological synergy from baseline differences, co-interventions, or nonrandom allocation.

The clinical outcomes strengthen the potential relevance of the laboratory findings. Subgroup ID had the lowest post-treatment NIHSS and CURB-65 scores and the shortest hospitalization. CURB-65 is a validated severity tool for CAP, with increasing scores associated with increasing mortality risk (Lim et al., 2003). The reduction from 2.7 to 1.0 in the combined subgroup therefore suggests movement toward a lower-risk clinical category, although CURB-65 was designed primarily for initial severity assessment and should not be treated as a stand-alone treatment-response instrument. Similarly, NIHSS is a validated measure of neurological deficit (Brott et al., 1989), but changes in patients remote from stroke may reflect multiple influences, including systemic illness, hydration, oxygenation, delirium, and rehabilitation, rather than direct neurorestorative effects of the adjunctive drugs.

The length-of-stay finding may be the most readily interpretable clinical signal. A mean stay of 10.4 days in subgroup ID compared with 14.2 days under standard therapy represents a 3.8-day difference. If replicated in a controlled trial, such a reduction could have substantial implications for bed utilization, rehabilitation transitions, and patient costs. Yet hospital stay is also susceptible to confounding by discharge criteria, social support, availability of post-acute care, clinician practice, and complications not captured in the dataset. For that reason, future studies should prespecify objective discharge criteria and report time-to-clinical-stability outcomes in addition to total days hospitalized.

From a broader clinical perspective, the data support a multimodal view of CAP in stroke survivors. Standard antimicrobial management remains fundamental and should follow established CAP guidance (Metlay et al., 2019). Adjunctive strategies should not distract from aspiration prevention, dysphagia screening, mobilization, respiratory support, and management of comorbidity. The stroke literature demonstrates that dysphagia substantially increases pneumonia risk (Chang et al., 2022), and the diagnosis of pneumonia after stroke is methodologically challenging when clinical signs overlap with neurological impairment (Kishore et al., 2015; Smith et al., 2015). Any future trial of L-arginine and NAC should therefore standardize swallowing assessment, aspiration risk, pathogen testing, antimicrobial therapy, and respiratory care to isolate the contribution of the adjunctive regimen.

The present study is best viewed as hypothesis-generating evidence for a combined endothelial-supportive and antioxidant/mucolytic approach. The consistency across several outcome domains—CRP, PCT, VEGF, NO, ET-1, NIHSS, CURB-65, and hospital stay—is encouraging. At the same time, mechanistic coherence can increase confidence only when methodological rigor is adequate. The strongest next step would be a prospective, randomized, adequately powered trial with concealed allocation; explicit L-arginine and NAC dosing; standardized antibiotic protocols; serial biomarker sampling; prespecified primary and secondary outcomes; adverse-event monitoring; and multivariable adjustment for age, dysphagia, stroke severity, comorbidities, renal function, and baseline pneumonia severity. Such a design would permit estimation of effect sizes and confidence intervals and would clarify whether the apparent advantage of combined therapy is reproducible and clinically meaningful.

**Limitations and Reporting Considerations**

Several limitations materially affect interpretation. First, the source manuscript reports 150 total participants, while the treatment table accounts for 100 patients across four subgroups of 25, and the



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baseline biomarker table reports group sizes of 38 and 20. The relationship between these denominators is not explained. This discrepancy should be reconciled against the original case report forms or study database before submission. Second, the allocation method is not described, so selection bias and baseline imbalance cannot be excluded. Third, treatment dose, route, duration, adherence, and adverse events are absent. Fourth, laboratory assay methods and post-treatment means with standard deviations are incomplete, preventing independent effect-size calculation.

Fifth, the statistical methods underlying reported p values are unspecified, and patient-level data were unavailable for reanalysis. Sixth, key confounders—including age distribution, sex, stroke location, dysphagia, aspiration status, functional dependence, renal function, smoking, diabetes, antimicrobial regimen, pathogen profile, and oxygen requirement—are not reported by subgroup. Seventh, the study appears to be single-center or limited-center, which may restrict generalizability. Finally, ethics approval and informed-consent information were not included in the supplied manuscript. These reporting gaps do not invalidate the observed numerical patterns, but they substantially limit causal interpretation and should be addressed in any final journal version.

**Conclusion**

Patients with CAP and a history of ischemic stroke demonstrated higher reported CRP, PCT, VEGF, and ET-1 concentrations and lower NO concentrations than patients with CAP without previous stroke, suggesting a combined inflammatory and endothelial-regulatory disturbance. Across the reported therapeutic subgroups, standard therapy supplemented with both L-arginine and NAC was associated with the largest reductions in CRP, PCT, VEGF, and ET-1, the largest increase in NO, the lowest post-treatment NIHSS and CURB-65 scores, and the shortest mean hospitalization.

These findings provide a biologically plausible rationale for investigating combined L-arginine and NAC as adjunctive therapy in neurologically vulnerable patients with CAP. However, incomplete reporting of participant flow, treatment allocation, dosing, assays, and statistical methods precludes firm causal conclusions. The regimen remains investigational and requires confirmation in rigorously reported prospective randomized trials before benefit beyond guideline-concordant CAP and stroke care can be established.

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# THE ROLE OF HMG-COA REDUCTASE INHIBITORS IN STABLE ANGINA ACROSS OCCUPATIONAL GROUPS: BASELINE CLINICAL, FUNCTIONAL, AND METABOLIC CHARACTERIZATION

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**ABSTRACT**
*Background: Stable angina reflects chronic coronary atherosclerotic disease in which ischemic symptoms interact with hemodynamic, lipid, inflammatory, oxidative, and occupational risk factors. Objective: To characterize the pretreatment clinical, functional, and metabolic profile of patients with stable angina assigned to different therapeutic groups before evaluating HMG-CoA reductase inhibitor-based regimens. Methods: The baseline analysis included 150 participants: 30 controls and 120 patients with stable angina distributed equally across four clinical groups. Occupational categories included medical professionals, programmers, marketing specialists, and drivers. Assessment comprised angina frequency, nitroglycerin use, Holter electrocardiography, ambulatory blood pressure monitoring, bicycle ergometry, lipid profile, apolipoprotein B, C-reactive protein, malondialdehyde, superoxide dismutase, catalase, ceruloplasmin, and nitric oxide metabolites. Results: Compared with controls, patients had higher LDL-C, apoB, CRP, MDA, blood pressure, heart rate, arrhythmic burden, and daily ST-segment depression, together with lower HDL-C, antioxidant enzyme activity, NOx, exercise threshold, and exercise duration. LDL-C correlated positively with MDA (r = .41) and ST-depression depth (r = .34) and inversely with NOx (r = -.47). Occupational risk patterns differed, particularly for smoking, night shifts, and stress. Conclusion: Stable angina was associated with a coordinated atherogenic, inflammatory, oxidative, endothelial, and functional phenotype before treatment. These findings provide a balanced baseline for subsequent evaluation of atorvastatin-containing regimens but do not independently establish therapeutic efficacy.*

**ACCEPTED**

**08.09.26**

***Keywords:*** *stable angina, HMG-CoA reductase inhibitors, atorvastatin, occupational risk, oxidative stress, endothelial dysfunction.*

CC BY

## Introduction

Stable angina is a manifestation of chronic coronary disease in which myocardial oxygen demand intermittently exceeds coronary supply, commonly during physical or emotional stress. Contemporary guidelines emphasize that management should extend beyond symptom relief to comprehensive reduction of atherosclerotic risk, including intensive control of low-density lipoprotein cholesterol (LDL-C), blood pressure, smoking, and physical inactivity (Vrints et al., 2024; Virani et al., 2023). HMG-CoA reductase inhibitors (statins) are central to this strategy because lowering LDL-C reduces major vascular events

across a broad range of cardiovascular risk profiles (Cholesterol Treatment Trialists' [CTT] Collaboration, 2010, 2012). The causal relationship between cumulative LDL exposure and atherosclerotic cardiovascular disease further supports lipid modification in established coronary disease (Ference et al., 2017).

The burden of stable angina is nevertheless heterogeneous. Patients with similar attack frequency may differ substantially in blood pressure, ambulatory ischemia, exercise tolerance, apolipoprotein B (apoB), inflammatory activity, oxidative stress, and endothelial nitric oxide availability. ApoB reflects the number of circulating atherogenic particles and may provide information not fully captured by LDL-C alone (Soffer et al., 2024). Inflammation, often indexed by C-reactive protein (CRP), and oxidative processes may further contribute to endothelial dysfunction and atherosclerotic activity (Fu et al., 2020; Ridker, 2004; Simantiris et al., 2023). Studies of statin therapy in stable coronary disease have also examined ambulatory ischemia, exercise-induced ischemia, endothelial function, and inflammatory markers, suggesting relevance beyond a single lipid measurement (Bogaty et al., 2003; Deanfield et al., 2010; Stone et al., 2005).

Occupational exposures may add another layer of cardiovascular burden. Shift work is associated with increased cardiovascular risk, while sustained job strain has been linked to coronary heart disease (Torquati et al., 2018; Xu et al., 2015). These exposures are relevant when comparing medical professionals, programmers, marketing specialists, and drivers, whose work patterns differ in night duty, stress, sedentary behavior, and smoking. Accordingly, the present paper characterizes the pretreatment clinical, functional, lipid-inflammatory, oxidative, and endothelial profile of patients with stable angina across occupational categories. The aim is to establish baseline comparability and pathophysiologic context before evaluation of atorvastatin-containing regimens; no post-treatment efficacy conclusions are drawn from this baseline dataset.

## Methods

### Study Design and Participants

This paper reports the baseline phase of a comparative clinical study. The analyzed sample comprised 150 participants: 30 individuals in the control group (Group I) and 120 patients with functional class II stable angina in Groups II-V, with 30 patients in each clinical group. The stable-angina groups were similar in age and duration of ischemic heart disease before therapy. The source material identifies the planned clinical arms as conventional therapy (Group II), atorvastatin (Group III), coenzyme Q10 (Group IV), and atorvastatin plus coenzyme Q10 (Group V). All values analyzed in this manuscript were obtained before treatment; therefore, the study findings reported here characterize baseline status rather than therapeutic response.

The occupational distribution of the 120 patients with stable angina consisted of 33 medical professionals, 28 programmers, 25 marketing specialists, and 34 drivers. Occupational risk factors included smoking, hypertension, dyslipidemia, overweight, night-shift work, stress burden, and physical inactivity. The control group served as a physiological reference for clinical, functional, lipid, inflammatory, oxidative, and nitric-oxide-related measurements.

### Clinical and Functional Assessment

Clinical assessment included the frequency of anginal attacks per week and weekly nitroglycerin requirement. Functional evaluation included daytime, nighttime, and maximum heart rate obtained by Holter electrocardiographic monitoring; the number and depth of ST-segment depression episodes; extrasystoles per hour; systolic and diastolic blood pressure on ambulatory blood pressure monitoring (ABPM); and graded exercise testing by bicycle ergometry. Bicycle-ergometry endpoints were threshold power in watts and exercise duration in minutes. Together, these measures were used to characterize symptomatic burden, hemodynamic load, daily ischemia, arrhythmic activity, and exercise tolerance.


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### Laboratory Assessment

The lipid-inflammatory panel included total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), LDL-C, the atherogenic coefficient, apoB, and CRP. Oxidative and antioxidant status was evaluated using malondialdehyde (MDA), superoxide dismutase (SOD), catalase, and ceruloplasmin. Total stable nitric oxide metabolites (NOx) were used as an index of NO-dependent vascular regulation. This combined laboratory panel permitted an integrated assessment of atherogenic particle burden, low-grade inflammation, lipid peroxidation, antioxidant defense, and endothelial-related nitric oxide availability.

### Statistical Analysis

Continuous variables were reported as mean ± standard deviation (M ± SD), and categorical variables as n (%). Analysis of variance was used for comparisons among Groups II-V where reported. Pearson correlation coefficients were calculated in the stable-angina cohort (N = 120), with 95% confidence intervals and exact p values. Control-group comparisons were interpreted using the significance levels stated in the source dataset. Because this paper is based on the supplied baseline report, no additional modeling, imputation, or post-treatment analysis was introduced.

## Results

### Baseline Demographic and Occupational Characteristics

The mean age was closely matched across the four stable-angina groups, ranging from 42.2 ± 4.2 to 43.4 ± 4.3 years. Duration of ischemic heart disease ranged from 2.9 ± 1.0 to 3.3 ± 1.0 years, and BMI ranged from 26.9 ± 2.0 to 27.6 ± 1.8 kg/m². No statistically significant differences were reported among the clinical groups for age, ischemic heart disease duration, or BMI. The control-group BMI was lower at 24.8 ± 1.7 kg/m², whereas the patient groups clustered near the overweight range.

Risk-factor distribution varied more clearly by occupation. Drivers had the highest smoking prevalence (61.8%), while medical professionals had the highest reported frequency of night shifts (81.8%) and stress burden (84.8%). Programmers also had high night-shift exposure (71.4%) and stress (75.0%). Marketing specialists showed lower overweight prevalence (36.0%) than the other categories but still had substantial stress (76.0%) and physical inactivity (40.0%). These patterns demonstrate that the stable-angina cohort was clinically comparable across treatment groups but not occupationally uniform in the exposures that could sustain cardiovascular risk.

**Table 1**

*Occupational Risk-Factor Profile of Patients With Stable Angina*

| Occupation | N | Smoking | HTN | Dyslipidemia | Overweight | Night shifts | Stress | Inactivity |
|---|---|---|---|---|---|---|---|---|
| Medical professional | 33 | 9 (27.3%) | 19 (57.6%) | 22 (66.7%) | 19 (57.6%) | 27 (81.8%) | 28 (84.8%) | 7 (21.2%) |
| Programmer | 28 | 9 (32.1%) | 13 (46.4%) | 18 (64.3%) | 16 (57.1%) | 20 (71.4%) | 21 (75.0%) | 7 (25.0%) |
| Marketing specialist | 25 | 8 (32.0%) | 11 (44.0%) | 15 (60.0%) | 9 (36.0%) | 17 (68.0%) | 19 (76.0%) | 10 (40.0%) |
| Driver | 34 | 21 (61.8%) | 19 (55.9%) | 24 (70.6%) | 16 (47.1%) | 13 (38.2%) | 23 (67.6%) | 12 (35.3%) |

*Note.* Values are n (%). HTN = hypertension. Occupational categories total N = 120.

### Clinical and Functional Profile

Anginal attack frequency was similar across Groups II-V, ranging from 5.3 ± 1.4 to 6.0 ± 1.8 episodes per week (p = .348). Nitroglycerin requirement differed more noticeably, from 4.5 ± 1.1 to 5.5 ± 1.3 tablets per week (p = .018), indicating that medication use was not determined solely by attack frequency. Mean daytime heart rate was approximately 80-82 beats/min in the patient groups compared with 68.0 ± 5.9 beats/min in controls. Mean systolic blood pressure was approximately 149-152 mmHg in Groups II-V compared with 125.7 ± 8.0 mmHg in controls, and mean diastolic pressure was approximately 89-91 mmHg compared with 78.4 ± 4.2 mmHg in controls.

No clinically significant ST-segment depression was recorded in controls, whereas Groups II-V experienced 1.63-1.88 episodes per day with a mean depth of 1.37-1.57 mm. Extrasystoles were also more


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frequent in patients, ranging from 4.7 ± 2.2 to 6.4 ± 2.2 per hour versus 1.0 ± 1.1 per hour in controls; the between-group difference among the clinical groups was significant (p = .026 in the narrative report). Exercise tolerance was consistently reduced. Threshold power was 120.4 ± 12.7 W in controls but only 77.1-79.9 W in Groups II-V, while exercise duration decreased from 9.8 ± 1.1 minutes to approximately 6.3-6.4 minutes. The close similarity of Groups II-V on these functional measures supports baseline comparability before the planned therapeutic comparisons.

**Table 2**

*Principal Baseline Deviations Relative to the Control Group*

| Parameter | Control | Groups II-V | Direction | p vs. control |
|---|---|---|---|---|
| LDL-C, mmol/L | 2.40 ± 0.36 | 4.11-4.29 | Higher | < .001 |
| ApoB, g/L | 0.75 ± 0.09 | 1.21-1.24 | Higher | < .001 |
| CRP, mg/L | 0.91 ± 0.38 | 3.41-3.52 | Higher | < .001 |
| MDA, nmol/mL | 16.6 ± 2.0 | 30.1-32.5 | Higher | < .001 |
| SOD, arb. units/mg Hb | 66.8 ± 6.5 | 36.0-37.2 | Lower | < .001 |
| NOx, µmol/L | 70.0 ± 5.4 | 39.0-41.7 | Lower | < .001 |
| ST-depression episodes/day | Not recorded | 1.63-1.88 | Higher | < .001 |
| Bicycle threshold power, W | 120.4 ± 12.7 | 77.1-79.9 | Lower | < .001 |
| SBP by ABPM, mmHg | 125.7 ± 8.0 | 149.4-151.6 | Higher | < .001 |

*Note.* Ranges summarize mean values across Groups II-V. ApoB = apolipoprotein B; CRP = C-reactive protein; MDA = malondialdehyde; NOx = stable nitric oxide metabolites; SOD = superoxide dismutase; SBP = systolic blood pressure; ABPM = ambulatory blood pressure monitoring.

### Lipid and Inflammatory Profile

All stable-angina groups showed a pronounced atherogenic profile. Total cholesterol ranged from 6.21 ± 0.44 to 6.44 ± 0.42 mmol/L, compared with 4.38 ± 0.40 mmol/L in controls. LDL-C ranged from 4.11 ± 0.46 to 4.29 ± 0.45 mmol/L in the patient groups versus 2.40 ± 0.36 mmol/L in controls. HDL-C was reduced to approximately 0.91-0.93 mmol/L compared with 1.41 ± 0.16 mmol/L in controls. The atherogenic coefficient was 5.76-6.26 arbitrary units in Groups II-V, compared with 2.14 ± 0.38 in the control group.

ApoB values were tightly clustered at 1.21-1.24 g/L among the patient groups compared with 0.75 ± 0.09 g/L in controls. CRP showed an even larger relative departure, reaching 3.41-3.52 mg/L compared with 0.91 ± 0.38 mg/L. For LDL-C, HDL-C, atherogenic coefficient, apoB, and CRP, each clinical group differed significantly from controls at p < .001, while differences among Groups II-V were not significant. Thus, the therapeutic groups entered the study with a broadly comparable atherogenic-inflammatory burden.

### Oxidative, Antioxidant, and NO-Related Profile

MDA was almost twice the control level, increasing from 16.6 ± 2.0 nmol/mL in controls to 30.1-32.5 nmol/mL in Groups II-V. In contrast, antioxidant defense markers were lower in patients. SOD decreased from 66.8 ± 6.5 to 36.0-37.2 arbitrary units/mg Hb; catalase decreased from 234.6 ± 11.9 to 156.2-161.6 mkat/L; and ceruloplasmin decreased from 257.9 ± 16.7 to 157.6-163.1 mg/L. NOx also fell substantially, from 70.0 ± 5.4 µmol/L in controls to 39.0-41.7 µmol/L in Groups II-V. Each of these patient-control differences was reported as significant at p < .001, whereas differences among the stable-angina groups were generally not significant.

The coordinated increase in lipid peroxidation, decrease in antioxidant activity, and reduction in NOx indicates that the baseline metabolic disturbance was multidimensional. Importantly, the descriptive parallelism between oxidative markers and functional ischemia should not be interpreted as causal without longitudinal or mechanistic evidence.



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### Correlations Among Lipid, Oxidative, Endothelial, and Ischemic Measures

Correlation analysis in the 120 patients with stable angina identified several statistically significant associations. LDL-C correlated positively with MDA (r = .41, 95% CI [.25, .55], p < .001) and inversely with NOx (r = -.47, 95% CI [-.60, -.32], p < .001). MDA was inversely related to NOx (r = -.41, 95% CI [-.55, -.25], p < .001). LDL-C also correlated with ST-segment depression depth (r = .34, 95% CI [.17, .49], p < .001). The association between apoB and LDL-C was weaker (r = .22, p = .014), and CRP correlated weakly but significantly with MDA (r = .28, p = .002). These findings support statistical coordination among atherogenic burden, oxidative stress, endothelial-related NO metabolism, and functional ischemia while remaining insufficient to demonstrate causal direction.

**Table 3**

*Pearson Correlations in Patients With Stable Angina*

| Variable pair | N | r | 95% CI | p |
|---|---|---|---|---|
| LDL-C - MDA | 120 | .41 | [.25, .55] | < .001 |
| LDL-C - NOx | 120 | -.47 | [-.60, -.32] | < .001 |
| MDA - NOx | 120 | -.41 | [-.55, -.25] | < .001 |
| LDL-C - ST-depression depth | 120 | .34 | [.17, .49] | < .001 |
| ApoB - LDL-C | 120 | .22 | [.05, .39] | .014 |
| CRP - MDA | 120 | .28 | [.11, .44] | .002 |

*Note.* N = 120 for all correlations. Correlations describe association and do not establish causation.

## Discussion

The principal finding of this baseline analysis is that stable angina in the studied cohort was characterized by an integrated clinical and metabolic phenotype rather than by isolated episodic chest pain. The patient groups had a comparable frequency of anginal attacks, similar exercise impairment, and broadly similar degrees of ambulatory ischemia. At the same time, they showed substantially higher blood pressure and heart rate, a markedly atherogenic lipid profile, higher apoB and CRP, increased lipid peroxidation, reduced antioxidant activity, and lower NOx. This convergence is clinically relevant because chronic coronary disease is driven by cumulative atherosclerotic burden and modifiable risk factors, not only by the immediate frequency of symptoms (Vrints et al., 2024; Virani et al., 2023).

The lipid findings provide a strong rationale for evaluating HMG-CoA reductase inhibitor therapy in this population. LDL-C values of approximately 4.1-4.3 mmol/L and apoB values of approximately 1.2 g/L indicate a high burden of atherogenic cholesterol and particle number. Large-scale randomized evidence has established that the magnitude of cardiovascular risk reduction tracks the achieved reduction in LDL-C, including with more intensive statin therapy (CTT Collaboration, 2010, 2012). The broader causal evidence for LDL in atherosclerotic cardiovascular disease also supports interpreting these baseline concentrations as clinically important treatment targets rather than passive biomarkers (Ference et al., 2017). The relatively weak correlation between apoB and LDL-C in this cohort further illustrates that cholesterol mass and atherogenic particle number are related but not interchangeable constructs, consistent with contemporary expert guidance on apoB (Soffer et al., 2024).

The inflammatory and oxidative data extend this interpretation. CRP was approximately four times the control value, while MDA was nearly doubled and antioxidant markers were substantially reduced. CRP is widely used as an indicator of inflammatory activity in cardiovascular research, although it should not be treated as a direct causal mechanism solely on the basis of association (Fu et al., 2020; Ridker, 2004). Likewise, MDA is a commonly studied marker of lipid peroxidation, but oxidative biomarkers have methodological limitations and require cautious interpretation (Simantiris et al., 2023). In the present dataset, the positive LDL-C-MDA correlation and inverse LDL-C-NOx and MDA-NOx correlations are therefore best understood as evidence of a coordinated risk phenotype rather than proof that any single marker directly causes another.



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The functional findings are also consistent with prior investigations that examined statins in stable coronary disease using outcomes beyond serum cholesterol. Earlier trials and clinical studies evaluated exercise-induced ischemia, ambulatory ischemic burden, endothelial function, and inflammatory biomarkers during atorvastatin therapy (Bogaty et al., 2003; Deanfield et al., 2010; Stone et al., 2005). The present report does not reproduce those treatment findings because it contains baseline data only. Instead, it establishes that Groups II-V entered treatment with similar objective limitations: approximately 1.6-1.9 ST-depression episodes per day, threshold exercise power around 77-80 W, and exercise duration around 6.3-6.4 minutes. Such similarity reduces the likelihood that subsequent between-group differences would simply reflect large baseline imbalances in ischemic severity.

Occupational exposures deserve separate consideration. Medical professionals had the greatest night-shift and stress burden, programmers also showed frequent night work and high stress, and drivers had the highest smoking prevalence. Meta-analytic evidence indicates that shift work is associated with higher cardiovascular risk and that high job strain is associated with coronary heart disease (Torquati et al., 2018; Xu et al., 2015). These findings do not prove that occupational exposures caused the biochemical or functional abnormalities observed here, but they strengthen the rationale for incorporating work schedule, stress management, smoking cessation, and physical activity into comprehensive secondary prevention rather than relying on pharmacotherapy alone.

**Implications for Atorvastatin and Coenzyme Q10 Treatment Comparisons**

The source study was structured to compare conventional therapy, atorvastatin, coenzyme Q10, and atorvastatin plus coenzyme Q10 after this baseline assessment. The present analysis supports the clinical relevance of the atorvastatin-containing arms because LDL-C, apoB, inflammation, oxidative stress, and endothelial-related NO metabolism were all abnormal before therapy. However, baseline differences cannot establish whether atorvastatin improves angina frequency, ST-segment ischemia, exercise tolerance, MDA, NOx, or other outcomes in this specific cohort. Those questions require the post-treatment measurements and prespecified between-group analyses. Coenzyme Q10 has been investigated as an adjunct for statin-associated muscle symptoms, with meta-analytic evidence suggesting possible benefit in some trials (Qu et al., 2018), but the current baseline dataset provides no evidence regarding its efficacy for stable angina or oxidative-endothelial outcomes.

**Limitations**

Several limitations should be considered. First, this manuscript is restricted to the baseline phase of the study and therefore cannot estimate the therapeutic effect of HMG-CoA reductase inhibitors, coenzyme Q10, or their combination. Second, the source document does not provide recruitment dates, sex distribution, detailed inclusion and exclusion criteria, randomization procedures, medication washout information, or an ethics committee identifier; these items should be supplied before journal submission. Third, the occupational analysis is descriptive, and the study does not report multivariable adjustment for smoking, hypertension, shift work, stress, or physical inactivity. Fourth, correlations among LDL-C, MDA, NOx, CRP, and ischemic measures are cross-sectional and cannot establish temporal or causal relationships. Finally, several biomarkers, particularly MDA and antioxidant enzyme measures, are useful in research but are not routinely standardized clinical endpoints. These limitations do not negate the baseline differences, but they define the appropriate scope of interpretation.

**Conclusion**

Before therapy, stable angina was characterized by symptomatic and electrocardiographic ischemia, higher hemodynamic burden, reduced exercise tolerance, atherogenic dyslipidemia, elevated apoB and CRP, increased lipid peroxidation, weakened antioxidant defense, and reduced NOx. Groups II-V were broadly comparable at baseline, supporting later treatment comparisons, while occupational subgroups differed in smoking, night work, stress, and physical inactivity. Correlations among LDL-C, MDA, NOx, and ST-segment depression suggest an interconnected atherogenic-oxidative-endothelial


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phenotype without establishing causality. Post-treatment analysis is required to determine the efficacy of HMG-CoA reductase inhibition.

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# RATIONAL USE OF ANTIPYRETICS (PARACETAMOL AND IBUPROFEN) IN THE MANAGEMENT OF FEVER IN CHILDREN: AN EVIDENCE-BASED NARRATIVE REVIEW

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**ABSTRACT**

*Fever is among the most frequent reasons for pediatric consultation and a persistent source of caregiver anxiety. Paracetamol (acetaminophen) and ibuprofen are widely used antipyretic agents, yet rational use requires a distinction between lowering temperature and improving clinically meaningful outcomes. This narrative evidence review critically evaluates comparative efficacy, safety, combined or alternating therapy, and caregiver-related determinants of medication use. Current meta-analytic evidence indicates that ibuprofen may produce a slightly greater and longer reduction in temperature than paracetamol in some age groups; however, this pharmacodynamic advantage does not establish universal clinical superiority because evidence for improved comfort and functional outcomes is less consistent. Both agents are generally safe at recommended doses in otherwise healthy children, although ibuprofen warrants particular caution in dehydration, renal impairment, and selected infectious contexts, whereas paracetamol toxicity is strongly associated with supratherapeutic or duplicated dosing. Guidelines consistently recommend treating distress rather than the numerical temperature and do not support antipyretics for prevention of febrile seizures. Combined or alternating regimens can improve short-term defervescence but increase regimen complexity and the potential for dosing errors; therefore, routine dual-agent use is difficult to justify. The central argument of this review is that rational antipyretic therapy should be symptom-centered, individualized, and safety-oriented, with weight-based dosing and caregiver education treated as core therapeutic interventions rather than secondary advice.*

**ACCEPTED**

**08.09.26**

***Keywords:*** *fever, children, paracetamol, acetaminophen, ibuprofen, antipyretics, rational pharmacotherapy, fever phobia.*

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## Introduction

Fever is one of the most common clinical presentations in childhood and accounts for a substantial proportion of pediatric office and emergency contacts. Contemporary guidance emphasizes that fever is a regulated host response rather than a disease in itself, and its height alone is usually a poor proxy for illness severity outside specific high-risk age groups (National Institute for Health and Care Excellence [NICE], 2021; Niehues et al., 2026). Nevertheless, caregivers frequently interpret fever as intrinsically dangerous and may attempt to normalize temperature rapidly, a pattern historically described as “fever phobia.” Systematic reviews show that misconceptions, anxiety, and inconsistent fever-management practices

remain common across settings and have changed less than expected despite decades of educational activity (Bertille et al., 2018; Purssell & Collin, 2016; Thompson et al., 2020).

Paracetamol and ibuprofen are the two principal antipyretics used in children. The clinically important question, however, is not simply which drug lowers temperature more effectively. A rational pharmacotherapeutic decision must integrate patient comfort, hydration, age, comorbidity, risk of toxicity, regimen simplicity, and caregiver capacity to administer medicines accurately. This review therefore advances the argument that the appropriate endpoint of antipyretic treatment is relief of distress and preservation of safety, not normalization of the thermometer reading. On this basis, a small statistical advantage in temperature reduction should not be interpreted automatically as evidence of superior pediatric care (Sullivan & Farrar, 2011; Tan et al., 2020).

**Methods**

A focused narrative evidence review was undertaken using PubMed-indexed literature and official guideline repositories. Priority was given to contemporary clinical guidelines, systematic reviews and meta-analyses, randomized controlled trials, pediatric safety studies, and systematic evidence on caregiver knowledge and behavior. Search concepts included childhood fever, paracetamol or acetaminophen, ibuprofen, antipyretics, alternating therapy, combined therapy, febrile seizures, fever phobia, dosing error, and caregiver education. The evidence base was synthesized thematically rather than statistically. Because this was not a preregistered systematic review and did not use duplicate screening or a formal risk-of-bias framework, its conclusions should be interpreted as a critical narrative synthesis rather than as a new systematic review.

**Fever as a Therapeutic Target: Distress Rather Than Temperature**

The most consistent principle across major guidance is that antipyretic treatment should be considered when a child is distressed, not simply because a measured temperature exceeds a particular threshold. NICE (2021) advises against using antipyretic agents solely to reduce body temperature, while the American Academy of Pediatrics similarly frames the therapeutic objective as improvement of comfort and well-being rather than restoration of normothermia (Sullivan & Farrar, 2011). The 2026 evidence-based outpatient guideline by Niehues et al. (2026) further reinforces this symptom-oriented approach and explicitly discourages routine antipyretic administration in children whose degree of suffering does not warrant drug treatment.

This distinction is academically important because temperature is a surrogate endpoint. A treatment can produce faster defervescence without necessarily improving hydration, activity, sleep, pain, caregiver reassurance, or the underlying illness. Accordingly, comparative trials should be interpreted according to the hierarchy of outcomes: patient-centered benefit and safety carry greater clinical weight than small differences in degrees Celsius. The same reasoning explains why antipyretics should not be used to prevent febrile seizures; multiple guidelines conclude that temperature-lowering treatment does not reliably prevent recurrence of febrile convulsions (Chiappini et al., 2017; NICE, 2021; Sullivan & Farrar, 2011).

**Comparative Efficacy of Paracetamol and Ibuprofen**

Both paracetamol and ibuprofen reduce fever effectively. Earlier randomized-trial meta-analysis found that ibuprofen produced greater temperature reduction than acetaminophen at several early time points, with broadly comparable safety in the included trials (Perrott et al., 2004). More recent evidence is directionally similar. In a systematic review and meta-analysis of 19 studies including 241,138 children younger than 2 years, ibuprofen was associated with lower temperature at less than 4 hours and between 4 and 24 hours, and with less pain at 4-24 hours, while adverse events were uncommon (Tan et al., 2020).

These findings support the conclusion that ibuprofen may have a modest antipyretic advantage under some conditions, but they do not establish a universal first-line hierarchy. The size of the temperature difference is generally small, and the evidence base is stronger for temperature outcomes than for child comfort. Therefore, the clinically defensible interpretation is that either medicine can be appropriate in an


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otherwise healthy child, with drug selection individualized to the clinical context rather than driven by a presumption that the agent producing the lowest temperature is necessarily superior (Sullivan & Farrar, 2011; Tan et al., 2020).

**Safety and Patient-Specific Risk**

At recommended pediatric doses, paracetamol and ibuprofen have broadly comparable short-term safety profiles in generally healthy children. A systematic review of pediatric pain and fever studies found no compelling evidence of a major overall safety difference, although the type of potential harm differs between the two drugs (Southey et al., 2009). Paracetamol has a narrow margin for error when repeated supratherapeutic dosing or unintentional duplication occurs, particularly when caregivers use multiple products containing acetaminophen. Its rational use therefore depends on accurate dose calculation, dosing intervals, and avoidance of ingredient duplication (Sullivan & Farrar, 2011).

Ibuprofen is an NSAID and requires more explicit attention to renal perfusion and hydration. NSAID exposure has been identified as an important cause of acute kidney injury in children, especially in settings in which intravascular volume is reduced (Misurac et al., 2013). Evidence in young infants suggests that short-term ibuprofen can be safe under selected conditions, but age, body weight, and hydration status remain important determinants of appropriate use (Ziesenitz et al., 2017). Guideline panels also advise caution or avoidance in dehydration and in certain infections such as varicella because potential harms may outweigh a modest antipyretic benefit (Chiappini et al., 2017).

Consequently, it is overly simplistic to characterize either agent as universally “safer.” Paracetamol may be preferable when renal perfusion or gastrointestinal risk is a concern, whereas ibuprofen may be reasonable when a longer antipyretic effect is desirable in a well-hydrated child without contraindications. The rational choice is therefore conditional rather than absolute.

**Combined and Alternating Therapy: Efficacy Versus Implementation Risk**

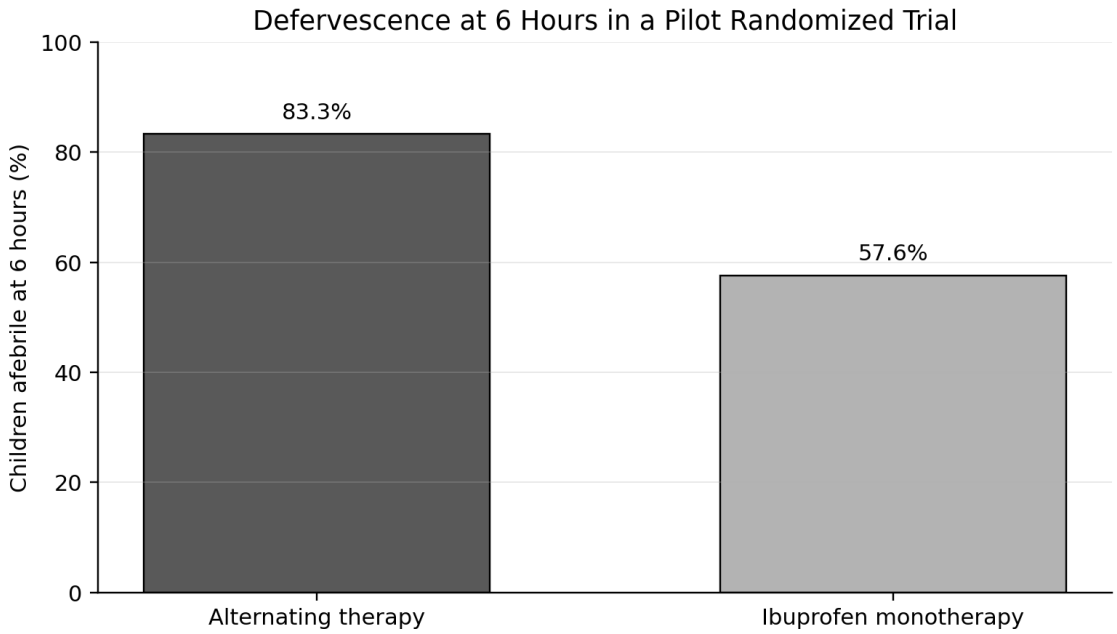
Combined or alternating regimens illustrate the difference between pharmacologic efficacy and rational clinical practice. In the PITCH randomized controlled trial, using paracetamol and ibuprofen together increased time without fever compared with either drug alone in young children managed in the community, although the relationship between additional temperature reduction and sustained improvement in discomfort was less straightforward (Hay et al., 2008). A Cochrane review similarly concluded that combined or alternating therapy can reduce temperature more effectively than monotherapy, but evidence for improved child discomfort was inconclusive and safety evidence was insufficient for confident routine recommendations (Wong et al., 2013).

A pilot randomized study by Nabulsi et al. (2006) provides a useful example of this tension. At 6 hours, 83.3% of children who received alternating ibuprofen and paracetamol were afebrile compared with 57.6% receiving ibuprofen monotherapy. Figure 1 visualizes this statistically significant difference. However, the study enrolled only 70 children, the outcome was defervescence rather than a validated patient-centered measure, and a more complicated schedule may create additional opportunities for dose duplication or interval errors. Therefore, the result supports biological efficacy but does not, by itself, justify routine alternating therapy.


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**Figure 1**

*Defervescence at 6 Hours in a Pilot Randomized Trial of Alternating Therapy Versus Ibuprofen Monotherapy*




*Note*. Data are from Nabulsi et al. (2006), n = 70. The figure illustrates a surrogate antipyretic outcome and should not be interpreted as evidence that alternating therapy provides superior patient-centered benefit or should be used routinely.

This interpretation is consistent with guideline logic. NICE (2021) advises against simultaneous administration and recommends considering alternation only when distress persists or recurs before the next dose is due. The central safety argument is that a modest incremental reduction in temperature may not compensate for the cognitive burden of maintaining two dosing schedules, particularly in anxious caregivers or households using multiple formulations. Regimen simplicity is therefore a clinically relevant component of medication safety.

**Caregiver Behavior, Fever Phobia, and Medication Safety**

Fever management occurs largely outside clinical settings, so caregiver behavior is part of the pharmacology of real-world treatment. Systematic evidence demonstrates persistent uncertainty about fever thresholds, variable use of temperature measurement, and frequent reliance on antipyretics even when fever-associated distress is limited (Bertille et al., 2018). A systematic review of 36 studies involving 15,727 participants found that caregivers commonly seek information about pediatric fever while simultaneously reporting misconceptions, anxiety, and heterogeneous management practices (Thompson et al., 2020). Fever phobia has also remained remarkably persistent across time and geography (Purssell & Collin, 2016).

These findings strengthen the argument that caregiver education is not an optional adjunct to prescribing; it is a risk-reduction intervention. A prescription or over-the-counter recommendation that does not communicate the treatment goal, weight-based dose, dosing interval, product concentration, and conditions requiring medical review is incomplete from a rational-pharmacotherapy perspective. Education should explicitly explain that the child's behavior, hydration, breathing, level of responsiveness, and other warning signs are more clinically informative than achieving a "normal" temperature. It should also discourage waking a comfortable sleeping child solely to administer an antipyretic and should emphasize safe storage and avoidance of duplicate acetaminophen-containing products (Sullivan & Farrar, 2011).

**Practical Framework for Rational Pharmacotherapy**

A rational approach can be organized around four decisions. First, determine whether medication is indicated: the presence of distress or pain, rather than fever alone, should drive treatment. Second, select


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a single agent according to the child's age, body weight, hydration, renal status, gastrointestinal considerations, prior tolerance, and local labeling. Third, calculate the dose by weight and use an appropriate measuring device. Common guidance supports paracetamol doses of approximately 10-15 mg/kg per dose and ibuprofen doses of approximately 5-10 mg/kg per dose, but maximum daily doses, minimum ages, and dosing intervals vary by jurisdiction and product; local pediatric guidance and product labeling should therefore be followed (Niehues et al., 2026; Sullivan & Farrar, 2011; Ziesenitz et al., 2017). Fourth, reassess the child rather than the thermometer: failure to reach normothermia is not, by itself, treatment failure if distress improves.

Routine simultaneous dual therapy should be avoided. Alternation should be exceptional rather than automatic and should be considered only when clinically meaningful distress recurs before the next dose of the initial agent is due and the caregiver can follow a clear written schedule (NICE, 2021). Nonpharmacologic management should emphasize fluids and avoidance of over-wrapping; routine tepid sponging is not recommended in major guidelines because it can increase discomfort without addressing the therapeutic goal (NICE, 2021).

**Academic Synthesis and Argument**

The evidence supports a hierarchy of reasoning for pediatric fever management. At the lowest level, temperature reduction is easy to measure and often favors ibuprofen or dual-agent regimens. At a higher clinical level, however, comfort, safety, caregiver comprehension, and recognition of serious illness are more consequential. This creates an important evidence-to-practice gap: interventions can appear "more effective" when efficacy is defined by temperature while being less attractive when effectiveness is defined by patient-centered benefit under real-world conditions. The rational response is not to dismiss comparative antipyretic efficacy, but to place it in its proper clinical context.

Accordingly, this review rejects two oversimplified positions: that paracetamol should always be the first-line drug, and that ibuprofen should be preferred simply because it may lower temperature more strongly. Instead, current evidence supports conditional equivalence: both agents are legitimate options when distress warrants treatment, and the preferred drug is the one that provides adequate symptom relief with the lowest foreseeable risk in the individual child. Similarly, evidence that alternating therapy lowers temperature more effectively does not justify its routine use because the added complexity can undermine medication safety. This interpretation aligns comparative trials with guideline recommendations rather than treating them as competing bodies of evidence (Hay et al., 2008; NICE, 2021; Tan et al., 2020; Wong et al., 2013).

**Limitations of the Evidence**

Several limitations should temper interpretation. First, many trials prioritize temperature endpoints over validated measures of comfort, activity, hydration, or caregiver-relevant outcomes. Second, the strongest comparative evidence is heterogeneous with respect to age, dose, indication, and follow-up duration. Third, rare adverse events are difficult to quantify in randomized trials and often depend on observational data. Fourth, recommendations on minimum age and maximum dosing vary across jurisdictions and formulations. Finally, this paper is a narrative synthesis rather than a systematic review, so it does not provide a new pooled estimate or formal certainty-of-evidence rating. These limitations reinforce the need for cautious translation of statistical efficacy into clinical recommendations.

**Conclusion**

The rational management of fever in children is best understood as a symptom-centered and safety-oriented process rather than a pharmacologic attempt to normalize body temperature. Paracetamol and ibuprofen are both effective antipyretics, and ibuprofen may provide somewhat greater or longer temperature reduction in some populations. Yet this difference is not sufficient to establish universal clinical superiority. Drug selection should be individualized, with particular attention to hydration, renal risk, age, comorbidity, previous tolerance, and the possibility of dosing error. Antipyretics should not be


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used to prevent febrile seizures, and routine simultaneous or alternating dual-agent treatment is not supported by the balance of evidence and implementation risk. The strongest academic and practical conclusion is therefore that correct indication, weight-based dosing, regimen simplicity, and caregiver education are not ancillary aspects of fever management; they are the core components of rational pediatric pharmacotherapy.

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# AGE-RELATED FEATURES OF THE MORPHOLOGICAL AND MORPHOMETRIC STRUCTURE OF THE BRONCHI IN THE SECOND CHILDHOOD

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**ABSTRACT**

*Today, respiratory diseases are considered one of the groups of diseases that have a serious impact on children's health worldwide. According to WHO, respiratory diseases are one of the leading causes of morbidity, medical care, hospitalizations, and preventable deaths among children. Asthma and bronchiolitis are among the most common causes of childhood respiratory distress and wheezing. In particular, lower respiratory tract infections, particularly pneumonia, are of particular epidemiological importance among children. The WHO also found that pneumonia is responsible for more than 700,000 deaths each year among children aged 5-8 years worldwide. Globally, there were more than 1400 pneumonia cases per 100,000 children. When looking at the incidence rate across regions, it was noted that in South Asia, there were approximately 2,500 cases per 100,000 children, while in West and Central Africa, there were 1,620 cases. It was found that the relevance of respiratory diseases remains high, especially in school-age children. Also, according to global assessments in 2024, lower respiratory infections, including pneumonia, among children aged 5-9, were one of the leading causes of death, with several leading diseases accounting for more than 40% of the main causes of death in this age group. The bronchi, as the air-conducting part of the respiratory system, are an important anatomical and morphofunctional structure in the development of respiratory diseases. The structural condition of the mucous membrane of the bronchial wall, the mucous membrane, the smooth muscle floor, the passage of airflow and the connective tissue components, the expansion and narrowing of the bronchi, the transport of mucous secretions and plays an important role in the mechanisms of local protection.*

**ACCEPTED**

**08.09.26**

***Keywords:*** *Bronchial tree, morphological changes, control group, children.*

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## Introduction

Studies have shown that a number of scientific studies are being conducted to optimize the indicators of postnatal ontogenetic development of the bronchial tubes of the lungs in humans in the second childhood period. Of particular importance in this regard are scientific studies aimed at assessing morphometric indicators of Wall morphology of trachea and lung bronchi in school-aged children, morphometric indicators of Wall morphology of trachea and lung bronchi in second childhood i.e. 8-12

years of age, morphometric indicators of Wall morphology of trachea and lung bronchi in children from birth to.

**Purpose of the Research**

study of postnatal ontogenetic development of the bronchi in children of different ages in the second childhood.

**Materials and Methods**

The study was conducted on 61 children's corpses who died in the second year of life, which arrived at the Republican Center for Pathological Anatomy of the Ministry of Health of the Republic of Uzbekistan in the second quarter of 2025-2026. The resulting children's corpses were studied in children's corpses who died as a result of mainly heart birth defects and other causes that did not have diseases in the pulmonary bronx pathways. The causes of death and underlying disease have been identified in forensic medicine and pathological anatomy conclusions. The examination material was obtained from the following parts of the lung: the right and left lungs were dissected and examined from the external and internal bronchi to the terminal bronchi of the lobar bronchi. In our study, instrumental (using a caliper), histological and histochemical, and morphometric methods were used. In our study, instrumental (using a caliper), general histological and histochemical, and morphometric methods were used. The obtained materials were fixed in formalin and then 5-8 μm sections were prepared. They were stained with hematoxylin-eosin and Schiff's reaction. The data in the pathoanatomical examination report, outpatient card, medical history, and autopsy reports were comprehensively studied for each case. Passport information (residence address, name, age of the patient, and other necessary information) was obtained from the medical history. The outpatient card collected information about what diseases the patient had and how they were treated before they arrived at the hospital. Also, in our study, we considered the following cases to be excluded from the material study, taking into account those with acute pathological changes in the bronchi, the detection of pneumonia, the observation of active inflammatory processes, as well as the fact that other pathological conditions are qaacdbhyuhb bhgv vgy6ytgvbhyd. The analysis of the data obtained is presented in Table 1 by age group. A total of 61 child corpses were obtained in our study. Of this, group 1 (8 years old) had 21 children (34.4%) of whom were two childhood children, divided into the following subgroups: Group A) counted 9 boy corpses and made up 14.7%, Group B) were 12 girl child corpses, accounting for 19.7%. And the 2 groups of our study (9-10 years old) were 18 ( 29.5%) second-childhood children, also divided into the following subgroups: (a) group was 11 boys 'corpses, accounting for 11%, and (B) group was 7 girls' corpses, accounting for 11.5%. And the 3 groups of our study (11-12 years old) were 22 (36 %) children of second childhood who also separated into the following subgroups: (a) group 10 were considered boys ' corpses and made up 16.4%, (B) group 12 were girl child corpses and made up 19.7%.

**Results**

As a result of our research, we studied in depth the morphological and morphometric changes of the bronchioles of the lung in the second childhood periods, segmental bronchi, intercostal bronchi, colon bronchi, intraosseous bronchioles. It is also observed that during the second childhood period, the processes of growth and development in the child's body accelerate. When studying the bronchi, a macroscopic examination was performed to study the general shape and diameter of the bronchi, including the thickness of their walls. Indicators were also determined during these periods.

- total length of the bronchus;
- external diameter;
- internal diameter;
- wall thickness;
- branching characteristics of the bronchi.

We also used the organometallic method in our research. In this, we mainly focused on the following. Organometry of the bronchi is a complex of methods for measuring anatomical and

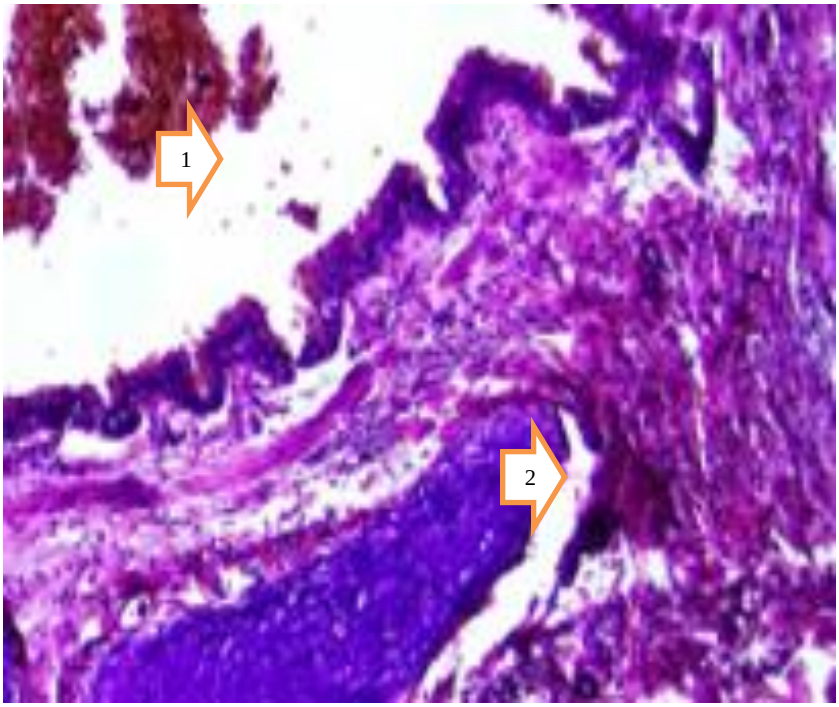

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morphometric indicators of the bronchi and includes the following parameters organometric examination of the bronchi carried out by determining their length, external and internal diameter, wall thickness, mass and size. The measurements were taken under standardized conditions, and the results were compared by age group, which included children from 8 to 12 years old, who are considered to be in the second childhood period.

In addition, organometric examination of the bronchi allows for quantitative determination of the macroscopic dimensions and geometric parameters of the bronchi in the second childhood, in particular, to assess their dependence on age, gender, and anthropometric indicators. It was also found that the organometallic method allows for an assessment of the general morphological state of the bronchi at the macroscopic level. Therefore, the use of this method in combination with histological and morphometric studies helps to comprehensively characterize the age-related morphological development of the bronchi. In particular, geometric parameters of the bronchi, such as length, internal and external diameter, are still used as key parameters in modern morphometric studies. In our study, we tried to obtain samples of bronchi that were as free of pathological changes as possible and were anatomically well preserved. We also used the following equipment to conduct the study: vernier caliper, millimeter ruler, micrometer, anatomical measuring instruments, and electronic scales. In our study, we prepared the bronchi for organometric examination as follows. First, we determined the anatomical orientation of the bronchial sample before examination and determined the following.

**Figure 1**

*Bronchus of the Lung Lobe, 8 Years Old*




*Note.* 1-The folds of the mucous membrane are reduced, 2-The smooth muscle bundles are thickened. Stain: H-E. Category: 10x10.

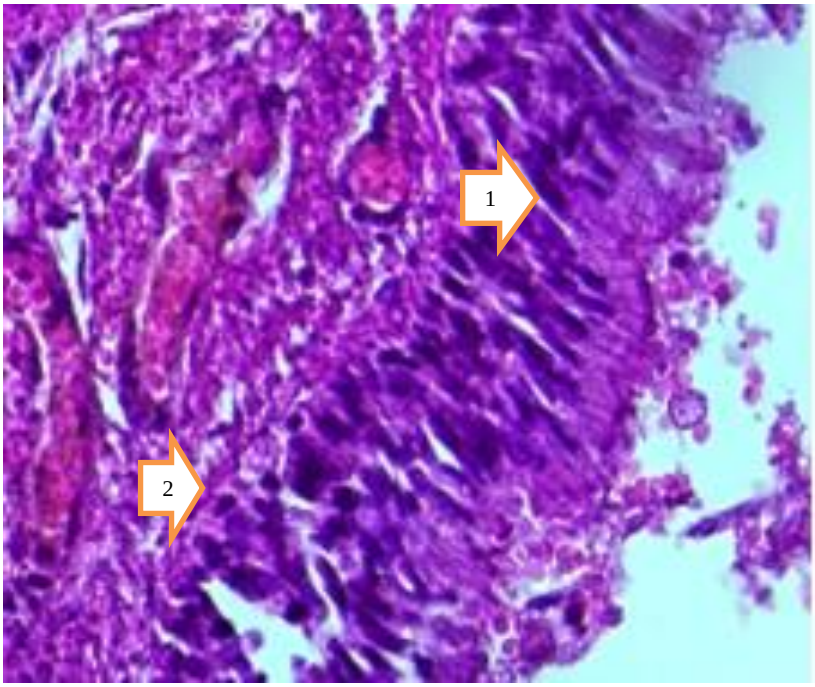
In our study, the hematoxylin-eosin method was used to study the histological structure of the bronchi in the second childhood period (8-12 years). This staining method allowed us to distinguish the main structural components of the bronchial wall and assess their morphological state. In particular, when stained with hematoxylin-eosin, it was found that the inner surface of the bronchial wall was covered with a multilayered ciliated epithelium. The basal membrane and lamina propria were also identified under the epithelium, and beyond that, the submucosa, smooth muscle elements, cartilage plates, and connective tissue components. At the same time, it was found that under the influence of hematoxylin-eosin, cell nuclei appear blue-violet, while the cytoplasm, muscle, and connective tissue elements appear pink-red in varying degrees. This also allowed for the microscopic delineation of the layers of the bronchial wall. In


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group I of our study, which included children aged 8 years, the bronchial mucosa was relatively thin, with an orderly arrangement of epithelial cells and preservation of the ciliated epithelial layer. In particular, the presence of small folds in the mucous membrane was detected. In addition, connective tissue elements are observed in the lamina propria. Bronchial glands were also observed in the submucosal layer. It was also found that the secretory parts and excretory ducts were well differentiated. In particular, it was found that the smooth muscle layer was relatively thin, and the muscle fibers were arranged in an orderly manner along the bronchial wall. There are also cartilage plates that serve as a mechanical support component for the bronchial wall. At the same time, it was found that, although the main structural components of the bronchial wall are formed in this age group, their morphometric parameters are smaller than in older age groups.

**Figure 2**

*Bronchiole Inside the Lung, Age 10 Years*




*Note.* 1-The covering epithelium is cylindrical, the lamina propria is rich in fibers, and the blood vessels are dilated. Paint: H-E. Category: 10x40.

In group III of our study, which included children aged 11–12 years, it was found that the structural components of the bronchial wall were more developed. It was also found that the bronchial epithelium was well formed and the arrangement of the cells along the layers was relatively orderly. However, the thickness of the mucous membrane and the degree of development of the lamina propria were found to be higher than in previous age groups. In particular, the development of glands in the submucosal layer and their location in the bronchial wall were clearly visible. In addition, an increase in the thickness of the smooth muscle layer and a denser arrangement of muscle fibers were found. It was also identified as a morphological marker associated with the structural strength of the bronchial wall and its functional improvement. In addition, it was observed that the cartilage plates were also well developed, and their area and thickness were found to change with age. It was also found that in the preparations of bronchi of this age group, the main structural components of the wall are highly formed. In particular, it was observed that the epithelial floor was relatively well developed and the morphological features of the arrangement and nuclei of ciliated cells were clearly visible.

**Discussion**

At the same time, the development of bronchial glands in the mucous membrane was also noted. It was also found that the smooth muscle floor is thicker compared to previous age groups. In addition, the cartilaginous plates were well-defined and were identified as an important structural component that


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provides the mechanical support function of the bronchial wall. Also, in the 11-12 age group, the morphological structure of the bronchial wall helps to approach a relatively mature state before the transition to the next growth period. During this period of the study, microscopic examination of the structures of the terminal bronchiolar wall showed that the covering epithelium had thinned, and the dimensions had decreased and become prismatic compared to previous periods. It was observed that the nuclei of these cells were relatively darkly stained and were located in a disordered manner. Also, microscopic examination of the bronchioles of the lung lobes of children of this age showed that they were located between the segments of the lung tissue. On the other hand, the lower ring was found to be made up of large and small fragments, mostly isolated, in contrast to the bronchi. By this stage of the examination, it was determined that the bronchi retained their tubular shape and were slightly elongated in length. It was also noted that the wall was thin, the cartilage rings were relatively well-developed, and the wall was thin and soft. In particular, it was observed that the cartilage rings consisted of several pieces. In contrast, by the age of 12, the togai ring was found to have a slightly flattened shape, compacted, relatively immature in composition, meaning that its cells were tiny and numerous and densely packed, with only some of its cytoplasm appearing vacuolated. In particular, it was observed that the intermediate chondroid substance of the cartilage was dense and darkly stained, and that the number of connective tissue bundles connecting the cartilage rings from the inner and outer surfaces was relatively increased. In addition, it was found to be surrounded by a thin, serous membrane on the outside. It was also noted that the mucous membrane folds were absent, smoothed, the surface was covered with a single-layered multi-row cylindrical epithelium, and in some areas the epithelium was reduced in height and depressions appeared.

**Conclusion**

1. The biliary bronchiole wall layers were formed from an incomplete state at a young age of children and were found to have a tactile finding State, a covering epithelium with folds, biliary cells smoothed from a low state, biliary cells into a multi-state, a private plate formed with fibers from a swollen, unformed connective tissue and muscle handles arranged in order.
2. At a young age, it was proven that the wall of the terminal bronchioles is semicircular, with a one-story cylindrical epithelium on one side, the other side is in a state adjacent to the alveoli, improved at the age of two, the covering epithelium turns into a prismatic type, a one-to-one junction consisting of connective tissue and muscle fibers, the private plate of which.

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