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MODERN PERSPECTIVES ON CHRONIC SINUSITIS ASSOCIATED WITH CHLAMYDIAL INFECTION

(Monograph)

Tashkent – 2025

UDK 616.216.1:579.822.11-07-08

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Modern perspectives on the clinical features and treatment of chronic sinusitis associated with chlamydial infection

Tashkent – 2025

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Annotation

The monograph presents data from both domestic and international researchers concerning the theoretical basis and the clinical–laboratory characteristics of sinusitis associated with Chlamydia infection. It also includes the authors' own research findings and specific methodological approaches developed during the study.

This monograph is intended for practical use by otorhinolaryngologists, general practitioners, as well as clinical residents and medical students of higher educational institutions.

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Abbreviation

AG	Antigens
AT	Antibodies
BTSH	*Chlamydial Heat Shock Protein* (HSP)
IL	Interleukins
ELISA	Enzyme-Linked Immunosorbent Assay
γ-IF	Gamma Interferon
KM	Method of *Chlamydia* Isolation in Cell Culture
CT	Computed Tomography
LPS	Bacterial Lipopolysaccharide
LCR	Ligase Chain Reaction
MOMP	Major Outer Membrane Protein of *Chlamydia*
MRI	Magnetic Resonance Imaging
NIF	Indirect Immunofluorescence Method
NRIF	Indirect Microimmunofluorescence Reaction
PNS	Paranasal Sinuses
DIF	Direct Immunofluorescence Method
LPO	Lipid Peroxidation
PCA	Polyclonal Antibodies
PCR	Polymerase Chain Reaction
IFR	Immunofluorescence Reaction
RBTL	Reaction of Blast Transformation of Lymphocytes
CFT	Complement Fixation Test
IIFR	Indirect Immunofluorescence Reaction
RB	*Chlamydial Reticulate Bodies*
TA	Transcriptional Amplification
EB	*Chlamydial Elementary Bodies*

INTRODUCTION

Relevance of the study Diseases of the nose and paranasal sinuses (PNS) continue to hold a leading position among upper respiratory tract pathologies [41]. The high level of air pollution and gas contamination, bacterial colonization of the environment, and the growing incidence of bacterial and viral respiratory infections affecting the nasal and sinus mucosa contribute to this trend. Studies show that the incidence of chronic sinusitis has doubled over the past eight years, while the proportion of hospitalized patients with nasal and sinus diseases increases annually by 1.5–2% [78].

The close anatomical proximity of the paranasal sinuses to vital structures of the brain and visual pathways (such as the sphenoid sinus and ethmoidal labyrinth), combined with the often subtle or latent course of chronic sinusitis that leads to overstrain and depletion of immune defense mechanisms, can result in severe intracranial complications and visual disorders—including purulent meningitis, meningoencephalitis, ventriculitis, sepsis, basal arachnoiditis with diencephalic syndrome, and cavernous sinus thrombosis, among others [40].

Among the numerous infectious diseases affecting humans, chlamydial infections occupy a significant place and represent a serious public health issue. According to WHO data (2006), 89 million new cases of chlamydiosis were registered worldwide; approximately 10 million cases occur annually in the European region, and about 4 million in the United States. The annual global economic burden of chlamydial infections amounts to billions of dollars. For instance, in the U.S. alone, economic losses attributed to chlamydiosis are estimated at 1 billion USD, while untreated infections result in losses of up to 4 billion USD annually [83].

Despite certain advances in the diagnosis and treatment of inflammatory diseases of the nose and paranasal sinuses, the issue of transition from acute to chronic inflammation remains unresolved. The causes of chronic inflammation in

the paranasal sinuses are multifactorial and include infectious agents, allergic reactions, morphological alterations of the mucosa, functional disturbances, and local anatomical anomalies. Data on the etiopathogenic role of *Chlamydia* in ENT (ear, nose, and throat) pathologies are inconsistent and sometimes contradictory. Many researchers regard *Chlamydia* as an etiological factor in both acute and chronic diseases of the ear, throat, and nose, based on the detection of these pathogens in clinical samples obtained from lymphoid tissues of the pharyngeal ring, nasal and pharyngeal mucosa, paranasal sinuses, and tympanic cavity [47, 94, 117, 138, 140, 143, 169, 170, 172, 194].

Pharmacological treatment of acute and chronic inflammatory diseases of the paranasal sinuses—despite the advances in the pharmaceutical industry [8, 64, 21] and the availability of modern antibacterial agents [30, 11, 73, 124]—still remains a challenging task. The main difficulties include the growing antibiotic resistance of microorganisms [82, 93, 7, 103, 104] involved in the inflammatory process, including *Chlamydia* species, irrational antibiotic therapy, and the complex interplay of viral-bacterial associations and fungal microflora that influence the development of both acute and chronic sinusitis [10, 40]. The chlamydiae, Gram-negative, obligate intracellular bacteria, cause a broad range of diseases, affecting a wide range of economically important non-human animals and humans. All chlamydiae share a biphasic developmental cycle. The primary developmental forms of chlamydiae are elementary bodies (EB) and reticulate bodies (RB). EB, the extracellular form of the bacteria, are small (0.2 μm) and infectious, targeting host mucosal epithelial cells. After attachment and entry into the host cell, EB develop within a membrane-bound endocytic vacuole called an inclusion. Inside the inclusion, EB differentiate into larger (0.8 μm), metabolically active but noninfectious RB, which undergo multiple rounds of division. RB re-differentiate into infectious EB, and mature EB complete the developmental cycle, exiting the host cell via lysis or extrusion of the inclusion [101]. Stressors of

developing chlamydiae, including the host immune response, nutrient deprivation, antibiotic exposure or co-infection with viruses or parasites, can result in a form called aberrant bodies (AB). AB develop when RB replicative division and maturation of RB to EB is interrupted, resulting in abnormally large chlamydiae. This divergence from the typical developmental cycle constitutes a viable but noninfectious form of chlamydiae, and is termed persistence or the chlamydial stress response, a reversible condition that can eventually allow continued production of infectious EB . In humans, chlamydiae usually cause eye, urogenital or respiratory infections. *Chlamydia trachomatis* is the most common bacterial sexually transmitted disease (STD) and the leading cause of infectious blindness worldwide. *Chlamydia pneumoniae*, an agent of respiratory infection, is nearly ubiquitous in humans, with seropositivity rates of 70–80 % in older populations, suggesting most people experience infection during their lifetime [6]. *Chlamydia psittaci,* a common pathogen of birds, has the best known zoonotic potential of the human pathogenic chlamydiae and causes relatively rare respiratory infections associated with severe clinical manifestations, while several other animal pathogenic chlamydial species, including *Chlamydia abortus*, *Chlamydia felis*, and *Chlamydia suis*, are known, or suspected, to cause infrequent human infections with various clinical presentations [9]. Chronic chlamydial infections in animals, particularly ruminants and pigs, are sub-clinical and ubiquitous in nature [19]. Although their pathogenic significance is debateable, recent data suggest clinical impact when these infections coincide with various epidemiological risk factors. Chronic chlamydial human disease has well-recognized medical significance, encompassing the most detrimental outcomes of chlamydial disease, and is the topic of this review.

By definition, chronic diseases are long-lasting conditions that can be controlled, but not cured. The term chronic, however, is usually applied when the disease lasts more than three months, regardless of the eventual outcome [89].

Chronic disease is the leading cause of death and disability in the United States . In Europe, chronic conditions account for 86 % of all deaths and 77 % of the disease burden [18]. Chronic diseases also significantly increase health care costs related to long-term medical care. Exposure to infectious agents has been implicated as a risk factor for development of chronic diseases, and strong association has been recently shown for five pathogens: human immunodeficiency virus (HIV), hepatitis C virus, *Helicobacter pylori*, and *Chlamydia (C.) pneumoniae* . Association of chlamydiae other than *C. pneumoniae* with chronic disease is also well supported.

In this article, we review the role of chlamydiae in chronic disease conditions including atherosclerosis, trachoma, urogenital infections and arthritis. Chlamydiae have been implicated in neurological chronic diseases, such as multiple sclerosis and Alzheimer's disease, and in neurobehavioral diseases such as autism and schizophrenia, but because supporting evidence is contradictory, these diseases will not be discussed here. Additionally, chlamydial infection has been associated with cervical, ovarian, and prostate cancers, but again, evidence supporting the association is inconsistent and this topic will not be discussed at length. Because of length limitations, we focus on the intensively investigated chlamydial species *C. trachomatis* and *C. pneumoniae* in humans. We will: 1) address the clinical significance and public health impact of chronic chlamydial diseases; 2) summarize pathogenesis emphasizing host-pathogen interactions, including host immune response and bacterial factors associated with disease; 3) discuss diagnostic methods and therapeutics in the light of chronicity; and 4) indicate future research directions.

Therefore, investigating the clinical characteristics of these diseases, implementing diagnostic methods for *Chlamydia* detection in otorhinolaryngological practice, and developing rational therapeutic protocols for chlamydial-induced inflammatory diseases of the paranasal sinuses are of great scientific and practical significance.

According to published data, inflammation of the maxillary sinus ranks first among paranasal sinus diseases by frequency of occurrence [111].

CHAPTER I. MODERN CHARACTERISTICS AND ASPECTS OF CHLAMYDIA INVOLVEMENT IN THE PATHOGENESIS OF CHRONIC SINUSITIS

1.1. Etiology, pathogenesis, clinical manifestations, and diagnosis of inflammatory diseases of the paranasal sinuses.

Inflammatory diseases of the nose and paranasal sinuses (sinusitis) remain the most common pathology of the upper respiratory tract. According to literature data, patients with sinusitis constitute approximately 30% of all individuals hospitalized in ENT departments [41,48,78]. It has been established that about 14% of the world's population suffer from sinusitis, and the annual cost of treatment exceeds 3.5 billion USD [153]. Environmental pollution, increased bacterial contamination of the air, rising numbers of bacterial and viral respiratory infections, and growing exposure to airborne allergens contribute significantly to the increasing incidence of nasal and paranasal mucosal diseases. Studies show that the incidence of chronic sinusitis has doubled over the past eight years, while hospitalizations due to nasal and sinus pathology increase annually by 1.5–2% [78]. Inflammatory foci in the paranasal sinuses may serve as sources of infectious sensitization for the lower respiratory tract and lungs, and may also cause severe orbital and intracranial complications. It has been reported that in 3.4–6.8% of sinusitis cases, the inflammatory process involves the orbit and its contents [6]. According to literature, maxillary sinusitis ranks first in incidence (57.6%), followed by ethmoiditis (56.2%), with frontal and sphenoid sinusitis accounting for

6.2% [108,111]. However, in many cases, more than one sinus is affected simultaneously (hemisinusitis or pansinusitis).

Modern MRI data show pathological changes in the paranasal sinuses in 39.3% of examined individuals, often without evident clinical manifestations. These findings confirm that sinusitis is among the most common human diseases. MRI results indicate that chronic inflammatory processes predominantly affect the maxillary sinuses (92.9%) and the anterior ethmoidal cells (80.4%) [51,46,89,124]. Sinusitis is a bacterial or viral infectious inflammation of the paranasal sinuses. It may present in various forms:

- **Acute:** catarrhal, purulent, necrotic.
- **Chronic:** catarrhal, purulent, hyperplastic, polypoid, fibrotic, cystic (mixed forms such as purulent-polypoid or cystic-purulent are also possible).
- **Complicated:** osteomyelitis, cholesteatoma, pyocele, or extension of inflammation to the orbit, venous system, or cranial cavity.
- **Vasomotor:** allergic or non-allergic sinusitis.
  By origin, sinusitis can be rhinogenic, odontogenic, or traumatic. By etiological agent: viral, bacterial (aerobic or anaerobic), fungal, or mixed. Depending on the distribution: ethmoiditis, maxillary sinusitis, frontal sinusitis, sphenoiditis, or combined forms such as hemisinusitis and pansinusitis (Piskunov Z.S., Piskunov G.Z., 1997).

In acute sinusitis, mucosal inflammation of the paranasal sinuses usually lasts less than three months and resolves spontaneously or after treatment. Chronic sinusitis is defined by persistence of symptoms for more than three months and radiological signs of inflammation for at least four weeks despite adequate antibacterial therapy and in the absence of acute symptoms. A recurrence of chronic sinusitis is characterized by reappearance or worsening of symptoms following a symptom-free period [163].

Staphylococci are the most common microorganisms found in both acute and chronic sinusitis. They are typically conditionally pathogenic, widely distributed in nature, and part of the normal human skin and mucosal flora. When host resistance decreases, these microorganisms can provoke inflammation, the severity of which depends on their virulence, inoculation site, and the host's immune reactivity [77].

Sterile sinus cultures are obtained in 35% of acute cases, 47% of chronic serous cases, and 8.7% of purulent sinusitis cases, likely due to the presence of viral, anaerobic, or allergic mechanisms [34,77]. In chronic sinusitis, in addition to coccal flora, enterobacteria (E. coli, *Citrobacter*, *Klebsiella*, *Proteus*, *Enterobacter*) are detected in 19.5%, and *Pseudomonas aeruginosa* in 3% of cases. Anaerobic flora (*Bacteroides melaninogenicus*, *Bacteroides fragilis*, *Peptostreptococcus*, *Fusobacterium* spp.) are found in up to 67% of cases, often in association with aerobic bacteria [24,53,61,62,122,124].

During inflammation, sinus ostia become obstructed by edematous mucosa, decreasing oxygen and increasing carbon dioxide concentrations within the sinus. This anaerobic environment promotes the growth of anaerobic bacteria, contributing to complications such as parapharyngeal abscesses, neck phlegmon, osteomyelitis, and sepsis [123,164]. Aerobic and anaerobic synergism in the respiratory tract occurs through mechanisms such as bacterial capsule formation (protecting against phagocytosis) and β-lactamase production, which inactivates antibiotics — thereby increasing bacterial virulence and the risk of complications [123,164].

Electron microscopic studies on experimental sinusitis in animals have shown that *Streptococcus pneumoniae* causes extensive ciliary damage, while *Bacteroides fragilis* induces prolonged submucosal inflammation with less ciliary destruction but persistent infection leading to chronicity [157,184,186,192].

A Finnish seroepidemiological study using complement fixation tests identified *Mycoplasma pneumoniae* as an important etiological factor in acute maxillary sinusitis, with elevated antibody titers in 32% of purulent and 35% of non-purulent cases [177]. Experimental work by Yoshida A. (1982) confirmed that viable *M. pneumoniae* organisms cause desquamation and paralysis of ciliated epithelium, while inactivated organisms do not induce such pathology [197].

Recent evidence indicates that *Mycoplasma* species persist in bone marrow and can reside in blood phagocytes of patients with chronic sepsis, sometimes manifesting as chronic fatigue syndrome [91,167]. This emphasizes the need for targeted diagnostic methods for *M. pneumoniae* in patients with chronic respiratory inflammation, including sinusitis.

Many researchers also point to fungal involvement in chronic sinusitis, especially when antibacterial therapy fails. Inadequate diagnostics and empirical antibiotic use often lead to chronic or hyperplastic sinusitis. Therefore, culture-based antibiotic sensitivity testing of sinus flora is essential for effective therapy [24,46,77,190].

These findings highlight the high incidence of chronic and recurrent upper respiratory tract diseases associated with anaerobic, mycoplasmal, and chlamydial microflora — justifying their inclusion as key etiological factors in this study. Another rationale for this research is the insufficient diagnostic capacity for such microorganisms in clinical practice due to their complex culture requirements and the lack of immunofluorescent diagnostic methods in otorhinolaryngology [60].

Anatomical defects such as nasal septum deviation, hypertrophy of the middle turbinate, or narrow nasal passages also contribute to impaired sinus ventilation, promoting inflammation [72].

The body's "second line of defense" consists of neutrophilic granulocytes, mononuclear phagocytes, and lymphoid immune cells interacting with humoral protective factors [16,57,105]. The mucosal immune system provides a barrier

against pathogenic colonization through secretory immunoglobulins (mainly sIgA), mucins, lysozyme, lactoferrin, and cytokines [5,120,173].

Secretory immunity plays a central role in the first-line defense of the upper respiratory tract. sIgA prevents microbial adhesion to epithelial surfaces and works in synergy with normal microflora and antimicrobial secretions such as lactoferrin, lactoperoxidase, and lysozyme [158]. However, studies show that sIgA and lysozyme levels may remain unchanged in acute sinusitis and are variably reduced in recurrent cases, often without direct correlation to disease onset [67,109,152,159,175]. Trachoma, caused by ocular strains of *C. trachomatis*, causes visual impairment of about 2.2 million people, of whom 1.2 million are irreversibly blind. Globally, it is estimated that more than 50 countries are endemic for blinding trachoma, mainly in Africa and the Middle East, but also in Asia, Latin America and the western Pacific. However, estimates for global trachoma vary considerably due to limited reliable survey data from endemic regions. Trachoma is associated with poor hygiene status and extreme poverty. It is a family-based disease clustering in certain communities and specific households within these communities. The disease is spread by direct contact with ocular and nasal discharges, contact with fomites, or contact with eye-seeking flies, which are vectors for the disease. Trachoma is thus a disease specific to poor rural regions in less developed countries and is part of the Neglected Tropical Diseases Program Ocular serovars (A, B, Ba, and C) of *C. trachomatis* have highly specific tropism for mucosal epithelia of ocular conjunctiva. Infection of the conjunctival epithelium leads to conjunctivitis and triggers an immune response characterized by a marked inflammatory cell infiltrate and release of pro-inflammatory cytokines in the conjunctiva. One episode of infection results in self-limiting chlamydial conjunctivitis, an acute phase referred to as active trachoma. The World Health Organization (WHO) estimates 40 million people worldwide have active trachoma. Infection is usually acquired in infancy in hyperendemic regions and active

trachoma is mostly seen in children, progressing to eyelid scarring and blindness in adulthood. Active trachoma is frequently found in the absence of detectable *C. trachomatis* infection, and is clinically represented by papillary and/or follicular inflammation of the tarsal conjunctiva. Repeated and/or persistent infections trigger sustained inflammation and scarring of the upper tarsal conjunctiva. Scarring and fibrosis, in turn, distort the upper eyelid and facilitate inturning of the eyelid (entropion) and eyelashes (trichiasis), causing irritation of the corneal surface and irreversible blindness. The scarring and trichiasis that lead to corneal opacity and sustained pathological tissue reaction to inflammation constitute the second phase of trachoma. The World Health Organization Simplified Trachoma Grading System divides active trachoma into two often coexisting phenotypes: Trachoma Inflammation Follicular (TF) and Trachoma Inflammation Intense (TI) . Chronicity and progression to inflammatory eye lesions are classified in the WHO system as Trachomatous Scarring (TS), reflected by tarsal conjunctiva scarring, and Trachomatous Trichiasis (TT), including at least one eyelash rubbing on the eyeball. The most severe disease sequela is blinding Corneal Opacity (CO). The immune response to *C. trachomatis* provides only partial protection, is serovar-specific and does not prevent reinfection. Tissue damage and scarring result from chronic, pathological immune reactions. Related immunity and immunopathogenesis have been studied in mouse and guinea pig animal models, and data more comparable to human trachoma have been obtained from non-human primate studies. Scarring complications result from complex interactions between infectious burden, local immune response and host genetic polymorphisms related to immune function. Repeated reinfections are implicated in the development of chronic scarring disease. The role of persistent, non-replicating chlamydial forms in ocular infections is unclear and controversial within the chlamydial field. Tissue damage and fibrosis in *Chlamydia*-related diseases are thought to result from cell-mediated immunity responses against

chlamydial antigens, either by delayed type hypersensitivity or molecular mimicry [21]. In trachoma, infected conjunctival epithelial cells secrete pro-inflammatory cytokines, chemokines, and growth factors, which recruit inflammatory immune cells. Inflammatory cells such as neutrophils and macrophages disrupt normal tissue architecture by releasing mediators such as toxic reactive oxygen and nitrogen species and matrix metalloproteinases (MMP). MMP9 can degrade collagen IV, leading to basement membrane disruption, and pro-fibrinogenic factors are thought to stimulate activated fibroblasts to produce collagen, causing scarring.

Key factors influencing trachoma development and progression are the presence of different strains circulating within communities, pathogen burden of infected individuals and polymorphisms in specific host genes. Host polymorphism in immune response genes is hypothesized to play a significant role in trachoma disease progression [30]. Single nucleotide polymorphisms in the Interleukin-10 (IL-10) gene, the tumor necrosis factor (TNF) locus and MMP-9 have been implicated in trachoma pathogenesis [28]. Recently, specific combinations of polymorphisms in Human Leucocyte Antigen C (HLA-C) ligands and their inhibitory Killer-cell Immunoglobulin-like Receptors (KIRs) were associated with increased risk of conjunctival scarring in trachoma patients [28.56]. Besides host polymorphisms, genetic variation of *C. trachomatis* impacts disease severity and tissue tropism [39]. Major outer membrane protein (MOMP) serovar predicts chlamydial disease biovars (A-C: endemic trachoma), but does not reflect disease severity differences. Polymorphisms in chlamydial genes such as Tarp, Inc, CT229, pmp and cytotoxin appear to influence disease severity and tissue tropism; however, clear links and mechanisms are unknown. Distinction between ocular and genital strains can also be made based on mutations in the tryptophan synthase genes [38].

Documented *C. trachomatis* infection correlates poorly with clinical sequelae, complicating diagnosis of trachoma. Nucleic acid amplification tests (NAATs) are sensitive and specific, but results do not correlate with clinical grading. In vivo confocal microscopy has been recently used to visualize progression of inflammatory and scarring changes. Commercial NAATs do not detect *Chlamydiaceae* species other than *C. trachomatis*. Single and mixed infections with *C. trachomatis*, *C. psittaci, C. suis, C. pecorum* and *C. pneumoniae* were detected in conjunctival samples of trachoma patients by ArrayTube microarray. This finding and the potential zoonotic origin of these *Chlamydiaceae* species other than *C. trachomatis* might have implications for immunopathology and disease outcome in trachoma patients, therapeutic treatment and future vaccine development.

The WHO launched an initiative with the ambitious goal of eliminating blinding trachoma globally by 2020. The SAFE strategy includes: surgery for trichiasis, antibiotics for active trachoma, facial cleanliness, and environmental improvement. Current WHO recommendations constitute mass treatment with a single dose of azithromycin. The risk of adverse events and possible antibiotic resistance development due to azithromycin treatment merit consideration, but ancillary benefits such as reduced infectious disease and decreased childhood mortality outweigh these concerns. Success of trichiasis surgery is impeded by high recurrence rate (5-40 %), poor surgical technique, limited accessibility to surgery and lack of acceptance of surgery among the local population . Limiting exchange of ocular secretions can be achieved by facial cleanliness and improvement of hygiene conditions (environmental improvement) to decrease transmission . *C. trachomatis* is the most common bacterial cause of STD worldwide. In the United States, 1.4 million chlamydial infections were reported by the Centers for Disease Control and Prevention (CDC) in 2011 [29], and the WHO estimates that more than 90 million persons are infected worldwide [30]. The greatest burden is in

sexually active women aged 14 to 19 years, with a prevalence of approximately 6.8 % in the United State. The major age groups for chlamydial STD are women aged 18 to 20 and men aged 20 to 24 years. Moreover, many patients are asymptomatic (70–90 % of women, 30–50 % of men), thus most cases likely remain undiagnosed/unreported. Risk factors include young adulthood, multiple sex partners, intermittent condom use, cervical ectopy, history of other STD such as HIV, low education status, low socioeconomic class, and anal receptive intercourse. High-risk types of human papillomavirus (HPV) are principle causative agents in cervical cancer, but *C. trachomatis* infection is a co-factor in development of cervical neoplasia . Women with untreated chlamydial diseases have increased risk of HIV infection. Additionally, HIV-infected women with reduced CD4+ T cell counts have increased risk for developing *C. trachomatis* pelvic inflammatory disease (PID) . Forty-six percent of men and women infected with *Neisseria gonorrhoeae* also have co-infection with *C. trachomatis* [29.58.93]. Nineteen serovars based on MOMP seroreactivity predict chlamydial disease biovars: A–C (endemic trachoma), D–K (genital diseases) and L1–L3 (lymphogranuloma venereum). *C. trachomatis* genital serovars infect superficial mucosal epithelia of the urethra in men or endocervix in women, initiating disease. In women, *C. trachomatis* cervical infections are mostly asymptomatic and can either resolve spontaneously or progress for weeks to months, causing complications . Approximately 25 % of women with chlamydial cervicitis have concomitant urethritis. Cervical infection can ascend into the endometrium and fallopian tubes and develop into chronic infection and PID. PID is characterized by infection and inflammation of the upper genital tract, frequently involving the endometrium, fallopian tubes, and pelvic peritoneum (endometritis, salpingitis or tubo-ovarian abscess and peritonitis). PID is caused by common sexually transmitted infections, such as *Neisseria gonorrhoeae*, *Mycoplasma genitalium, C. trachomatis* (in 30 % of clinical cases), and by anaerobic vaginal

microbes causing bacterial vaginosis. Presumptive diagnosis of PID is made clinically (women of reproductive age with pelvic or abdominal pain), while definitive diagnosis is made by laparoscopy. If untreated, 8–10 % of *C. trachomatis*-infected women develop PID. Tubal damage is mediated by innate immune responses and adaptive T-cell responses. Long-term sequelae of PID include tubal infertility, ectopic pregnancy, and chronic pelvic pain caused by tubal damage and scarring from inflammation. The duration of an infection or repeated infections affect the pathogenesis of PID, but the relative importance if each has not been elucidated. Repeated *C. trachomatis* infections are common, indicating limited natural immunity. Women with active infection can transmit *C. trachomatis* to their infant during delivery, leading to conjunctivitis and pneumonia in the newborn. *C. trachomatis* infection in pregnant women has been also linked to chorioamnionitis, placentitis, premature rupture of membranes, and preterm birth, however, existing evidence is weak . In men, *C. trachomatis* causes non-gonococcal urethritis, epididymitis, prostatitis, and proctitis. Urethritis is the most frequent STD syndrome in men, and *C. trachomatis* is the causative agent in 15–40 % of cases. The more invasive strains causing lymphogranuloma venereum (LGV) are named L1, L2, L2a and L3. LGV serovars infect and replicate within macrophages, spread systemically through lymph nodes, and cause necrosis and abscesses in inguinal and femoral lymph nodes. LGV proctitis can vary from clinically silent to severe. Traditionally, LGV is found most often in Africa, India, Southeast Asia, and the Caribbean, and almost exclusively in men who have sex with men (MSM). Since 2004, increasing incidence has been found in North America, Europe, and Australia and occurs mostly in MSM with proctitis [29.56.63.87].*C. trachomatis* infection of the female genital tract is recognized by Toll- like receptor (TLR)-2 and TLR-4 and nucleotide-binding oligomerization domain (NOD)1, leading to induction of interferon (IFN) gamma. Cell-mediated immunity is important in clearance of *C. trachomatis* infection. However, the

immune response against *C. trachomatis* infection does not provide long-lasting protection and may contribute to pathology. Th1 T helper cell response helps resolve the infection, but also leads to secretion of pro-inflammatory factors such as TNF alpha, IL-1alpha and IL-6. Induction of IL-10 might down regulate the chlamydial-specific T-cell responses, leading to chronic inflammation and tissue damage in persistent infections [44]. Matrix metalloproteinase 9 (MMP9) expression by fallopian tube cells infected with *C. trachomatis* is associated with scarring. Clearance of *C. trachomatis* infection might be delayed by pathogen immune evasion strategies, such as enhanced survival inside and outside host cells, reduced inflammatory and adaptive immune responses and ability to persist within host cells as AB . Adding complexity, sex hormones modulate female genital tract immune responses . Women are more susceptible to chlamydial infection under the influence of estradiol, and estradiol enhances disease sequelae . T-cell-driven INF gamma and Th17 responses are critical for clearing infection and play a role in protection from disease. Initiation of autoimmunity by molecular mimicry has been suggested in the pathogenesis of PID [56]. The most important factor in molecular mimicry might be chlamydial heat shock protein 60 (Hsp60). Chlamydial Hsp60 is considered the key antigen in immunopathogenesis of tubal infertility, stimulating humoral and cell mediated immune responses in women with PID/tubal infertility [43]. Increased antibody response to chlamydial Hsp60 in women is strongly associated with PID, ectopic pregnancy, and tubal infertility [58] Variability in the MOMP gene (ompA) is unrelated to disease severity and MOMP serovars fail to correlate with virulence. However, recent data indicate that variation in the pmp genes may contribute to disease severity. Pmps B, D, and H are strongly immunogenic and elicit pro-inflammatory cytokine responses. Genital, but not ocular, strains of *C. trachomatis* possess functional tryptophan synthase (trpBA) to convert indole, secreted by local vaginal flora, into tryptophan. A perturbed vaginal microbiome (bacterial vaginosis) might provide a source of indole,

enabling genital *C. trachomatis* serovars to circumvent tryptophan limiting bacteriostatic/bactericidal effects of IFN gamma and establish persistent infection. Persistence versus clearance is likely driven by IFN gamma responses. High levels of IFN gamma eradicate chlamydiae, but low levels result in the persistent state [58]. Inflammation of infected tissues promotes local oxygen consumption, resulting in hypoxia [56]. A recent study indicates hypoxia reactivates IFN gamma-induced persistent *C. trachomatis*, causing increased bacterial growth and progeny, while dampening the host inflammatory response [48].

The *C. trachomatis* genome is highly conserved, and diversity seems to have evolved through genetic recombination [71] and might result in hypervirulent strains [11]. Deletion events also occur and have been described in the cryptic plasmid of *C. trachomatis.* Chlamydial plasmids are present in *C. trachomatis*, but are non-conjugative and nonintegrative; they do not encode antibiotic resistance nor show signs of genetic flexibility. Therefore, they are targeted for NAAT diagnosis of *C. trachomatis* infection. However, emergence of the new Swedish variant (nvCT), a mutated strain from serovar E strains carrying a 377-base-pair deletion within its plasmid, was reported in 2006. Several commercial NAATs targeted this region, leading to diagnostic failure. Retrospective studies suggest nvCT in the Swedish population arose after 2000, perhaps by importation of the variant or by spontaneous mutation. Genetic predisposition and host immune response are also important in pathogenesis of long-term complications of genital *C. trachomatis* infection. Specific HLA DQ alleles and polymorphisms in the promoter of IL-10 and TNF alpha are associated with high risk of tubal infertility, whereas polymorphisms in TLR-2 are associated with protection against tubal disease following *C. trachomatis* infection. Diagnosis of *C. trachomatis* infection is recommended by NAAT from urine, vaginal, or endocervical swabs. NAAT from non-genital samples, such as rectal swabs, is performed but not US Food and Drug Administration (FDA)-approved and is essential to diagnose LGV

proctitis. Self-collected vaginal or urine swabs are most commonly used in screening programs. The Centers for Disease Control and Prevention (CDC) recommends annual screening for *C. trachomatis* in sexually active women aged 25 years and younger. Upon diagnosis, primary uncomplicated urogenital infections can be effectively treated with antibiotics. The CDC recommends either single-dose azithromycin or a 7-day course of doxycycline in adolescent and adult men and women, and amoxicillin in pregnant women. Early treatment of *C. trachomatis*-infected individuals shortens infection duration and prevents sexual transmission and complications including PID, while treatment of pregnant women prevents transmission to the infant during delivery [48]. However, most chlamydial infections are asymptomatic and undiagnosed/untreated. Treatment failure occurs, perhaps due to re-infection, persistent infection or, less likely, acquired antibiotic resistance. Recurrent *C. trachomatis* infections result from re-infection from an untreated partner or infection from a new partner. Moreover, prevalence of anorectal chlamydia is high; almost all women with anorectal chlamydia had concurrent urogenital chlamydia. This finding has implications for the diagnosis of *C. trachomatis* infections (both sites should be tested) and for the therapy (anorectal chlamydial infections are more difficult to treat). Moreover, anorectal infection might lead to recurrent vaginal infection by autoinoculation . Treatment of LGV infection requires prolonged therapy (21 days) and the CDC recommends doxycycline [58.86]. Screening programs aim to identify and treat asymptomatic cases of cervicitis before *C. trachomatis* infection can progress to PID. Trials indicate that *Chlamydia* screening and treatment reduce risk of PID among young women . Screening has contributed to the decline of PID; however, the magnitude of benefit might have been overestimated in initial trials. Asymptomatic chlamydial infections may have been present for months when detected by screening, and thus might have already progressed to chronic inflammation in the upper genital tract. The role of chlamydial screening in reducing complications has

not been confirmed and benefit on an individual level is difficult to assess . Future focus should include screening young, sexually active women; determining optimal frequency of screening and benefit of screening for repeat infections; and, of major importance, treatment of partners of infected women. In addition to preventing adverse sequelae of *C. trachomatis* infection, reducing the incidence of new infections through interruption of transmission might be equally important. Despite screening and control programs, reported *C. trachomatis* cases have not exhibited sustained declines. This may be explained by the arrested immunity hypothesis: early treatment interrupts acquisition of protective immunity, increasing risk of reinfectio. A recent clinical study provides data supporting this concept, indicating spontaneous resolution of chlamydial infection in the absence of antibiotic treatment may reduce risk of subsequent reinfection . Development of a safe and effective *C. trachomatis* vaccine to prevent acquisition and transmission of infection, and prevent development of inflammatory sequelae, remains the ultimate goal The characteristic pathology of acute sinusitis involves catarrhal or purulent inflammation with mucosal edema, hyperemia, and exudation. The mucosa thickens significantly, obstructing sinus drainage. In severe cases, periostitis or osteomyelitis may develop [15]. Chronic sinusitis presents with milder, sometimes latent symptoms but may cause prolonged immune exhaustion [69].

1.2. Chlamydial infections: prevalence, epidemiology, biological properties, pathogenesis, clinical features, and diagnosis

In recent years, human chlamydial infections have become a pressing public-health concern owing to their wide prevalence and substantial adverse impact on population health. The global economic burden runs into billions of US dollars annually [106]. Fundamental work on the systematics of *Chlamydia* has clarified the taxonomic position of members of the order Chlamydiales and led to a revised classification. The family Chlamydiaceae comprises two genera: Chlamydia and the newer genus Chlamydophila. The species formerly designated *C. pecorum*, *C. pneumoniae*, and *C. psittaci* are now placed in Chlamydophila. The genus Chlamydia includes, in addition to *C. trachomatis*, two newer species: *C. muridarum* and *C. suis* [112]. While chlamydiae share a genus-specific antigen, they differ in species- and type-specific antigens. Transmission to humans by anthropozoonotic and zoonotic agents occurs via multiple routes: sexual, contact-household, and airborne droplets [35].

Chlamydia trachomatis is transmitted predominantly through sexual contact. A "vertical" route—antenatal (transplacental) or intrapartum (during delivery)—and a "horizontal" intrapartum route are also recognized [92,200]. In families where parents have urogenital chlamydiosis, approximately 30–35% of children are affected, and about 7% present with extragenital forms [42]. Vertical transmission of *C. trachomatis* occurs in 30–70% of deliveries. Among children aged 2–14 years infected perinatally, chronic follicular conjunctivitis is observed in combination with recurrent muco-purulent rhinitis, otitis, chronic pneumonia, vulvitis, and enteritis of chlamydial etiology [100]. Chlamydial diseases are ubiquitous, display a wide spectrum of clinical manifestations, and present in diverse courses (acute, chronic, recurrent, latent). In most cases (≈70–80%), the initial stage is subclinical and lacks pathognomonic signs. Chlamydiae frequently occur in association with other pathogens; for example, pneumochlamydiosis often

co-occurs with pneumococci, streptococci, staphylococci, *Bacteroides*, mycoplasmas, and common respiratory viruses [49,155].

Recent reports describe generalized forms of infection caused by Chlamydia species (*C. psittaci*, *C. pneumoniae*). The most challenging presentations include meningitis, meningoencephalitis, endocarditis, thrombophlebitis, polyarthritis, sepsis, and others [99,137,138]. Similar generalized forms have been documented in young individuals infected with *C. trachomatis* [27,28,55,104,179].

Animal experiments modeling generalized infection with *C. trachomatis* and *C. psittaci* have shown that pathogens may disseminate via leukocytes (predominantly neutrophils and macrophages) and subsequently involve synovium, brain, eyes, and the respiratory tract [42,49,76]. In humans, the existence of generalized forms is supported by Reiter's disease [49], oculogenital chlamydiosis [20,49], neurochlamydioses [49,63], and cardiovascular manifestations [14,185]. In all such cases, authors note primary infection foci (*C. trachomatis*) within the urogenital tract.

Chlamydophila pneumoniae is a common cause of acute respiratory illness, chiefly pneumonia (≈50% of cases attributed within its spectrum), as well as other respiratory conditions (≈25%—acute respiratory disease and acute bronchitis; >15%—sinusitis, otitis, and pharyngitis) [140,198]. Although most infections with *C. pneumoniae* are non-fatal, deaths can occur, particularly in the elderly [154]. Extrapulmonary acute infections are less frequent and may present as isolated fever, cardiovascular disease (acute myocarditis, pericarditis, endocarditis), or neurologic pathology (encephalitis, meningitis) [137,138]. Many clinical, epidemiological, and therapeutic aspects of chlamydial infections remain unresolved and require further study.

Chlamydiae resemble classical Gram-negative bacteria in structure and chemical composition but lack many metabolic mechanisms required for autonomous replication. Key features include energy-dependent parasitism on the host and a

unique developmental cycle. Bacteria-like properties of the chlamydial cell include recognizable morphology, division of vegetative forms, presence of a cell wall, DNA and RNA content, characteristic enzymatic activity, susceptibility to several broad-spectrum antibiotics, and a genus-specific antigen [70].

During primary infection, the *elementary body* (EB)—the mature, infectious form (0.2–0.3 μm)—enters the human host and is internalized by endocytosis into a susceptible cell (predominantly ciliated columnar epithelium), forming an intracellular vacuole. EBs reorganize into metabolically active, non-infectious *reticulate bodies* (RBs) (0.8–1.2 μm). RBs undergo binary fission within the endosome, utilizing host substrates for RNA and protein synthesis. After 8–12 replication cycles, RBs convert back into EBs; subsequent rupture of the inclusion membrane compromises host-cell integrity, leading to cell death and release of progeny EBs that infect neighboring, previously uninfected cells. The full chlamydial life cycle spans 48–72 hours [20,70].

Chlamydiae are thought not to invade deeply into tissues on their own; they parasitize exclusively in the apical region of epithelial cells, and progeny exit apically without penetrating the basolateral domain or basement membrane [19]. Under the influence of cytokines, a functional equilibrium may develop between chlamydiae and host cells. Phagocytosed chlamydiae are not completely eradicated intracellularly; their antigenic and genetic material can persist and be transferred to subsequent macrophage populations. Macrophages live for one month or longer; circulating cells localize within lymph nodes, spleen, lungs, serous cavities, and migrate to inflammatory foci [125]. The capacity of *C. pneumoniae* and *C. psittaci* to persist in monocytes and macrophages has been demonstrated in vitro and in vivo by several authors [103,118,135,195,196]. Consequently, detection of chlamydiae in peripheral blood leukocytes (chlamydemia) is an important laboratory criterion that may indicate generalization of the infectious process [49].

1.3. Immune system status in patients with chlamydial infection and chronic sinusitis

Numerous authors have established that the course and outcome of chronic and recurrent inflammatory diseases of the paranasal sinuses depend largely on the immune reactivity of the host organism [2,21]. According to foreign studies, most patients suffering from chronic sinusitis (87%) demonstrate defects in the T-cell arm of immunity and reduced concentrations of monocyte chemotactic factors in serum [180,188,189]. Several reports have also shown high efficacy of local recombinant cytokine therapy in the management of sinusitis [17,81,113].

In recent years, interest in the use of recombinant cytokines for infectious diseases has increased substantially [20,4,65,84,86]. Through modern biotechnology, a recombinant cytokine preparation—Roncoleukin—was produced using a non-pathogenic yeast strain (*Saccharomyces cerevisiae*) into whose genome the human *IL-2* gene was inserted. This agent exhibits the same functional activity spectrum as native interleukin-2 (IL-2). IL-2 is a 15.3-kDa polypeptide composed of 133 amino acids, synthesized primarily by T-helper/inducer cells ($CD4^+$), particularly Th0 and Th1 subsets. Th1 cells arise from Th0 differentiation under the influence of γ-interferon (γ-IF) and IL-12. Serum IL-2 levels correlate directly with the number of producing T-suppressor/cytotoxic lymphocytes.

IL-2 is a key cytokine that induces the development of specific immune responses. It exerts broad immunostimulatory activity: enhancing proliferation of cytotoxic T lymphocytes, natural killer cells, and B lymphocytes. It is required for IL-2 receptor expression on T and B cells and autocrine regulation of IL-2 synthesis. Moreover, IL-2 enhances the production and secretion of numerous other cytokines—interleukins, interferons, and colony-stimulating factors—by T cells, NK cells, and monocytes, as well as immunoglobulin secretion by B cells.

Thus, IL-2 is a critical component of the human immune system, playing a decisive role in immune activation, the development of an adequate response, and

the coordinated functioning of major immune elements. Another cytokine, IL-1β, stimulates leukocyte and lymphocyte reactivity during inflammation and immunity. IL-1β also activates the neuroendocrine system, hematopoiesis in bone marrow, fibroblasts, and endothelial cells, and promotes wound healing [39,65,85].
It is generally accepted that immunopathological mechanisms are central to the pathogenesis of chlamydial infection, particularly in *C. trachomatis* persistence. According to Glazkova L.K. and Akilov O.E. (1999), *Chlamydia* can inhibit fusion of phagosomes with lysosomes, rendering phagocytosis non-productive. Within macrophages, the organism's growth halts between the *elementary body* (EB) and *reticulate body* (RB) stages. At this point, only lipopolysaccharide (LPS) of the chlamydial cell wall is detectable in monocyte cytoplasm, while the *major outer membrane protein* (MOMP) is absent. Consequently, macrophages present LPS antigen to T-helpers but not the protective MOMP antigen, producing an immune response directed against the variable LPS—non-specific to *C. trachomatis*.
The immune response to chlamydial infection is primarily Th1-type, with Th1 activation being crucial for recovery. Activated Th1 cells produce IL-2 (a true T-cell lymphokine), tumor necrosis factor-β (TNF-β, or lymphotoxin), and other mediators. TNF-β stimulates fibroblast proliferation and extracellular matrix synthesis (glycosaminoglycans, collagen), contributing to fibrosis. IL-1, secreted by macrophages, further promotes fibroblast proliferation.

Simultaneously, macrophages release large quantities of cytokines that trigger a "respiratory burst." However, the reactive oxygen species (ROS) generated cannot destroy the rigid chlamydial cell wall—whose strength derives from disulfide crosslinks within MOMP—or the polysaccharide microcapsule of RBs. Instead of exerting a microbicidal effect, ROS activate lipid peroxidation (LPO), damaging host cell membranes.

Activated macrophages also produce γ-interferon (γ-IF), TNF-α, and IL-1. The main functions of γ-IF include:

- upregulation of membrane antigen expression (MHC class I and II);
- activation of macrophages, fibroblasts, and epithelial “non-professional” phagocytes, increasing cellular adhesiveness and susceptibility to infection (first vicious cycle);
- stimulation of IL-1 and IL-2 synthesis and enhancement of phagocytic activity (second vicious cycle);
- induction of B-cell immunoglobulin production;
- and activation of microbicidal oxygen metabolism products.

High γ-IF concentrations completely inhibit chlamydial growth, while low doses induce morphologically aberrant inclusions. In epithelial cells, γ-IF stimulates synthesis of indoleamine-2,3-dioxygenase—an enzyme initiating the tryptophan degradation pathway, leading to intracellular tryptophan depletion and chlamydial stress-response formation. Persistent chlamydiae exhibit altered morphology and antigen expression, with decreased synthesis of MOMP, the 60-kDa cell wall protein, and LPS, while continuously producing chlamydial heat shock protein (HSP60).

HSP60 plays a crucial role in the immunopathogenesis of persistent infection and chronic inflammation. It leads to antigenic overload, hyperproduction of IgG and IgA, delayed-type hypersensitivity with lymphocytic and monocytic infiltration, and cross-reactive autoimmune responses due to structural similarity with eukaryotic proteins. It also induces stress reactions in host cells and halts the chlamydial cycle at the RB stage.

Activated macrophages release TNF-α, which indirectly (via IL-1) promotes fibroblast proliferation and tissue fibrosis, increases lymphocyte adhesion to vascular endothelium, and reactivates macrophages.

Thus, a key mechanism preventing RB redifferentiation into EB is the influence of specific cytokines that block synthesis of outer membrane proteins and maintain

chlamydial persistence. This leads to continued microbial growth without division [19].

Chlamydiae, like Gram-negative bacteria, possess DNA and RNA, a cytoplasmic membrane, and a cell wall, and are susceptible to broad-spectrum antibiotics. Experimental studies show that chlamydiae are most sensitive to tetracyclines, macrolides, and fluoroquinolones [42]. Penicillin does not affect primary EB→RB transformation but disrupts binary fission, inducing enlarged abnormal RBs and blocking reverse RB→EB conversion. Ultrastructural analyses have demonstrated giant RBs (up to 5,000 nm) and numerous vesicular inclusions within deformed RBs. Penicillin withdrawal restores normal EB morphology [10,110,193].

Few in-vivo studies have examined the morphological features of persistent chlamydial forms in humans; most work has been conducted in cell culture (in vitro) [10,145,146,193].

For this reason, it is particularly important to examine nasal and sinus smears in patients with sinusitis associated with chlamydial infection to detect persistent chlamydial forms, since these patients often receive prolonged antibiotic therapy, increasing the likelihood of aberrant pathogen transformation.

1.4. The etiopathogenetic role of *chlamydia* in otorhinolaryngologic pathology

Information regarding the role of *Chlamydia* in otorhinolaryngology remains inconsistent and, in some cases, contradictory. Many researchers consider chlamydiae to be an etiological factor in chronic diseases of the ear, throat, and nose [47,94,135,136,169]. Lin'kov V.I. et al. (1995) detected *Chlamydia* in 44.3% of patients with chronic adenoiditis, 41.7% with chronic tonsillitis, and 45% of children with combined chronic inflammation of the nasopharyngeal and palatine tonsils [47]. However, the study did not specify the species composition of the pathogens.

Kawai A., Sato Y., and Yamamoto H. (1993) noted that due to more liberal sexual behavior in recent years, the oral cavity and pharynx are increasingly becoming colonization sites for sexually transmitted pathogens. Consequently, cases of pharyngitis and inguinal lymphadenitis caused by orogenital infection with *C. trachomatis* have become more frequent [156]. There are also reports of laryngitis of chlamydial etiology [25].

According to investigators, most cases of chlamydial laryngitis arise through hematogenous or lymphogenic spread of infection from the urogenital tract, though direct household transmission via contaminated objects cannot be ruled out. In recent years, it has been established that among patients with chlamydial eye lesions, 75.5% have concomitant chronic rhino-pharyngitis of chlamydial origin. In generalized forms of chlamydial infection, 21.4% present with chronic pharyngitis and 24.5% with chronic tonsillitis [83].

C. pneumoniae is most frequently detected in middle-aged and elderly populations. Infection typically occurs during childhood or early adulthood (e.g., during military service) and tends toward chronicity [154,198]. The upper respiratory tract serves as the main portal of entry. The pathogen primarily affects the mucous membranes of the upper respiratory tract, pharynx, and paranasal sinuses, with possible hematogenous dissemination, systemic intoxication, and

vascular involvement. Spontaneous recovery rarely occurs [20]. The infection source is symptomatic or asymptomatic individuals, the latter being the main reservoir. Transmission occurs via the respiratory route—specifically, aspiration and airborne droplets.

Hashiguchi K. et al. (1992) performed serological studies assessing antibody titers to *C. pneumoniae* in patients with acute ENT infections (sinusitis, otitis media, tonsillitis, laryngitis, bronchitis) using immunofluorescence assays. *C. pneumoniae*-specific IgG antibodies in diagnostic titers (indicating past infection) were found in 46.2% of patients, while elevated IgM and IgA titers—signifying acute or subacute infection—were identified in 10.5% of sinusitis cases, 19.2% of tonsillitis, 23.5% of otitis media, 18.2% of laryngitis, and 22.8% of bronchitis. These findings confirm *C. pneumoniae* as an important pathogen in otorhinolaryngology [143].

Later studies by Ducroix Y.P. (1998) detected *C. pneumoniae* in 20% of patients with paranasal sinusitis [94]. Hashiguchi K., Ogawa H. et al. (1992) described recurrent maxillary sinusitis associated with *C. pneumoniae* infection [138,193,165].

A review of the literature shows that sinusitis is among the most common human diseases. Inflammatory diseases of the paranasal sinuses are diverse in microbial etiology. Acute sinusitis is more often associated with monoculture infections, whereas chronic sinusitis typically involves mixed microbial associations [34,77,3,40,63,28]. The frequently observed “sterile” sinus cultures in sinusitis likely reflect undetected anaerobic bacteria (*Bacteroides*) [122,124] or mycoplasmal infection [94].

A significant issue remains the limited diagnostic capacity for such microflora in clinical practice, due to the difficulty of cultivating *Bacteroides* under anaerobic conditions and the lack of standardized immunofluorescence diagnostic methods for ENT infections.

The pathogenesis of chronic sinusitis is based on persistent impairment of mucociliary clearance, caused by irreversible epithelial alterations [171]. Another contributing factor is the failure of the second line of local mucosal immunity, mediated by cellular resistance phenomena involving granulocytic and macrophage systems and cytokine interactions. Cationic proteins released during these processes can cause extensive tissue damage when antigen elimination is unsuccessful within the mucosal barrier [56].

Chlamydia species are a likely contributing factor due to their unique intracellular developmental cycle, capacity to evade the host immune system, persistence within macrophages, and potential to disseminate through epithelial and urogenital tissues. This often results in secondary immunodeficiency. Because of multiple transmission pathways, *Chlamydia* infections are widespread among various population groups [134].

Chlamydial diseases can occur as outbreaks of pneumonia and acute respiratory infections (*C. pneumoniae*), primarily affecting organized groups and families, and frequently leading to ENT complications such as sinusitis, tonsillitis, pharyngitis, and otitis, as well as to broader systemic manifestations—meningitis, conjunctivitis, and others [20,43,63,134,137,138,154,155,198]. Hence, the widespread prevalence of this pathogen may have a detrimental impact on national public health and life expectancy.

In conclusion, the problem of acute and chronic sinusitis of chlamydial etiology remains highly relevant. It requires the introduction of new diagnostic methods into otorhinolaryngological clinical practice and closer interdisciplinary cooperation—particularly with infectious disease specialists, urologists, gynecologists, and pediatricians—to ensure effective management and treatment.

CHAPTER II. MATERIALS AND METHODS OF RESEARCH

2.1. General and clinical characteristics of the examined patients

The study focused on assessing the condition of the paranasal sinuses in patients with acute and chronic sinusitis, along with microbiological and immunological parameters and the clinical features of the disease course.

Clinical observations were carried out from 2007 to 2011 in the Otorhinolaryngology Department of City Clinical Hospital No. 1, Tashkent (Chief Physician – *S.B. Bakhirdikhanov*). The hospital serves as the clinical base for the Department of Otorhinolaryngology (Head – *Professor, MD K.D. Jabbarov*) of the Tashkent Institute for Advanced Medical Training (Rector – *Professor, MD Zh.M. Sabirov*).

Laboratory and bacteriological diagnostics were performed at the Republican Specialized Scientific and Practical Medical Center of Dermatology and Venereology, Ministry of Health of the Republic of Uzbekistan. Immunological studies were conducted at the Institute of Immunology, Academy of Sciences of the Republic of Uzbekistan.

The study employed the classification of sinusitis proposed by Piskunov Z.S. and Piskunov G.Z. [104].

Inclusion Criteria

1. Hospitalized patients aged 11 to 74 years, of both sexes, diagnosed with acute or chronic sinusitis of uncomplicated course.
2. Diagnosis confirmed by two ENT specialists through clinical and instrumental examination.
3. Voluntary informed consent obtained from each participant.

Exclusion Criteria

1. Complicated rhinosinusitis (e.g., rhinogenic intracranial or orbital complications, bony wall destruction of paranasal sinuses, sepsis).
2. Decompensated somatic diseases.

3. Pronounced dysfunction of endocrine organs, autonomic nervous system, or metabolic disorders.
4. Unsanitized oral cavity.
5. Refusal to participate in the study.

A total of 126 patients with sinusitis meeting inclusion criteria were examined. In 66 patients, the presence of IgG antibodies in blood serum was determined using enzyme-linked immunosorbent assay (ELISA).

All patients with sinusitis were divided into five age groups, as shown in Table 2.1.

Age Group (years)	Men (n)	%	Women (n)	%	Total (n)	%
11–17 (children, adolescents)	5	3.1	3	2.4	8	6.5
18–29 (young adults)	24	19.0	29	23.0	53	42.0
30–44 (mature age)	26	20.6	15	12.0	41	32.5
45–59 (middle age)	11	8.7	7	5.6	18	14.2
60–74 (elderly)	3	2.4	3	2.4	6	4.8
Total	69	54.8	57	45.2	126	100

2.1. General and clinical characteristics of the examined patients (continued)

Among the examined patients, 54.8% were men and 45.2% were women. The mean age of all participants was 33.1 years.

This, the study sample represented a broad distribution across all age groups, though the majority were young and middle-aged individuals of working age.

The control group consisted of 30 conditionally healthy individuals who, according to clinical examination and medical history, had no acute or chronic inflammatory ENT diseases. This group included patients who underwent surgical treatment for nasal septal deviation and reported acute respiratory infections no more than 1–2

times per year. The control group also represented different age categories but had a predominance of men (19 men) compared to women (11 women).

The first treatment group included 39 patients diagnosed with chronic sinusitis associated with chlamydial infection. Most of these patients were of middle age (22 individuals). Within this group, there were 6 men and 16 women.

The second treatment group consisted of 27 patients with acute sinusitis associated with chlamydial infection. In this cohort, men predominated (16 individuals) compared to 11 women.

The control treatment groups were represented by 30 patients with chronic sinusitis of non-chlamydial etiology and 30 patients with acute sinusitis without chlamydial involvement. The age and sex distribution of these groups was statistically comparable to that of the previous groups.

In summary, both acute and chronic sinusitis were found to occur frequently in both men and women of young and middle age, with a slight predominance of acute sinusitis among younger men.

2.2. Methods of investigation

2.2.1. Clinical and instrumental methods

In all patients, the diagnoses of acute and chronic sinusitis were established on the basis of a composite assessment of clinical and laboratory findings, plain radiography, and, when indicated, computed tomography (CT), magnetic resonance imaging (MRI), as well as endoscopic examination.

Examination of the ENT organs was performed using standard techniques—anterior and posterior rhinoscopy, mesopharyngoscopy, indirect laryngoscopy, and otoscopy. During routine and endoscopic assessments, special attention was paid to: the presence of pathological nasal discharge; the condition of the nasal mucosa; the position of the nasal septum; discharge within the nasal cavity; the condition of the inferior turbinates (including their posterior ends) and middle turbinates

(including their anterior ends); the state of the pharyngeal mucosa, pharyngeal and lingual tonsils; and the external auditory canal and tympanic membranes

Rhinoscopy was complemented by nasal endoscopy. We performed endoscopic examination with a flexible endoscope HN-2 (diameter 3.7 mm, light guide, 0° viewing angle). The procedure began without prior topical vasoconstrictors or anesthetics to allow an unbiased evaluation of the mucosa. Thereafter, nasal decongestion with adrenaline solution and topical anesthesia with 10% lidocaine (applied by spray/pledget) were administered

All patients also underwent bacteriological testing to determine the characteristic microflora, antibiotic susceptibility, and to track changes in the composition and quantity of microflora after therapy. The microbial spectrum was assessed by culture on nutrient media Olfaction was evaluated using the standard V. I. Voyachek method, applying odorants in ascending order of intensity: 0.5% acetic acid, ethyl alcohol, valerian tincture, and ammonia

In all 126 patients with sinusitis, following external inspection (exoscopy), endoscopy, and review of radiographs, CT and MRI scans, therapeutic–diagnostic puncture and probing of the paranasal sinuses (PNS) were performed. After drainage via polyvinyl-chloride catheters, medications were instilled, and microbial antibiotic sensitivity was determined.

2.2.2. Cytoscopic method for the detection of *chlamydia*

Two methods of sample collection were used, conventionally divided into invasive and non-invasive techniques.

The invasive method involved obtaining material directly from the maxillary sinus contents during diagnostic puncture using a Kulikovsky needle. The aspirated content was centrifuged at 1,500 rpm for 10 minutes, after which the sediment was used to prepare smears.

The non-invasive method consisted of collecting mucosal material from the nasal cavity using disposable cytobrushes. After nasal decongestion with 0.1% naphthyzinum and topical anesthesia of the middle nasal meatus with 2% lidocaine solution (0.3 mL), the cytobrush was gently rotated for 10–15 seconds between the medial surface of the middle turbinate and the lateral nasal wall in the region of the sinus ostium.

The collected material was evenly spread onto a glass slide, air-dried, and fixed in acetone at 4–6 °C for 10 minutes. Prepared smears could be stored up to 2 weeks at 2–6 °C before staining.

Staining was performed according to the Romanowsky–Giemsa method: the dye was freshly diluted with distilled water at a 1:10 ratio. The slides were placed in Petri dishes on wooden supports with the smear facing downward, and the space between the slide and the dish bottom was filled with dye. Staining was performed for 45 minutes, followed by careful rinsing in running water, drying with filter paper, and differentiation in acidified ethanol (100 mL of 96% ethanol + 10 drops of glacial acetic acid).

Microscopic examination was carried out under a light microscope with oil immersion (×90 objective).

- The cytoplasm appeared light blue,
- nuclei — violet-blue,
- chlamydial inclusions — as dark-blue or pink microcolonies on a blue cytoplasmic background.

  At the elementary-body stage, inclusions stained pink; at the initial-body stage, they appeared blue [95].

To increase the diagnostic value of the morphological method, it was supplemented with cytological assessment to identify the neutrophilic–histiocytic–macrophage reaction (NHMR). This allowed evaluation of the severity of the inflammatory process in *Chlamydia*-infected tissue [82]. In our study, the numbers

of neutrophils, lymphocytes, and macrophages were counted in prepared smears before treatment and during therapy to monitor inflammatory dynamics under the influence of administered medications.

2.2.3. Direct immunofluorescence method

To detect chlamydial structures (antigens and DNA), the direct immunofluorescence (DIF) method was employed using the commercial diagnostic kit “ChlaMonoScreen” (*Niarmedik*, Russia).

Smears prepared from scraping materials and blood samples were stained with a working solution consisting of fluorescent polyvalent anti-chlamydial immunoglobulin and rhodamine-labeled bovine albumin, the latter serving to enhance background contrast.

Prepared slides containing the test material and dye were placed into a humid chamber and incubated in a thermostat at 37 °C for 30 minutes. The slides were then removed and thoroughly washed in phosphate-buffered saline (PBS, pH 7.2) on a magnetic stirrer for 1 hour, replacing the buffer every 30 minutes.

After washing and drying, one drop of buffered glycerol (prepared by mixing 9 mL glycerol with 1 mL PBS) was applied to each smear. The slides were then covered with a coverslip and gently pressed with filter paper to remove excess glycerol [95]. Microscopic examination was performed using fluorescence microscopes MLD-2 and LUMAM-I 3 equipped with oil immersion objective ×90, ocular ×10, and binocular magnification ×1.5.

Results were evaluated visually. The test was considered positive when morphologically typical *Chlamydia* elements were observed, exhibiting specific fluorescence of emerald-green or yellow-green color:

- Reticulate bodies (RBs): intracellular chlamydial clusters within the cytoplasm, appearing as compact or diffusely stained microcolonies of varying size (0.25–1.5 μm).

- Elementary bodies (EBs): predominantly extracellular spherical or ovoid forms, characterized by a sharply defined fluorescent peripheral ring or semicircle (0.25–0.5 μm).
- Intercellular inclusions: large, bright green fluorescent areas formed by dense aggregates of adjacent EBs.

Smears of nasal secretions from the paranasal sinuses that exhibited emerald- or yellow-green fluorescence of EBs and RBs were interpreted as positive for chlamydial infection.

2.2.4. Microbiological diagnosis of the associated bacterial microflora

The material for microbiological examination was obtained by aspiration of paranasal sinus contents during puncture, as well as by nasal lavage and impression smears. Cotton swabs with the collected material were placed into sterility-control transport medium (SCS).

For the diagnosis of *Bacteroides fragilis*, 3–5 mL of pathological material was introduced deep into the transport nutrient medium and delivered to the bacteriological laboratory within 1 hour, while samples for other infections were processed within 2 hours of collection. The diagnosis was carried out by cultivation of bacteroides on selective nutrient media in anaerobic incubators using oxygen-free gas mixtures.

Stages of Microbiological Diagnosis

The diagnostic procedure consisted of three main stages:

Stage 1 – Microscopy. Smears were prepared from the obtained material, Gram-stained, and examined microscopically.

- *Staphylococci* appeared as Gram-positive cocci, either solitary or in grape-like clusters.
- *Streptococci* appeared as Gram-positive spherical or slightly elongated cells arranged in chains of variable length.

- *Enterobacteria* were identified as Gram-negative rods, irregularly distributed across the field of view.
- *Enterococci* appeared as slightly elongated Gram-positive cocci, typically found in pairs or short chains.
- *Bacteroides* were identified as Gram-negative rods.

Stage 2 – Primary Culture.Primary inoculations were performed on various universal and selective nutrient media, incubated at 37°C for 18–48 hours. For selective isolation of *B. fragilis*, anaerobic blood agar with bile and kanamycin was used, incubated anaerobically at 37°C for 48–72 hours [59].

Colonial morphology (appearance, color, hemolysis, pigment formation, etc.) was then evaluated. Smears from selected colonies were again Gram-stained for preliminary identification, and pure cultures were obtained by subculturing onto enrichment media.

Stage 3 – Species Identification and Antibiotic Susceptibility Testing.Species identification of the isolated microorganisms was based on the study of their biochemical and biological properties. Antimicrobial susceptibility was determined by the disk diffusion method. Differentiation of microorganisms was performed using standard biochemical tests, including:

- Catalase, cytochrome oxidase, DNase, phosphatase, CAMP, and PYR tests [59].

Rapid Diagnostic Methods

Given that the complete isolation and identification of *Bacteroides* species may require 5–10 days [107], direct immunofluorescence (DIF) was additionally used for rapid diagnosis of *B. fragilis* and mycoplasmal infections.

For this purpose, samples fixed on glass slides were prepared according to the same protocol used for chlamydial detection. Polyvalent and monovalent fluorescent sera against *B. fragilis*, produced at the Research Institute of

Dermatology and Venereology, Ministry of Health of the Republic of Uzbekistan, were employed.

The antigens for animal immunization were obtained from reference strains of *B. fragilis* (Nos. 2393, 49/73, 2). Prepared slides were examined under fluorescent microscopes MLD-2 and LUMAM-I 3, and the results were assessed visually.

A positive result was defined by the presence of capsulated forms of *Bacteroides* exhibiting specific emerald-green or yellow-green fluorescence. The intensity of fluorescence was evaluated using a standard four-point (cross) scale [18].

2.2.5. Methods for assessing the immunological status of patients with sinusitis

Additional 10 mL sample of venous blood was collected into a clean, dry test tube. After clot formation, the clot was gently detached from the tube wall using a sterile glass rod and placed in a refrigerator at +4 °C. After 18 hours, the separated serum was aspirated and centrifuged at 1,500 rpm for 10 minutes.

For the preparation of heparinized blood, disposable 10 mL Euro-tube plastic vials were used, containing heparin at a concentration of 20 IU/mL.

Isolation and Counting of Lymphocytes

The lymphocyte count was determined using the method of density-gradient centrifugation, which separates cells based on their density. Peripheral blood was carefully layered onto a Ficoll–Urotrast solution with a density of 1.077 g/cm³. During centrifugation, lymphocytes and monocytes, being denser, separated into a distinct layer, while erythrocytes and granulocytes, having lower densities, sedimented below.

The normal relative lymphocyte count ranged from 28–39%, with an absolute count of $1.6–2.4 \times 10^6$ cells/μL.

Assessment of Cytokine Activity (IL-8 Production)

To evaluate the cytokine component of the immune response, the production of interleukin-8 (IL-8) by peripheral blood cells and cells in the inflammatory focus (sinus exudate) was studied. Heparinized blood or exudate (0.6 mL) was diluted

with 2.4 mL of Eagle's medium (Igle) supplemented with 2 mM glutamine and 80 μg/mL gentamicin. A working solution of the IL-8 synthesis inducer was prepared using lipopolysaccharide (LPS) contained in prodigiosan. The mixture consisted of 2.4 mL of Eagle's medium and 0.8 mL of 0.005% prodigiosan solution.

In a 96-well culture plate, 100 μL of the prodigiosan solution was added to six wells, followed by 100 μL of Eagle's medium to the remaining wells.Prepared blood or exudate samples were then added (100 μL per well) and incubated in a CO_2 incubator for 24 hours. Following incubation, IL-8 and IgJ levels were measured using the enzyme-linked immunosorbent assay (ELISA) method.Results were recorded with an automatic photometer at a wavelength of 492 nm.

The obtained IL-8 values were evaluated relative to normal reference ranges, established from measurements in healthy individuals.

2.3. Characteristics of the drugs used

In the present study, aimed at treating chronic sinusitis associated with chlamydial infection, the following drugs representing different pharmacological classes were employed:

1. Sumamed® (Azithromycin) – 500 mg, a macrolide antibiotic of the third generation.
2. Ofloxacin – 200 mg, a fluoroquinolone group antibiotic.
3. Derinat® (Sodium deoxyribonucleate) – 0.25% solution (2.5 mg/mL), an immunomodulator.

Azithromycin (Sumamed)

Azithromycin, a macrolide antibiotic of the azalide subclass, was first synthesized in 1980 by researchers Slobodan Dokic, Gabrijela Kobrehel, Gorjana Radobolja-Lazarevski, and Zrinka Tamburasev at Pliva (Croatia) and patented in 1981.In 1986, Pliva and Pfizer (USA) signed a licensing agreement under which Pliva marketed the drug in Central and Eastern Europe under the trade name Sumamed®

(1988), while Pfizer marketed it in Western Europe and the United States as Zithromax (1991).It was officially registered in Russia in 1994.

Pharmacological action:Azithromycin is a broad-spectrum antibacterial agent acting bacteriostatically by binding to the 50S ribosomal subunit, inhibiting peptidyl transferase activity during translation, thereby suppressing protein synthesis. In high concentrations, it exhibits bactericidal effects.It is effective against both extracellular and intracellular pathogens, including *Chlamydia trachomatis* and *Chlamydia pneumoniae*.

Spectrum of activity:

- Gram-positive: *Streptococcus spp.*, *Staphylococcus aureus*, *Staphylococcus epidermidis*.
- Gram-negative: *Haemophilus influenzae*, *Moraxella catarrhalis*, *Neisseria gonorrhoeae*, *Bordetella pertussis*, *Legionella pneumophila*, *Campylobacter jejuni*.
- Anaerobes: *Bacteroides bivius*, *Peptostreptococcus spp.*, *Clostridium perfringens*.
- Atypical bacteria: *Chlamydia spp.*, *Mycoplasma pneumoniae*, *Ureaplasma urealyticum*, *Mycobacterium avium complex*.

Indications: Upper and lower respiratory tract infections (pharyngitis, tonsillitis, sinusitis, bronchitis, pneumonia), otitis media, skin and soft tissue infections, urogenital infections (urethritis, cervicitis), Lyme disease, and *Helicobacter pylori*-associated ulcers (as part of combination therapy).

Contraindications:Hypersensitivity to macrolides, severe hepatic or renal insufficiency. Caution in pregnancy, cardiac arrhythmias (prolonged QT), and in children under 16 years (for tablets/injections).

Adverse effects:Gastrointestinal disturbances (diarrhea, nausea, abdominal pain), allergic skin reactions, transient liver enzyme elevations, and photosensitivity. Overdose may cause nausea, vomiting, diarrhea, and temporary hearing loss.

Ofloxacin

Pharmacological action:Ofloxacin is a broad-spectrum fluoroquinolone that exerts a bactericidal effect by inhibiting DNA gyrase and topoisomerase IV, enzymes essential for bacterial DNA replication. It is especially active against Gram-negative bacteria, including strains resistant to other antibiotics and sulfonamides.

Pharmacokinetics:

Rapidly absorbed from the gastrointestinal tract (bioavailability >95%), reaching peak plasma concentrations in 30–60 minutes. The elimination half-life is 6–7 hours, and 75–90% of the dose is excreted unchanged in urine within 24 hours.

Indications:

Used for infections of the respiratory tract, ENT organs, skin and soft tissues, urinary tract, reproductive organs, and osteomyelitis. It is also effective against Mycobacterium tuberculosis, and can be included in complex tuberculosis therapy.

Adverse effects:Occasional allergic reactions (rash, itching), gastrointestinal disturbances (nausea, abdominal pain, diarrhea), headache, dizziness, or sleep disturbances.Rarely causes hematologic changes (leukopenia, agranulocytosis, thrombocytopenia).Patients should avoid UV exposure during treatment due to the risk of photosensitization.

Derinat® (Sodium Deoxyribonucleate)

Pharmaceutical form:0.25% aqueous solution for topical and local use, colorless and transparent.Each mL contains 2.5 mg sodium deoxyribonucleate and 1.0 mg sodium chloride. Available in 10 mL dark glass bottles.

Pharmacological action:Derinat is an immunomodulatory agent that enhances both cell-mediated and humoral immune responses, increasing nonspecific resistance to infections. It normalizes inflammatory responses and promotes optimal immune function against bacterial, viral, and fungal pathogens.

Mechanism of action:

- Stimulates lymphatic drainage and detoxification functions in inflammatory foci.
- Enhances phagocytosis, tissue regeneration, and angiogenesis.
- Exhibits anti-inflammatory and cytoprotective properties.
- Promotes healing of trophic ulcers, burns, and wounds. In cases of gangrenous lesions, it facilitates natural rejection of necrotic tissue and accelerates epithelialization.

Indications:Used for rhinitis, sinusitis, ARVI, trophic ulcers, gangrene, chronic non-healing wounds (including diabetic ulcers), burns, frostbite, mucosal inflammation (oral, ocular, nasal, vaginal, rectal), and hemorrhoids.

Contraindications:

Hypersensitivity to any component of the drug.

Rationale for Drug Selection

Based on the pharmacological profiles, Sumamed (Azithromycin) was selected as the primary antimicrobial agent due to its activity against intracellular pathogens, including *Chlamydia spp.*.Ofloxacin provided a bactericidal effect against secondary bacterial flora and prevented microbial superinfection.Derinat was used as an immunomodulatory adjunct, aimed at enhancing host immune response, reducing inflammation, and promoting mucosal recovery in patients with chronic chlamydial sinusitis.

CHAPTER III. RESULTS OF THE STUDY ON THE PATHOGENETIC MECHANISMS OF CHLAMYDIAL INVOLVEMENT IN THE PARANASAL SINUSES

3.1. Clinical and laboratory characteristics of sinusitis associated with chlamydial infection

According to published data, the etiology of both acute and chronic sinusitis is highly heterogeneous and represented by numerous viral–bacterial associations [34, 77]. Given the wide variety of causative agents, it is often difficult to identify specific clinical features that would clearly distinguish inflammation of the paranasal sinuses of different etiologies. However, several researchers have noted that in patients with serous forms of chronic sinusitis, there is frequently a “lack of microbial growth” in cultures. This phenomenon is thought to be related to allergic mechanisms, anaerobic microorganisms, or viral pathogens [34].

Despite the large body of national and international literature devoted to the study of sinusitis etiology, the etiopathogenetic role of Chlamydia species in these diseases has not received sufficient scientific attention. Meanwhile, the results of clinical observations indicate that in patients suffering from chronic and recurrent acute sinusitis of chlamydial origin, both surgical interventions and prolonged courses of antibiotic therapy (even when guided by microbial sensitivity testing) often prove to be inadequate. Such patients typically require extended bacteriological and immunological rehabilitation to achieve clinical improvement [9].

This limited therapeutic response appears to be determined by a combination of factors, including the peculiarities of the host immune response and the unique life cycle of chlamydiae, as well as the ability of these microorganisms to enhance their pathogenic potential through synergistic interactions with other bacteria. These features contribute to the diverse clinical manifestations and variable course of chlamydial infections.

Accordingly, to improve the clinical and laboratory diagnosis of chlamydial lesions of the upper respiratory tract, a special diagnostic algorithm was developed and applied in the course of this research.

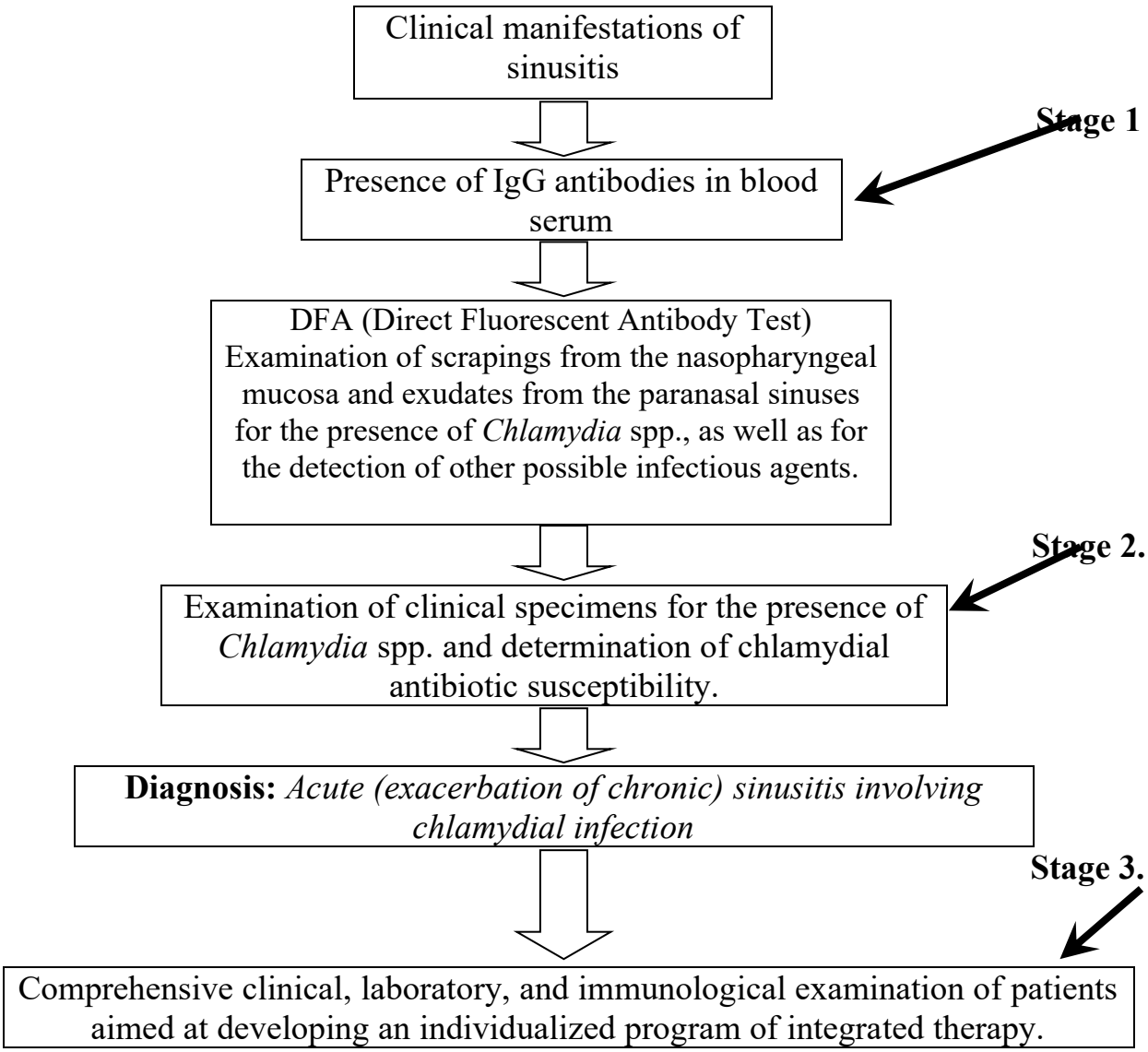

Fig. 3.1. Algorithm of clinical and laboratory diagnosis of *Chlamydia*-associated sinusitis.*(Adapted from Glaznikov L.A., Poznyak A.L., Ponidelko S.N., 2023).*

Using this diagnostic algorithm, we examined 126 patients, among whom 69 individuals (55%) had chronic sinusitis, 57 (45%) presented with acute recurrent sinusitis, and 30 participants without otorhinolaryngological pathology comprised

the control group. The diagnostic process was structured according to a three-stage principle.

At the first stage, screening of patients' blood sera was performed to detect anti-chlamydial antibodies indicating an active infection, using enzyme-linked immunosorbent assay (ELISA), along with verification of the chlamydial species (*C. pneumoniae*, *C. trachomatis*).

At the second stage, direct immunofluorescence (DIF) was employed to identify *Chlamydia* directly within the inflammatory foci and in peripheral blood leukocytes, in order to determine possible generalization of infection.

At the third stage, antibiotic susceptibility of the pathogens was assessed, the diagnosis of "Acute (exacerbation of chronic) sinusitis of chlamydial etiology" was established, and patients underwent a comprehensive clinical, laboratory, and immunological evaluation aimed at developing an individualized program of complex therapy.

Table 3.1

Comparative informativeness of various laboratory diagnostic methods for chlamydial infection in patients with sinusitis (n = 126)

Methods	C.pneumoniae	C.trachomatis	Total
DIF	68 (54%)		
DIF	38 (31%)	10 (8%)	48 (39%)
Cytoscopic Method	33 (27%)	14 (11,5%)	47 (38,5%)

As shown in Table 3.1, *Chlamydia* was detected in the clinical samples of 68 patients (54%) using polyclonal group-specific anti-chlamydial antibodies. However, the use of additional diagnostic methods enabled full identification of the infectious agents. It was established that *C. pneumoniae* was found 3.6 times more frequently than *C. trachomatis* in blood serum. The detection rates by

different diagnostic techniques were as follows: direct immunofluorescence (DIF) — 54%, enzyme-linked immunosorbent assay (ELISA) — 39%, cytoscopic method — 38.5%. The detection rate using DIF was 1.4 times higher than that obtained by ELISA and 1.5 times higher than by cytoscopy.

This, the results of this comparative analysis of diagnostic methods for chlamydial infection demonstrated a high detection rate of chlamydia in sinusitis, which justified the use of the term “sinusitis of chlamydial etiology” in our subsequent studies and made it possible to identify a number of distinct clinical features characteristic of this disease group**.**

Table 3.2

Clinical features in patients with acute sinusitis of chlamydial etiology (n = 27)

Clinical Symptoms	**Number of patients by comparative parameters**		
Localization of pain	Затылочная и теменная область	Лобная и височная область	
	16(59,3%)	11(40,7%)	
Nature of pathological discharge from the sinuses	Серозное	Гнойное	
	18(66,7%)	9(33,3%)	
Radiological findings	Parietal mucosal thickening	Fluid level	
	10(37%)	17(63%)	
Duration of the disease	More than 14 days	Up to 14 days	
	14(51,9%)	13(48,1%)	
Effectiveness of Conventional therapy	Recurrent medical consultations		
	After 6 months.	After 1 months	After 1 weeks.
	6(22,2%)	9(33,3%)	12(44,5%)

As shown in table 3.2 The clinical presentation in patients with acute sinusitis of chlamydial etiology (n = 27) was characterized by catarrhal (serous)

inflammation in 66.7% of cases and purulent inflammation in 33.3%.Radiological examination revealed a fluid level in the paranasal sinuses in 17 patients (63.0%), while mucosal thickening was detected in 10 patients (37.0%).

A notable feature in patients with acute chlamydial sinusitis was the prolonged course of the disease, with 51.9% experiencing symptoms lasting up to 14 days.Conventional baseline therapy typically used for the treatment of acute sinusitis proved to be insufficiently effective.This was evidenced by the rates of recurrent visits to inpatient care: 44.5% of patients returned within 2 weeks, 33.3% within 1 month, and only 22.2% within 6 months.

Most of those who sought repeated consultations complained of headache, mainly localized in the occipital and parietal regions (59.3%), as well as scant, thick, whitish nasal discharge, nasal obstruction, general weakness, malaise, and low-grade evening fever.

This, acute sinusitis of chlamydial etiology often presented as mild catarrhal (serous) inflammation with a recurrent course, and posed significant therapeutic challenges when treated with traditional therapeutic regimens.

Table 3.3 The table presents the characteristic clinical features of the disease in patients with chronic sinusitis of chlamydial etiology.

As shown in Table 3.3, among 39 patients with chronic chlamydial sinusitis, the clinical picture was characterized by purulent inflammation in 53.8% of cases and polypous-purulent inflammation in 46.2%.

Most patients reported headache predominantly in the occipital and parietal regions (64.1%), scant mucopurulent nasal discharge, general weakness, malaise, and low-grade fever.

Radiological examination revealed cyst-like formations of the paranasal sinuses in 38.5% of patients, fluid levels in 38.5%, and mucosal thickening in 23%.

Table 3.3

Clinical features in patients with chronic sinusitis of chlamydial etiology (n = 39)

Nature of Pain Syndrome	Occipital and/or parietal region		Frontal and/or temporal region
	25 (64,1%)		14 (35,9%)
Type of Inflammation	Polypous-purulent		purulent
	18 (46,2%)		21 (53,8%)
Radiological findings (CT, MRI)	Cystic formation in the sinuses	Fluid level	Mucosal thickening along the sinus walls
	15 (38,5%)	15 (38,5%)	9 (23%)
Duration of sinusitis exacerbation	More than 14 days		Up to 14 days
	31 (79,5%)		8 (20,5%)
Effectiveness of conventional therapy after sinus surgery	Recurrent consultations		
	After 6 months.	After 1 months	After 1 weeks.
	6 (15,4%)	14 (35,9%)	19(48,7%)
	Duration of the postoperative period		
	Up to 10 days	Up to 14 days	Up to 18 days
	10 (25,6%)	13 (33,3%)	16 (41%)

Duration of exacerbations and postoperative period

The duration of sinusitis exacerbations exceeded 14 days in 79.5% of cases. All patients with chronic sinusitis underwent surgical treatment, which included maxillary sinusotomy with the formation of an artificial anastomosis through the inferior nasal meatus and/or enlargement of the natural ostium.

The duration of the postoperative period was 18 days in 41% of patients, 14 days in 33.3%, and 10 days in 25.6%.

Evaluation of the effectiveness of traditional postoperative therapy, based on the rate of recurrent consultations, demonstrated that 48.7% of patients experienced relapse of sinusitis within two weeks after completion of standard treatment, 35.9% relapsed within 1 to 6 months, and 15.38% had recurrence after more than 6 months.

Thus, patients with chronic chlamydial sinusitis were characterized by prolonged postoperative rehabilitation, often complicated by frequent exacerbations. The clinical picture of these relapses largely resembled that observed in patients with acute sinusitis and manifested as low-symptom, sluggishly progressive purulent inflammation.

It was established that the diversity of clinical forms of chlamydial infections may be associated with generalization of the infection, involving the mucous membranes of multiple organs and systems, including those of the ear, nose, and throat (ENT) region [87].

3.2. Results of the examination of the control group

Results of the examination of the control group An analysis of the literature has shown that, due to various mechanisms of transmission — sexual, contact-household, aerosol, and others — *chlamydial infections are widely distributed among different population groups*, with more than 50% of individuals worldwide infected, according to screening serological studies [20,114,134,138,140]. Chlamydiae exhibit a pronounced tendency for long-term persistence in the host organism, often without any manifest clinical symptoms.

his epidemiological situation made it possible to form only a conditionally defined control group in our study, as some individuals—despite the absence of clinical manifestations—were found to be infected with Chlamydia.

In accordance with the objectives of this research, the control group included practically healthy individuals without any acute or chronic inflammatory diseases of the ENT organs (such as sinusitis, tonsillitis, pharyngitis, or otitis) according to

their clinical examination and medical history. The majority of this group consisted of patients who underwent surgical correction of nasal septum deviation and who reported acute respiratory illnesses no more than once or twice per year.

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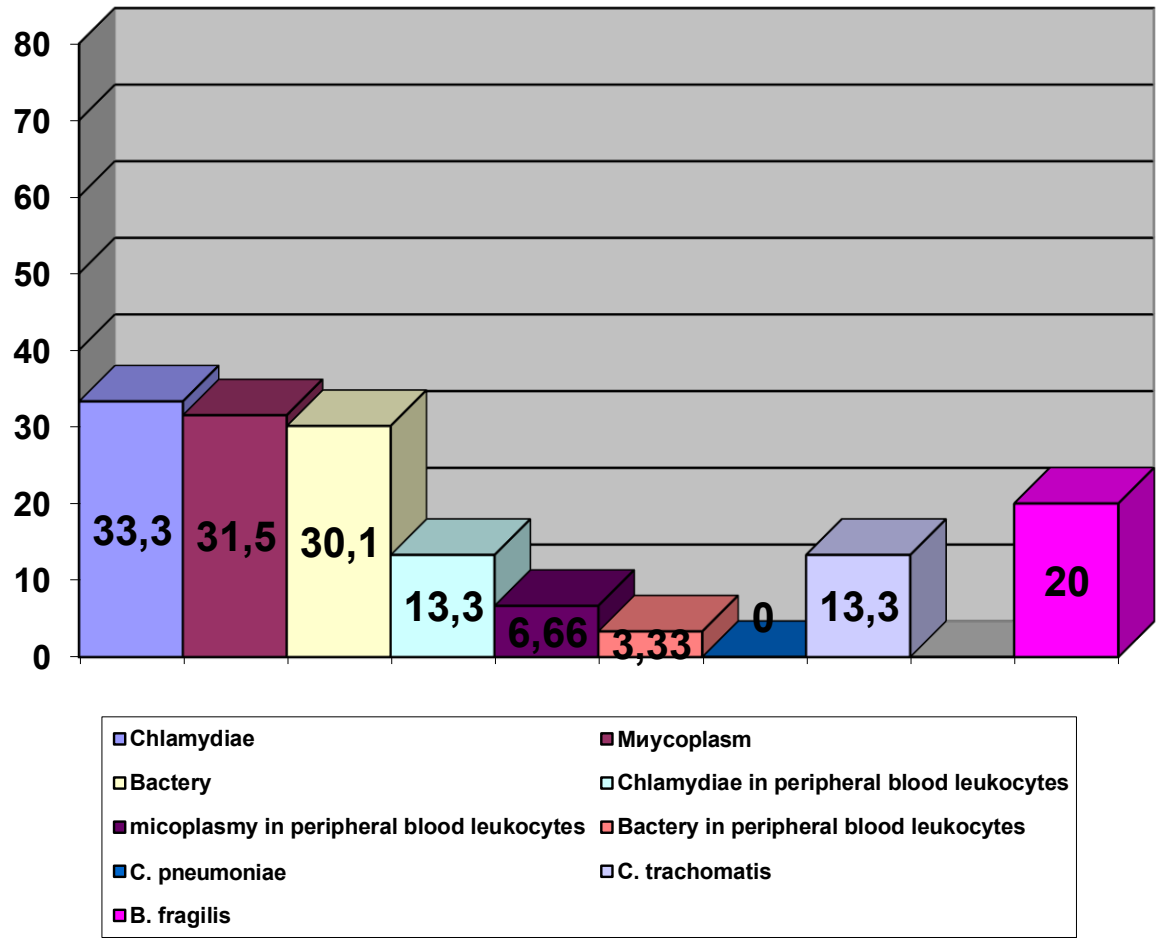

Fig. 3.2. Results of the Microbiological Examination of Individuals in the Control Group (n = 30)

As shown in Figure 3.2, *Chlamydiae* and *Mycoplasma* were detected in the epithelial scrapings of 10 individuals (33.3%) from the control group, *Mycoplasma* alone in 9 cases (31.5%), and *Bacteroides* in 9 individuals (30.1%).

Chlamydiae were identified within peripheral blood leukocytes in 2 individuals (6.0%), *Mycoplasma* in 3 (9.1%), and *Bacteroides* in 3 (10.2%). Elevated serum antibody titers against *Chlamydia pneumoniae* were found in 3 cases (11.2%), and against *Chlamydia trachomatis* in 4 (13.3%). Anti-bacteroidal antibodies with titers above 1:160 were detected in 6 cases (21.4%).

The data of the bacteriological examination of nasopharyngeal smears obtained from individuals in the control group are presented in Table 3.4. As shown in the table, more than half (56.7%) of the samples exhibited no identifiable bacterial growth. In 10 individuals (33.3%), *staphylococcal flora* was isolated—among them, pathogenic *Staphylococcus aureus* was found in 16.7%, and conditionally pathogenic strains (*Staphylococcus saprophyticus*, *Staphylococcus epidermidis*) in another 16.7%. *Streptococcal* species were represented by *Streptococcus viridans* in 6.7% of cases.

Table 3.4.

Species composition of the microflora isolated from nasopharyngeal smears of individuals in the control group

Species composition of the microflora	Control Group (n=30)	
	Number of strains	
	Abs	%
Staphylococcus aureus	5	16,7
Staphylococcus saprophyticus	2	6,7
Staphylococcus epidermidis	3	10
Streptococcus viridians	2	6,7
Escherichia coli	1	3,3
Not differentiated	17	56,7

Table 3.5

Indices of lymphocyte count and their subpopulations in peripheral blood (m±m) in the lymphocytotoxic test (lctt) among individuals of the control group (n = 30)

Total leukocytes	Relative (%		Absolute (×10⁶/μL)	
Lymphocytes	35,3±7,222	N28-39	5,0±0,925	N4-8
CD3 + (T-Lymphocytes)	48,1±6,060*	N50-76	1,85±0,532	N1,6-2,4
CD4 + (Т-хелперы)	27,5±3,422*	N31-46	0,89±0,280**	N1,1-1,7
CD8 + (Т-супрессоры)	19,1±2,925*	N26-40	0,51±0,154**	N0,7-1,1
Отношение CD4/CD8 ИРИ	1,44±0,100	N1,0-1,5	0,36±0,128**	N0, –0,9
CD20+(B-Lymphocytes)	16,1±6,185	N11-16	0,35±0,072	N0,2-0,4
CD25(T-suppressor ratio ИЛ-2)	16±7,590	N13-24	0,31±0,088**	N0,34-0,72
CD16 + NK- T-suppressor ratio	12,8±5,045	N9-19	0,26±0,076	N0,2-0,4

Note: Statistical significance of differences compared with normal values: $p < 0.01$; **p** < 0.05.

As shown in Table 3.5 The total leukocyte count was 5 ± 0.925 × 10⁶/μL, which falls within normal reference values. The relative (35.3 ± 7.222%) and absolute 1.85 ± 0.532 × 10⁶/μL) numbers of lymphocytes in peripheral blood were also within physiological limits.

However, both the relative (48.1 ± 6.060%, $p < 0.01$) and absolute (0.89 ± 0.280 × 10⁶/μL, $p < 0.05$) counts of $CD3^+$ T lymphocytes were reduced. A similar decrease was observed in $CD4^+$ T helper cells (relative – 27.5 ± 3.422%, $p < 0.01$; absolute – 0.51 ± 0.154 × 10⁶/μL, $p < 0.05$) and $CD8^+$ T suppressor cells (relative – 19.1 ± 2.925%, $p < 0.01$; absolute – 0.36 ± 0.128 × 10⁶/μL, $p < 0.05$). Despite this, the

$CD4^+/CD8^+$ ratio (immunoregulatory index, IRI) remained within normal range at 1.44 ± 0.100.

Normal values were also observed for $CD20^+$ B lymphocytes (relative – 16.1 ± 6.185%; absolute – 0.35 ± 0.072 × 10^6/μL) and $CD16^+$ NK cells (relative – 12.8 ± 5.04%; absolute – 0.26 ± 0.076 × 10^6/μL).Notably, a slight decrease in the absolute count of $CD25^+$ cells (IL-2 receptor) was detected (0.31 ± 0.088 × 10^6/μL, $p < 0.05$), while the relative value (16 ± 7.590%) remained within normal limits.

Thus, in apparently healthy individuals with asymptomatic chlamydial carriage, there was evidence of immune system tension manifested by a mild deficiency in the T-cell component of immunity.

Table 3.6

Levels of Interleukin-2 (IL-2) and Interleukin-8 (IL-8) Production by Peripheral Blood Cells in Individuals of the Control Group

Interleukin-2 (IL-2) and Interleukin-8 (IL-8) production by peripheral blood cells						
Cytokines	Serum concentration		Cytokine production			
			Spontaneous		Induced	
ИЛ-2(pg/ml)	0	N0	0	N0	2,1±0,36	N10-25
ИЛ-8(pg/ml)	0	N0	375±113	N0-500	5160±1099**	N<500

Note: The difference from normal values is statistically significant; **p < 0.05.**

As shown in Table 3.6, individuals in the control group demonstrated a moderate increase in induced IL-8 production, amounting to 5160 ± 1099 pg/mL ($p < 0.05$).

According to the data presented in Figure 3.2, the total leukocyte count was 5 ± 0.925 × 10^6/mL (normal range = 4–8 × 10^6/mL). The band neutrophils accounted for 1.5 ± 0.271 % (N = 1–6), segmented neutrophils — 53 ± 6.124 % (N = 47–72), basophils — 0.55 ± 0.127 % (N = 0–0.5), eosinophils — 2.25 ± 0.310 % (N = 0.5–

5.0), monocytes — 8.5 ± 0.299 % (N = 3–11), and lymphocytes — 35.3 ± 2.22 % (N = 28–39).

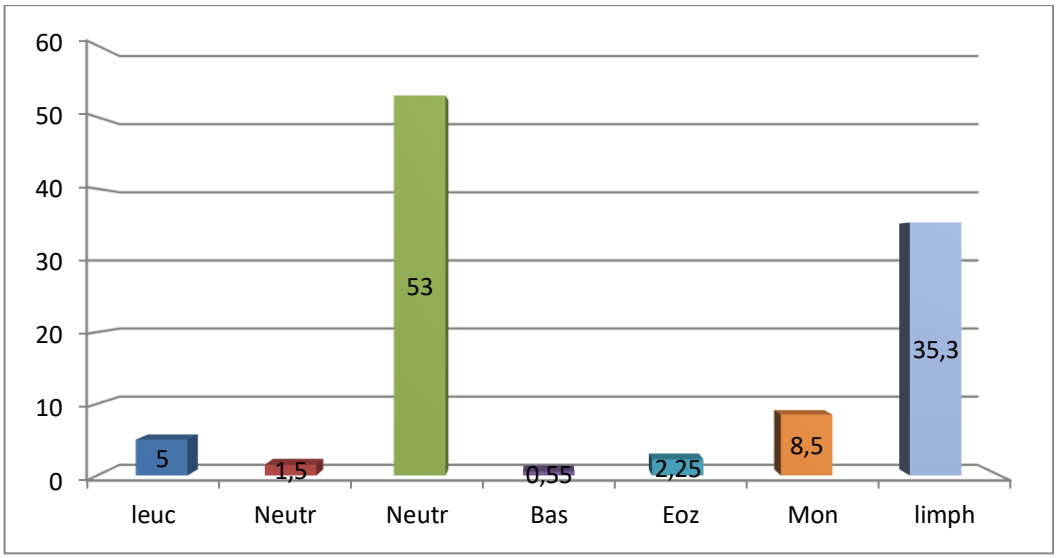

Figure 3.3. Routine hematological parameters in the control group.

Overall, the routine hematological parameters in individuals of the control group remained within normal limits.

3.3. Results of the examination of patients with acute sinusitis

The findings of the microbiological assessment of patients with acute sinusitis are illustrated in Figure 3.4.

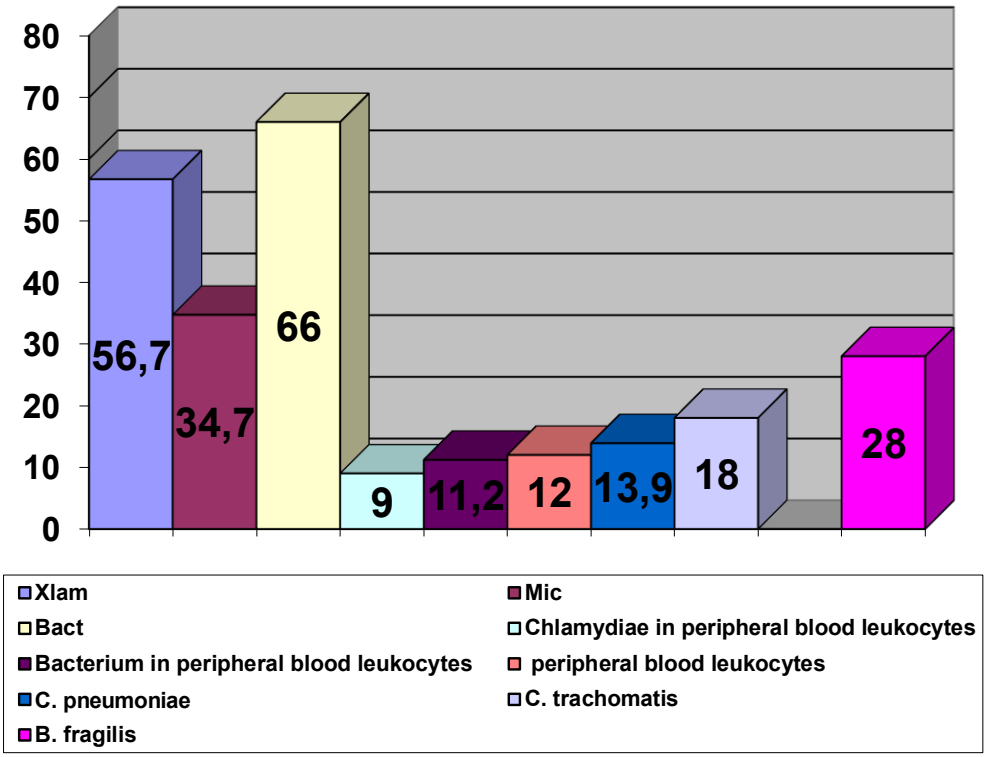

Figure 3.4. Results of microbiological examination in patients with acute sinusitis *(n = 27)*

As shown in Figure 3.4, among patients with acute sinusitis, *Chlamydiae* were detected in the scraping material and inflammatory exudate from the sinuses in 15 (56.7%) cases, *Mycoplasma* in 9 (34.7%), and *Bacteroides* in 18 (66.0%) of the examined patients. *Chlamydiae* were identified in the peripheral blood leukocytes of 2 (9.0%) individuals, *Mycoplasma* in 3 (11.2%), and *Bacteroides* in 3 (12.0%) cases. Elevated antibody titers to *C. pneumoniae* were detected in 4 (13.9%) cases, and to *C. trachomatis* in 5 (18.0%) cases. Antibodies to *Bacteroides* in titers exceeding 1:160 were found in 7 (28.0%) patients.

A bacteriological study of the discharge from the paranasal sinuses (PNS) was also conducted to determine the predominant microflora. A total of 27 patients with acute sinusitis were examined. The results of the bacteriological analysis of the sinus discharge are presented in Table 3.7.

Table 3.7.

Species composition of microorganisms isolated from paranasal sinus discharge

Alternative (more formal scientific phrasing):	Acute sinusitis (n=27)	
	Number of strains	
	Abs	%
Streptococcus pyogens	3	11,1
Staphylococcus aureus	6	22,2
Streptococcus viridians	3	11,1
Enterococcus faecium	4	14,81
Neiseria spp.	2	7,4
No differ	9	33,3

Table 3.8

The etiopathogenetic role of *Chlamydia–Mycoplasma–Bacteroides–Streptococcus* associations in patients with acute sinusitis (n = 27)

Chlamydia–Mycoplasma–Bacteroides association	Abs	%
Chlamydia–Mycoplasma–Bacteroides–Streptococcus association	5	18,5
Chlamydia–Bacteroides association	2	7,4
Chlamydia–Bacteroides–Streptococcus association	6	22,2
Chlamydia–Mycoplasma association	2	7,4
Mycoplasma–Bacteroides association	1	3,7
Bacteroides–Streptococcus association	2	7,4
Bacteroides (monoinfection)	2	7,4
Mycoplasma–Streptococcus association	3	11,1
Mycoplasma (monoinfection)	1	3,7
Streptococcus (monoinfection)	2	7,4
Chlamydia–Mycoplasma–Bacteroides association	1	3,7

Table 3.9 Indices of lymphocyte counts and their subpopulations in peripheral blood in the lymphocytotoxicity test (LCTT) in patients with acute sinusitis of *Chlamydia* etiology (M ± m)

Parameter	**Relative (%)**		**Relative (%)**	
Общие лейкоцит			6,8±1,020**	N4-8
Lymphocytes	41,0±4,932*	N28-39	1,05±0,481**	N1,6-2,4
CD3 + (T-lymphocytes)	49,0±0,300*	N50-76	0,44±0,481**	N1,1-1,7
CD4 + (T-helpers)	28,6±2,848*	N31-46	0,25±0,115**	N0,7-1,1
$D8^+$ (T-suppressors))	20,0±2,993*	N26-40	0,19±0,074**	N0,5-0,9
CD4/CD8 ratio (Immunoregulatory index, IRI)	1,44±0,101	N1,0-1,5		
$CD20^+$ (B-lymphocytes))	18,6±4,573	N11-16	0,16±0,056**	N0,2-0,4
$CD25^+$ (IL-2 receptor)	20,5±8,482	N13-24	0,29±0,045	N0,34-0,72
$CD16^+$ NK cells (Natural killer cells)	19,6±6,117	N9-19	0,11±0,032**	N0,2-0,4

Note: The indicators differ significantly from those of the control group;

- – $p < 0.01$; ** – $p < 0.05$.

As shown in Table 3.9, the total leukocyte count was **6.8 ± 1.020 × 10^6/mL**, which remained within the normal range but was higher than the corresponding values in the control group ($p < 0.05$). A moderate increase in the relative content of lymphocytes (**41.0 ± 4.932%**, $p < 0.01$) was observed against the background of a decrease in the relative levels of T-lymphocyte subpopulations. The CD4/CD8 ratio remained within normal limits (**1.44 ± 0.101**).

It should be noted that, despite normal relative values of B-lymphocyte subpopulations, there was a decrease in the following absolute parameters compared with the norm and control: **$CD20^+$ (B-lymphocytes)** — relative **18.6 ± 4.573%**, absolute **0.16 ± 0.056**; **$CD16^+$ NK cells** — relative **19.6 ± 6.117%**, absolute **0.11 ± 0.032**. In contrast, the parameters of **$CD25^+$ (IL-2 receptor)** —

relative **20.5 ± 8.482%**, absolute **0.29 ± 0.045** — were practically within normal limits.

Thus, in patients with **acute chlamydial sinusitis**, a relative lymphocytosis was accompanied by a statistically significant decrease in the absolute number of all lymphocyte subpopulations, most pronounced in the T-cell compartment**.**

Table 3.10.

Indicators of IL-2 and IL-8 production by peripheral blood cells in patients with acute chlamydial sinusitis.

Alternative (expanded scientific phrasing, suitable for tables or figure captions): Cytokine production (IL-2 and IL-8) by peripheral blood mononuclear cells						
Cytokin	Serum concentration		Cytokine production			
			Spontan		Induced	
Il -2 (Id/ml)	0	N0	0	N0	4,17±0,43	N10-25
Il-8(Pg/ml)	0	N0	2006±495**	<500	8075±2196**	N<500

Note: The indicators differ significantly from those of the control group; **p < 0.05**

As shown in Table 3.10, patients with acute sinusitis demonstrated a significant increase in both spontaneous (2006 ± 495 pg/mL; $p < 0.05$) and induced production of IL-8 (8075 ± 2196 pg/mL; $p < 0.01$) in the blood serum compared with normal values and the control group. These findings indicate an active inflammatory response of the host organism and enhanced migration of neutrophilic granulocytes..

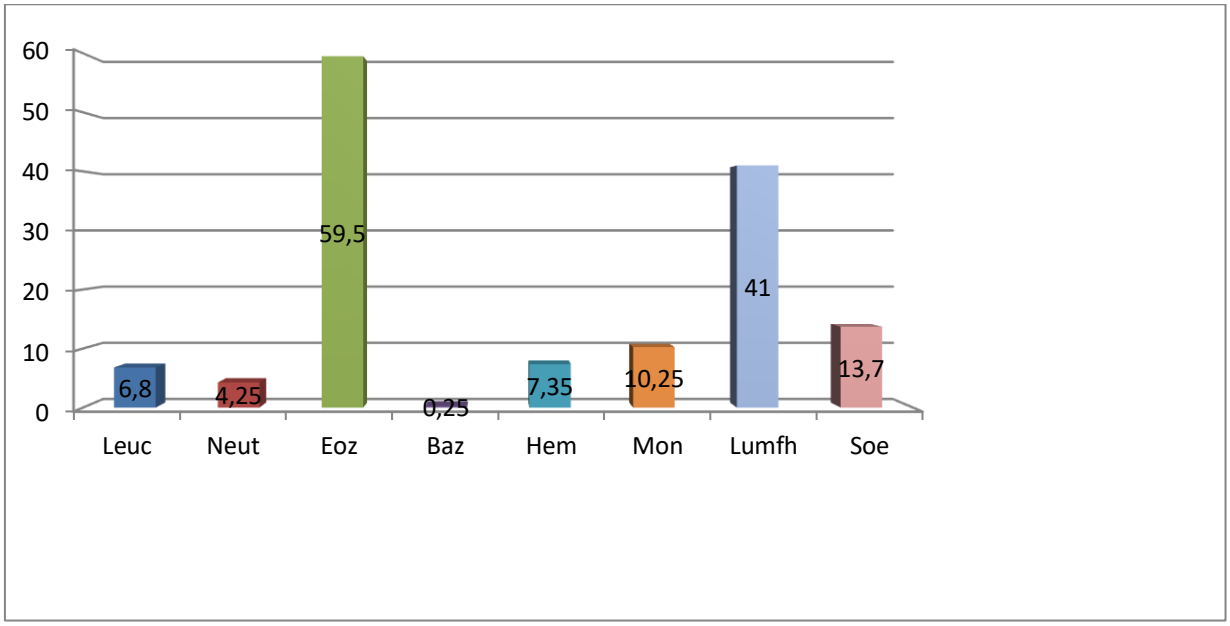

Figure 3.5. General clinical blood parameters in patients with acute sinusitis of chlamydial etiology.

As shown graphically in Figure 3.5, the general hematological parameters in patients with acute sinusitis of chlamydial etiology differed from those in the control group by an increase in ESR (13.7 ± 2.54 mm/h), stab neutrophils (4.25 ± 1.019%), segmented neutrophils (59.5 ± 4.119%; N = 47–72), eosinophils (1.35 ± 0.833%; N = 0.5–5.0), monocytes (10.25 ± 2.577%; N = 3–11), and relative lymphocytosis (41 ± 4.932%; N = 28–39; $p < 0.05$), indicating a moderate inflammatory response.

The increased production of IL-8 (a neutrophil chemotactic factor) in the inflammatory focus likely stimulated macrophage activity in intracellular chlamydial destruction, since the contact interaction between neutrophilic granulocytes and macrophages leads to neutrophil denaturation with the release of lysosomal cationic proteins possessing high antichlamydial activity, which are subsequently engulfed by macrophages. The resulting heterolysosomal macrophages acquire the ability to induce the destruction and death of phagocytosed chlamydiae [76].

Thus, acute sinusitis of chlamydial etiology was characterized by a more pronounced local inflammatory response, which was probably associated with a higher antigenic load on the protective mechanisms of the mucous membranes of the upper respiratory tract due to the involvement of intracellular pathogens (*Chlamydia*) as part of polymicrobial associations.

3.4. Results of examination in patients with chronic sinusitis

In patients with chronic sinusitis, *Chlamydia* was detected in 27 cases (69.3%) in the scraping material and inflammatory exudate obtained from the paranasal sinuses. *Mycoplasma* was identified in 13 cases (32.6%), and *Bacteroides* in 48.2% of the examined patients. In the peripheral blood leukocytes, *Chlamydia* was found in 4 patients (12.0%), *Mycoplasma* in 8 (21.2%), and *Bacteroides* in 8 (20.0%). Elevated antibody titers to *C. pneumoniae* were diagnosed in 13 cases (32.7%), and to *C. trachomatis* in 7 cases (18.7%). Anti-*Bacteroides* antibodies at titers above 1:160 were detected in 20 patients (52.7%).

Thus, an increase in the number of *Chlamydia*-infected patients was noted among those with chronic sinusitis, while the incidence of *Mycoplasma* involvement remained practically unchanged compared to both the control group and patients with acute sinusitis.

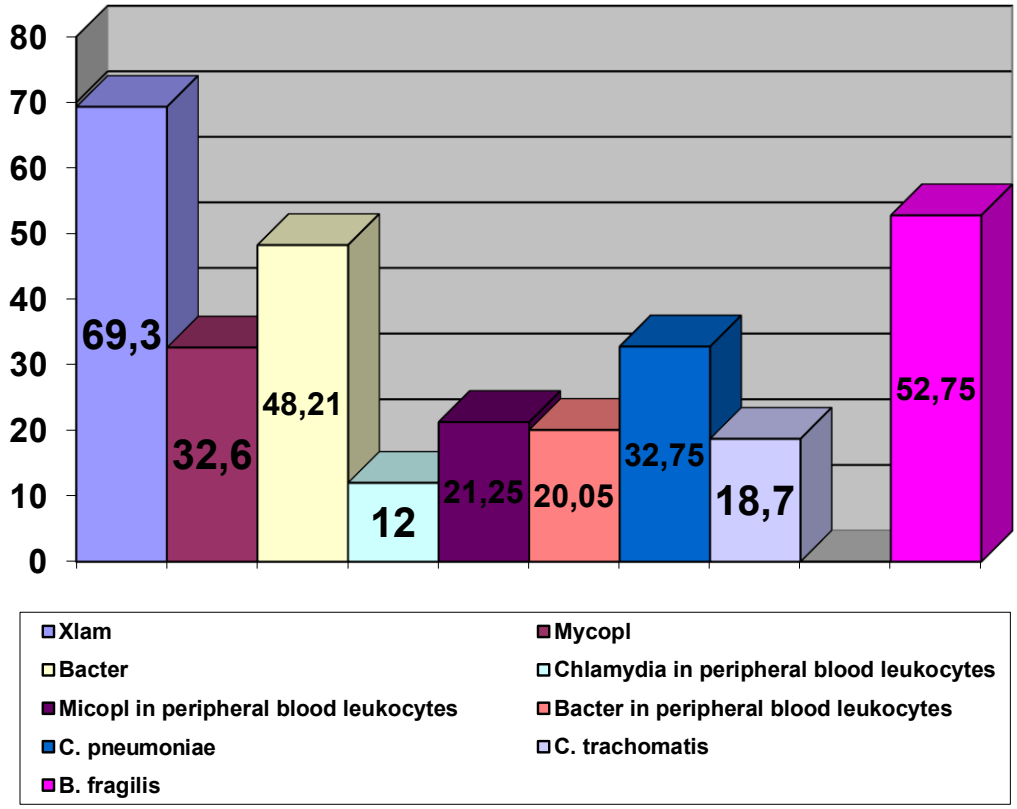

Figure 3.6. Results of microbiological examination in patients with chronic sinusitis (n = 39).

It was established that approximately 33.2% of clinically healthy individuals were asymptomatic carriers of *Chlamydia*, *Mycoplasma*, and *Bacteroides*. The development of acute sinusitis was accompanied by an increase in the proportion of patients infected with *Chlamydia* (56.7%) and *Bacteroides* (66.0%). Based on the obtained data, it can be concluded that *Chlamydia*—primarily *C. pneumoniae*—is an important etiological factor contributing to the chronicity of sinusitis. *Bacteroides*, in association with *Chlamydia* infection, was found to be equally responsible for both acute (66.0%) and chronic (48.2%) inflammation of the paranasal sinuses. *Mycoplasma* infection, on the other hand, did not appear to be a significant independent etiological factor in the development of sinusitis, since it was detected with similar frequency across all study groups; however, when present in bacterial associations, it likely aggravated the course of the disease.

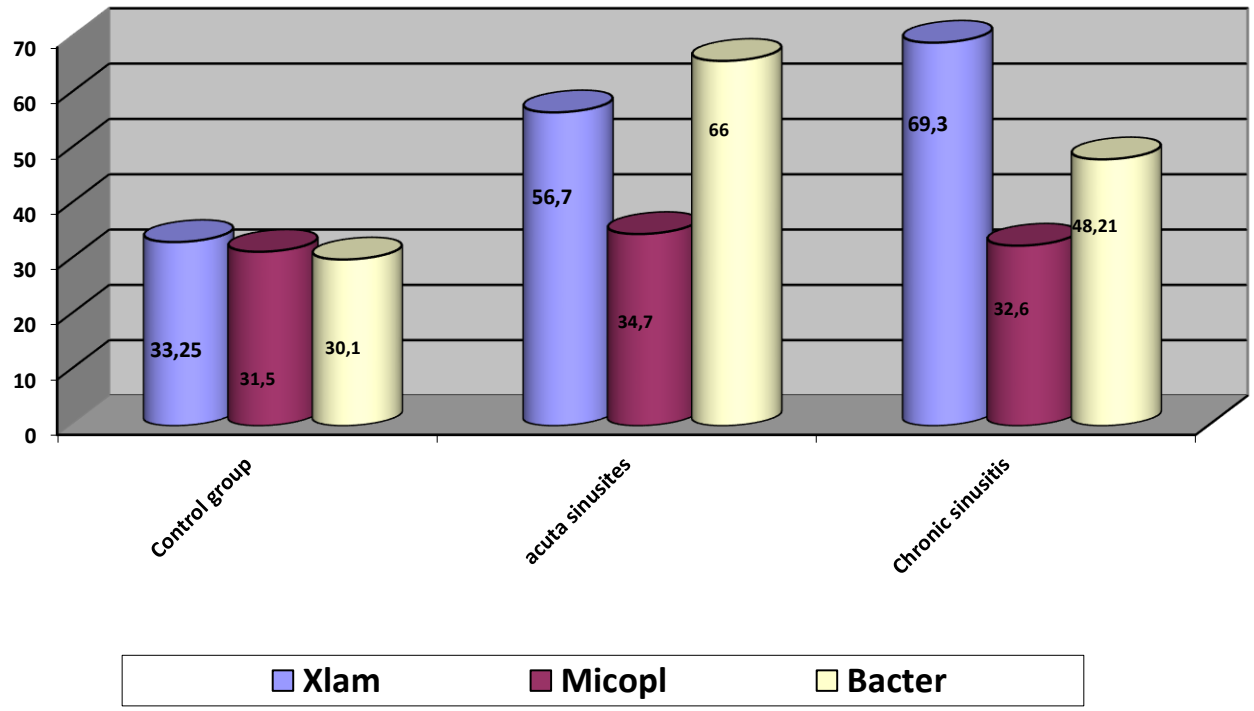

Figure 3.7. Comparative analysis of the etiopathogenetic role of Chlamydia, Mycoplasma, and Bacteroides in the development of acute and chronic sinusitis, and in asymptomatic carriage in the control group.

Furthermore, in the group of patients with chronic sinusitis, there was an observed increase in the indicators of transient bacteremia (generalization) of *Mycoplasma* and *Bacteroides* infections. Specifically, *Mycoplasma* was detected in the peripheral blood leukocytes of 21.2% of cases, and *Bacteroides* in 20.0%, compared with 15.0% and 11.0% in the control group and among patients with acute sinusitis, respectively. These findings were not significantly different from similar parameters in the control group (13.3%).

These observations may indicate the development of chlamydial chroniosepsis, involving multiple organs and systems in the pathological process—occurring to a comparable degree among patients with acute and chronic sinusitis of chlamydial etiology, as well as in asymptomatic carriers.

Table 3.11

Species composition of the microflora isolated from the inflammatory exudate of the paranasal sinuses in patients with chronic sinusitis (n = 39)

Species composition of the microflora	Cronic sinusites (n=39)	
	Number of strains	
	Абс	%
Staphylococcus epidermidis+Str.viridans	13	33,3
Staphylococcus aureus	6	15,4
Streptococcus viridans	4	10,3
Pseudomonas aeruginosa	7	17,9
Citrobacter	3	7,7
Enterobacter	2	5,1
No growth	4	10,3

As seen from the data presented in Table 3.11, the microflora could not be differentiated in 10.2% of the examined cases. Almost half of the patients (48.7%) exhibited staphylococcal flora (*Staphylococcus aureus* and *Staphylococcus epidermidis*), with 33.3% of these occurring in association with streptococci.

Thus, in chronic sinusitis of chlamydial etiology, pathogenic staphylococci were most frequently identified as microbial associates — in 48.7% of cases.

As shown in Table 3.12, chlamydiae as a monoinfection were detected only in 3 (7.7%) patients, while in the remaining cases of chronic sinusitis, chlamydiae were found in combination with other microorganisms.

Table 3.12

Etiopathogenetic role of chlamydia–mycoplasma–bacteroides–staphylococcus associations in patients with chronic sinusitis

Microbial Associations	Abs	%
Chlamydia–Mycoplasma–Bacteroides	5	12,8
Chlamydia–Mycoplasma–Bacteroides–Staphylococcus	6	15,4
Chlamydia–Bacteroides	5	12,8
Chlamydia–Bacteroides–Staphylococcus	7	17,9
Chlamydia–Mycoplasma	4	10,3
Mycoplasma–Bacteroides–Staphylococcus	2	5,1
Chlamydia *(monoinfection)*	3	7,7
Bacteroides *(monoinfection)*	3	7,7
Mycoplasma *(monoinfection)*	1	2,6
Staphylococcus *(monoinfection)*	3	7,7

Chlamydia–Mycoplasma–Bacteroides associations were identified in 28.2% of cases, and in half of these patients (15.4%) the microorganisms were found in combination with Staphylococcus species. Chlamydia–Bacteroides associations were also diagnosed in 12.8% of cases. Bacteroides and Staphylococcus (as monoinfections) were each detected in 3 patients (7.7%).

Thus, the microflora in chronic sinusitis was polymicrobial in nature, predominantly represented by various Chlamydia–Mycoplasma–Bacteroides–Staphylococcus associations.

Table 3.13

Indices of lymphocyte count and their subpopulations in peripheral blood (m ± m) in the lymphocytotoxic test (lctt) in patients with chronic sinusitis of chlamydial etiology

	Relative (%) (%)		Abs (bl\mkl)	
Total leukocytes			4,8±0,342	N4-8
Lymphocytes	30,0±5,235	N28-39	2,16±0,439	N1,6-2,4
CD3+(T-lim)	53,0±4,131	N50-76	1,05±0,202**	N1,1-1,7
CD4+(T-xel)	30,0±2,451*	N31-46	0,46±0,026**	N0,7-1,1
CD8 + (T-supres)	21,0±2,818*	N26-40	0,41±0,059**	N0,5-0,9
CD4/CD8 ratio (Immunoregulatory Index – IRI)	1,31±0,059	N1,0-1,5		
CD20+(B-lymph)	16,5±2,927	N11-16	0,35±0,037	N0,2-0,4
CD25+(Receptor IL-2)	10,0±2,248*	N13-24	0,15±0,010**	N0,34-072
$CD16^+$ (Natural killer – NK cells)	10,8±1,507	N9-19	0,24±0,025	N0,2-0,4

Note: The indicators differ significantly from those in the control group and in patients with acute sinusitis; *$p < 0.01$; **$p < 0.05$.

As shown in Table 3.13, the total leukocyte count in peripheral blood was $4.8 \pm 0.342 \times 10^6/\mu L$. The relative lymphocyte content was 30.0 ± 5.235 %, and the absolute count was $2.16 \pm 0.439 \times 10^6/\mu L$, both within normal limits and not significantly different from those in the control group or in patients with acute sinusitis.

The relative number of $CD3^+$ T-lymphocytes (53.0 ± 4.131 %) remained within normal values, while their absolute count ($1.05 \pm 0.202 \times 10^6/\mu L$) corresponded to that of the control group but was significantly higher than in patients with acute sinusitis ($p < 0.05$).

The $CD4^+$ T-helper subset demonstrated a relative value of 30.0 ± 2.451 % ($p < 0.01$) and an absolute count of $0.46 \pm 0.026 \times 10^6/\mu L$ ($p < 0.05$). The $CD8^+$ T-suppressor (cytotoxic) subset showed relative values of 21.0 ± 2.818 % ($p < 0.01$) and absolute values comparable to those observed in acute sinusitis.

Examination of B-lymphocyte subpopulations revealed a marked decrease in the $CD25^+$ (IL-2 receptor) population, with relative values of 10.0 ± 2.248 % ($p < 0.01$) and absolute values of 0.15 ± 0.010 × 10^6/μL ($p < 0.05$) compared with normal and control data. Meanwhile, $CD20^+$ (B-lymphocytes) remained within normal limits (relative – 16.5 ± 2.927 %, absolute – 0.35 ± 0.037 × 10^6/μL), as did $CD16^+$ (NK cells) (relative – 10.8 ± 1.507 %, absolute – 0.24 ± 0.025 × 10^6/μL).

Thus, in patients with chronic sinusitis of chlamydial etiology, in contrast to those with acute forms, there was a moderate reduction primarily in the absolute number of $CD4^+$ (T-helper) and $CD8^+$ (T-cytotoxic) subpopulations, as well as a decrease in lymphocyte IL-2 receptor expression ($CD25^+$), reflecting mild suppression of cellular immune activation mechanisms.

Table 3.14

Indices of il-2 and il-8 production by peripheral blood cells in patients with chronic sinusitis of chlamydial etiology

Production of IL-2 and IL-8 by peripheral blood cells						
Cytokine |	**Serum concentration (pg/mL)**		Cytokine Production (pg/mL)			
			Spontaneous |		**Induced**	
Il-2	0	N0	0	N0	5,81±0,325	N10-25
Il-8	0	N0	1575±917**	N<500	11200±1185**	N<5000

Note: The indicators differ significantly from those in the control group and in patients with acute sinusitis; **$p < 0.05$.

As shown in Table 3.14, in patients with chronic sinusitis of chlamydial etiology, examined during the postoperative period (after surgical opening of the paranasal sinuses), there was a marked alteration in cytokine activity.

Thus, surgical intervention in the paranasal sinuses (PNS) contributed to a worsening of the existing immunodeficiency state in patients with chronic sinusitis. A significant increase was observed in both spontaneous IL-8 production

(1575 ± 917 pg/mL) and induced IL-8 production (11 200 ± 1185 pg/mL; $p < 0.05$) in serum compared with normal and control values.

This pattern indicated a heightened inflammatory response of the host organism and enhanced migration of neutrophilic granulocytes, similar to the response seen in patients with acute sinusitis.

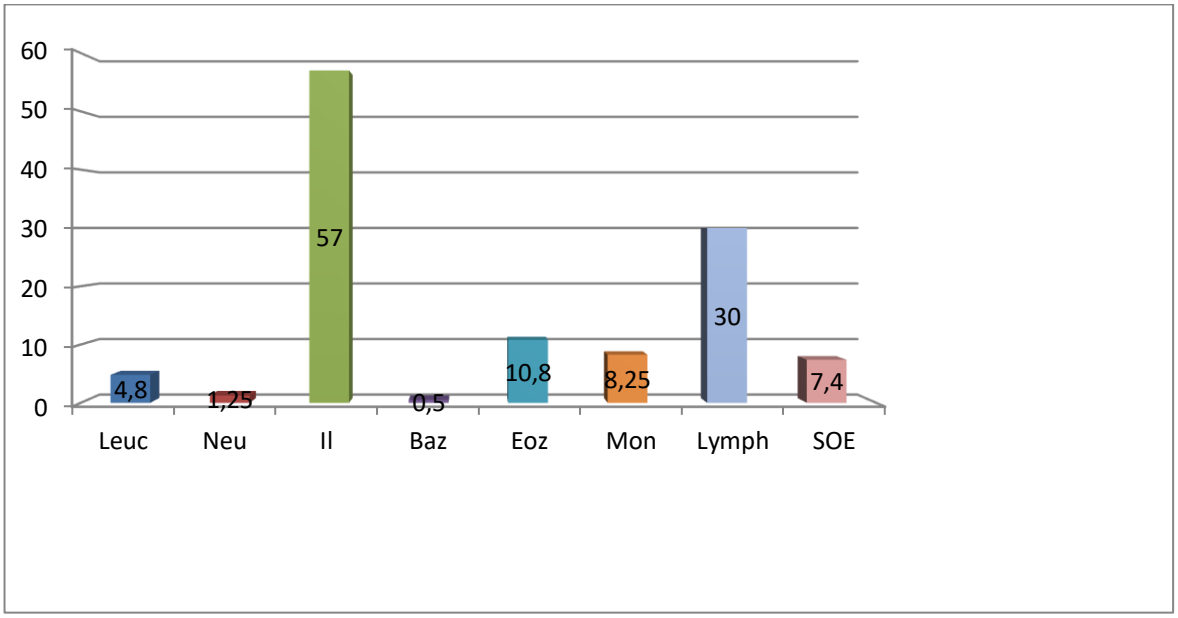

Fig. 3.8. General hematological parameters in patients with chronic sinusitis of chlamydial etiology.

As shown in Figure 3.8, the general blood parameters in patients with chronic chlamydial sinusitis were virtually within normal limits and did not significantly differ from those of the control group: erythrocyte sedimentation rate (ESR) — 7.4 ± 2.029 mm/h, band neutrophils — 1.25 ± 0.170%, segmented neutrophils — 57.0 ± 10.758%, monocytes — 8.25 ± 1.236%, and lymphocytes — 30.0 ± 5.235%.

However, these patients demonstrated a more pronounced eosinophilia in peripheral blood (10.1 ± 3.794%) compared to patients with acute sinusitis ($p < 0.05$).

Figure 3.9 presents the comparative levels of spontaneous and induced IL-8 production by inflammatory exudate cells from the paranasal sinuses (PNS) in

patients with chronic sinusitis of chlamydial etiology and in those not infected with Chlamydia.

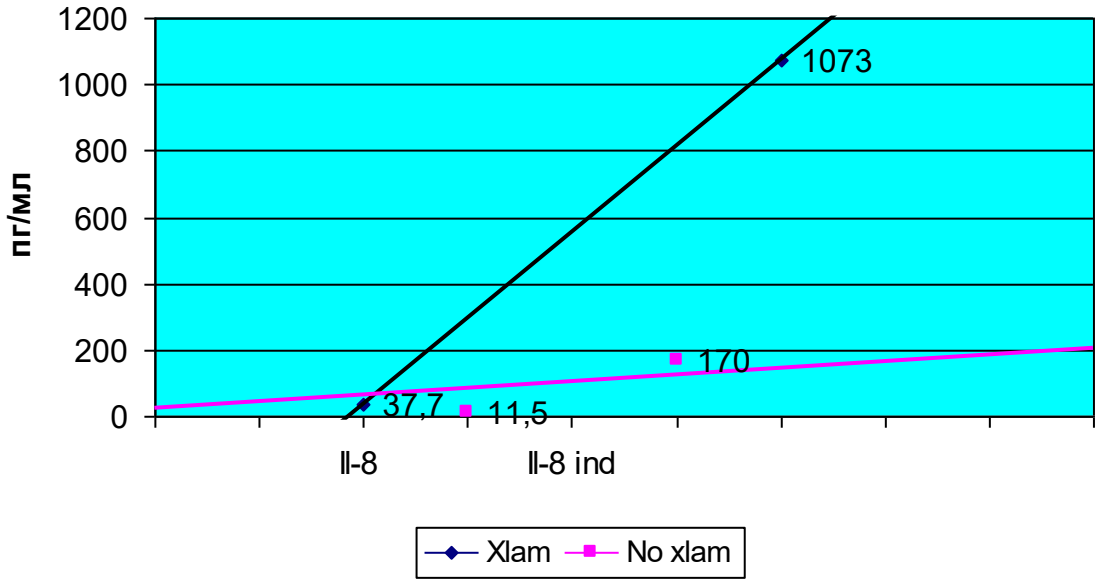

Fig. 3.9. Comparative indicators of spontaneous and induced IL-8 production by inflammatory exudate cells from the paranasal sinuses in patients with chronic sinusitis.

As shown in Figure 3.9, in the group of patients with chronic sinusitis of chlamydial etiology, the spontaneous production of IL-8 by inflammatory exudate cells from the paranasal sinuses was significantly lower (11.5 ± 3.37 pg/mL; $p < 0.05$) than in those not infected with Chlamydia (37.7 ± 8.291 pg/mL). Conversely, the induced production of this cytokine in chlamydia-infected patients was significantly higher (1073 ± 210 pg/mL) compared to uninfected individuals (170 ± 73.77 pg/mL; $p < 0.05$).

At the same time, both spontaneous and induced cytokine production values were reduced compared to those observed in patients with acute sinusitis, indicating a less pronounced local inflammatory response in the chronic form of the disease.

An increase in local IL-8 production and the development of inflammation are inevitably accompanied by changes in the cellular composition of nasal secretions. Therefore, a cytological examination of the inflammatory exudate from the paranasal sinuses and nasal lavage samples was performed. The results are presented in Table 3.15.

Table 3.15

Cellular composition (M ± m) of inflammatory exudate from the paranasal sinuses and nasal lavages in patients with sinusitis and in the control group

	Acute sinusitis and exacerbation of chronic sinusitis (%)	Control (%)
Neutrophils	71,8±4,380*	53,8±3,950
Macrophages	11,3±1,894*	12,8±1,425
Lymphocytes	14,7±1,939*	30,2±1,888
Eosinophils	2,2±0,926*	3,2±0,761

Note: The indicators differ significantly from those in the control group; *p < 0.05.

The cytogram data of the inflammatory exudate from the paranasal sinuses presented in Table 3.15 indicate a statistically significant increase in the relative number of neutrophils (71.8 ± 4.380; $p < 0.05$), which correlates with enhanced local production of IL-8, alongside a decrease in the content of lymphocytes (14.7 ± 1.939; $p < 0.05$) and macrophages (11.3 ± 1.894; $p < 0.05$).

Thus, the mechanisms of local immune defense in sinusitis are largely determined by the massive migration of neutrophilic granulocytes into the inflammatory focus under the influence of IL-8.

In summary, the obtained results justify the need for anti-chlamydial therapy in patients with chronic sinusitis of chlamydial etiology (including asymptomatic forms), taking into account the antibiotic susceptibility of all microbial associates

as well as the development of individualized regimens of local and systemic immunotherapy.

CHAPTER IV. PRINCIPLES OF TREATMENT OF INFLAMMATORY DISEASES OF THE PARANASAL SINUSES OF CHLAMYDIAL ETIOLOGY

4.1. Rationale for rational treatment regimens for inflammatory diseases of the paranasal sinuses of chlamydial etiology

According to numerous researchers, the treatment of chlamydial infection should be comprehensive, incorporating antibiotic therapy, immunotherapy, bacteriotherapy, and local treatment of mucosal lesions [88,102].

Our analysis of the antibiotic susceptibility of Chlamydia to macrolide group drugs, which are currently the main agents used for etiotropic therapy of chlamydial infections, is presented in Figure 4.1.

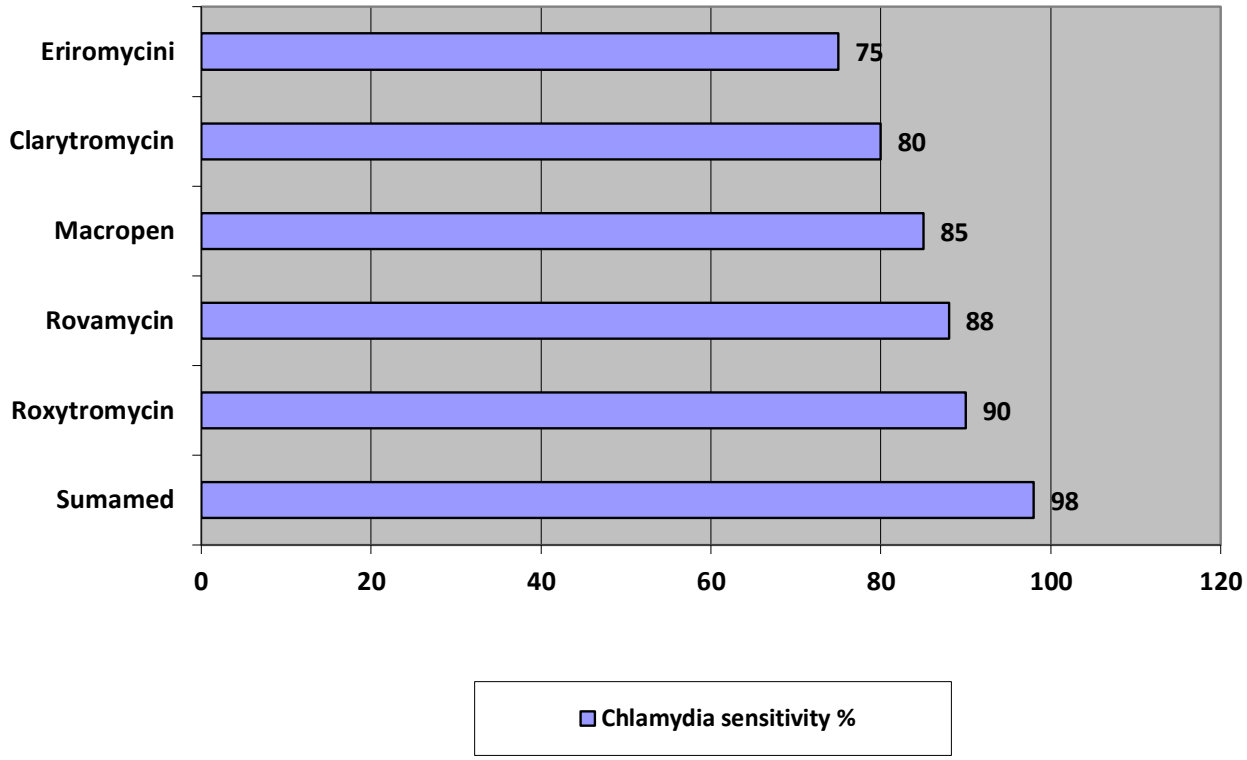

Figure 4.1. Comparative sensitivity of *Chlamydia* to macrolide group antibiotics according to literature data.

As shown in Figure 4.1, *Chlamydia pneumoniae* demonstrated the highest sensitivity to Sumamed (Azithromycin) — 98.0%, and Roxithromycin — 90.0%, with a somewhat lower sensitivity to Rovamycin (88.0%), Macropen (85.0%), Clarithromycin (80.0%), and Erythromycin (75.0%).

Thus, based on the obtained results of antibiotic susceptibility testing, the most effective etiological agent against *Chlamydia* was found to be the third-generation macrolide Sumamed (Azithromycin) produced by *Teva*. Consequently, this antibiotic was used as the primary anti-chlamydial drug within the basic etiotropic therapy regimen for patients with sinusitis of chlamydial etiology.

According to multiple recent studies, Sumamed also exhibits high activity against the most frequently encountered microbial associates observed in our work — namely, Mycoplasma, Bacteroides, Streptococcus, and Staphylococcus species [54, 90, 91].

To ensure the objectivity of therapeutic outcomes, patients were grouped according to the clinical form of sinusitis (based on disease duration) and PIF test results (Direct Immunofluorescence Method).

Group I – Patients with **chronic sinusitis associated with chlamydial infection** (n = 39);

Group II – Patients with **chronic sinusitis of non-chlamydial etiology** (n = 30);

Group III – Patients with **acute sinusitis associated with chlamydial infection** (n = 27);

Group IV – Patients with **acute sinusitis of non-chlamydial etiology** (n = 30).

All 39 patients with chronic sinusitis underwent surgical treatment. Among them, 23 patients (59%) underwent bilateral surgery on the maxillary sinuses according to the Caldwell–Luc procedure, with the formation of an anastomosis through the inferior nasal meatus, while the remaining 16 patients (41.1%) underwent unilateral maxillary sinusotomy.

It should be noted that, depending on the clinical indications, during both types of surgical interventions, patients also underwent submucosal resection of the nasal septum, as well as opening of the ethmoidal labyrinth cells according to the Halle and Winkler techniques.

In parallel with the study of chlamydial antibiotic susceptibility, we also investigated the antibiotic sensitivity of the associated microbial flora isolated from these patients.

Table 4.1

Results of the Study on the Sensitivity of Associated Microorganisms to Various Antibiotics and Chemotherapeutic Agents

Microorganisms	Antibiotic and chemotherapeutic sensitivity %							
	Sumamed		Ofloxacin		Cefuroxime		Roxithromycin	
	1	2	1	2	1	2	1	2
Staphylococcus spp.	81,25	97	93,75	100	-	-	56,25	66,6
Streptococcus spp.	74,9	93	98,6	95	-	-	58,3	92,5
Mycoplasma pn.	87	90	81,2	-	92,8	-	-	-
B. fragilis	58	91	75,4	82	87	-	-	-

Note: 1 – **Author's own data; 2 – Literature data [54, 90, 91].**

As shown in Table 4.1, the most frequently identified microorganisms (chlamydial associates) in our study demonstrated the following distribution of antibiotic and chemotherapeutic sensitivity:

- *Staphylococci* were sensitive to Sumamed (azithromycin) in 81.3% of cases, to ofloxacin in 93.8%, and to roxithromycin in only 56.3% of patients.
- *Streptococci* exhibited sensitivity to Sumamed in 74.9%, to ofloxacin in 98.6%, and to roxithromycin in 58.3% of cases.
- *Mycoplasmas* were most sensitive to cefuroxime (92.8%) and Sumamed (87.0%).
- *Bacteroides* showed the highest sensitivity to cefuroxime (87.0%) and ofloxacin (75.4%).

Thus, the obtained results of antimicrobial sensitivity testing of the sinus microflora provided the basis for selecting etiotropic therapy regimens for patients with chlamydial sinusitis, depending on the species composition of chlamydial-

associated microorganisms. The following rational combinations of antibacterial drugs were proposed:

- Ofloxacin + Sumamed — for the eradication of *Chlamydia–Mycoplasma–Streptococcus (or Staphylococcus)* associations.

Pharmacological rationale: Sumamed (Azithromycin) possesses a broad-spectrum antimicrobial activity against Gram-positive and Gram-negative, aerobic and anaerobic, spore-forming and non-spore-forming bacteria, both as monocultures and within microbial associations — including hospital strains with multidrug resistance. The drug is particularly active against Gram-positive cocci (e.g., *Staphylococcus*, *Streptococcus*) and has a pronounced inhibitory effect on pathogens of sexually transmitted infections (*Neisseria gonorrhoeae*, *Treponema pallidum*, *Trichomonas vaginalis*, *Chlamydia trachomatis*, etc.).

One of the key pharmacological advantages of macrolide antibiotics lies in their ability to penetrate cellular membranes and accumulate intracellularly, thereby achieving high local concentrations. This property determines their bactericidal efficacy against intracellular pathogens, especially *Chlamydia trachomatis*. Due to its unique pharmacokinetic characteristics — rapid absorption, achievement of peak serum concentration within one hour, and rapid distribution in extravascular compartments, combined with low toxicity and minimal adverse effects, azithromycin reaches its highest concentration in phagocytic cells, which serve as natural reservoirs for *Chlamydia* and other intracellular microorganisms. Hence, Sumamed is considered the first-line agent in the complex therapy of chlamydia-associated sinusitis.

4.2. Immunological basis for the rational therapy of inflammatory diseases of the paranasal sinuses of chlamydial etiology

Inflammatory diseases of the paranasal sinuses (PNS) are frequently accompanied by significant immunological alterations in affected individuals. In recent years, studies have demonstrated that up to 87% of patients with chronic sinusitis exhibit various T-cell immune deficiencies, as well as a reduction in leukocytic chemotactic factors in the blood serum [180, 188, 189]. Furthermore, 75–80% of patients with chlamydial infections present with disturbances in their immune status, primarily associated with defects in the T-cell component of the immune response [20, 42, 50, 64].

According to numerous authors, such findings necessitate the inclusion of immunocorrective therapy as part of the comprehensive treatment regimen, conducted alongside etiological (antimicrobial) therapy. Several recent studies have highlighted the effectiveness of local immunomodulatory therapy in patients with sinusitis [17, 81, 113]. However, these observations are mostly empirical and unsystematic, lacking scientific justification for the use of specific immunocorrective agents. Therefore, this section presents an immunological rationale for the development of rational immunotherapy protocols for inflammatory sinus diseases of chlamydial origin.

Analysis of Immune Parameters Analysis of immune status revealed that, even among control subjects infected with *Chlamydia*, there was a decrease in relative ($48.1 \pm 6.06\%$, $p < 0.01$) and absolute (0.89 ± 0.28, $p < 0.05$) numbers of T lymphocytes (CD3+), as well as a reduction in CD8+ T-suppressors ($19.1 \pm 2.93\%$, $p < 0.01$). This was accompanied by a moderate increase in induced IL-8 production (5160 ± 1099 pg/mL, $p < 0.05$), along with a decrease in neutrophil chemotactic indices to lipopolysaccharide (FMLP = 2.1 ± 0.48) and to IL-8 (1.26 ± 0.58, $p < 0.01$), and reduced spontaneous (12.7 ± 4.27) and induced adhesion (25.8 ± 9.82, $p < 0.05$).

In patients with acute chlamydial sinusitis, relative lymphocyte counts were elevated (41.0 ± 4.93%, $p < 0.01$), while absolute lymphocyte counts were reduced (1.05 ± 0.48, $p < 0.05$). Both CD3+, CD4+ (T-helpers), and CD8+ (T-suppressors) subpopulations showed marked absolute depletion, despite only moderate relative decreases. Specifically:

- CD3+: 49 ± 0.30% (absolute – 0.44 ± 0.17, $p < 0.05$)
- CD4+: 28.6 ± 2.85% (absolute – 0.25 ± 0.12, $p < 0.05$)
- CD8+: 20 ± 2.99% (absolute – 0.19 ± 0.07, $p < 0.05$)

Although B-cell subpopulations were within normal relative limits, their absolute numbers were significantly decreased, as were NK-cells:

- CD20+: 18.6 ± 4.57% (absolute – 0.16 ± 0.056, $p < 0.05$)
- CD16+ NK cells: 19.6 ± 6.12% (absolute – 0.11 ± 0.032, $p < 0.05$).

Moreover, there was a significant elevation in both spontaneous (2006 ± 495 pg/mL, $p < 0.05$) and induced IL-8 production (8075 ± 2196 pg/mL, $p < 0.01$) in serum compared to controls.

Hematological findings in this group also indicated moderate inflammatory activity, with elevated ESR (13.7 ± 2.54 mm/h), increased band and segmented neutrophils, eosinophilia (7.35 ± 0.83%), monocytosis (10.25 ± 2.58%), and relative lymphocytosis (41 ± 4.93%, $p < 0.05$).

Chronic Sinusitis In patients with chronic chlamydial sinusitis, relative CD3+ levels (53.0 ± 4.13%) were within normal limits, and absolute counts (1.05 ± 0.20) matched the control group but exceeded those in acute sinusitis ($p < 0.05$). Both CD4+ and CD8+ subsets were reduced but remained higher than in acute cases:

- CD4+: 30 ± 2.45% (absolute – 0.46 ± 0.03, $p < 0.05$)
- CD8+: 21 ± 2.82% (absolute – 0.41 ± 0.06, $p < 0.05$).

A pronounced decrease was noted in CD25+ (IL-2 receptor) expression — relative (10 ± 2.25%, $p < 0.01$) and absolute (0.15 ± 0.01, $p < 0.05$) — suggesting

diminished proliferative potential of activated lymphocytes. In the postoperative period, a decline in T- and B-cell functional activity was observed, though not statistically significant compared with the preoperative state.

Serum cytokine analysis demonstrated increased spontaneous (1575 ± 917 pg/mL) and induced IL-8 production (11200 ± 1185 pg/mL, $p < 0.05$), similar to the inflammatory response seen in acute sinusitis. Additionally, a pronounced eosinophilia (10.8 ± 3.79%, $p < 0.05$) was noted compared to the acute group.

Immunotherapeutic Rationale Based on these findings, rational immunotherapy protocols were developed for patients with acute and chronic chlamydial sinusitis. The main principle of systemic immunotherapy was the postoperative administration of immunomodulators aimed at increasing CD25+ (IL-2 receptor) expression, thereby enhancing T-cell responsiveness. This approach is justified by the fact that the immune response to *Chlamydia* infection is predominantly T-helper mediated, with IL-2 serving as the key cytokine regulator of T-cell proliferation, differentiation, and activation of NK and B cells [84–86, 98].

Local immunotherapy strategies were guided by data on IL-8 production by sinus exudate cells and cytogram analysis of sinus contents. It was established that acute chlamydial sinusitis was characterized by a more pronounced local inflammatory response compared to non-chlamydial cases, with significantly higher induced IL-8 levels (2680 ± 203.5 pg/mL vs. 1636 ± 232.6 pg/mL; $p < 0.05$). This likely reflected a greater antigenic load on the mucosal immune defense mechanisms due to the participation of intracellular pathogens within polymicrobial associations.

In contrast, patients with chronic sinusitis demonstrated markedly lower spontaneous (11.5 ± 3.37) and induced IL-8 production (170 ± 73.77 pg/mL, $p < 0.05$), indicating a weaker local inflammatory response typical of prolonged, sluggish infection. Cytological examination of sinus exudates revealed an increase

in neutrophils and a reduction in lymphocytes, macrophages, and eosinophils, consistent with enhanced IL-8–mediated neutrophil chemotaxis.

Conclusion The findings provide a scientific basis for immunotherapy in chlamydial sinusitis:

In chronic forms, it is advisable to administer the immunomodulator *Derinat* (sodium deoxyribonucleate) locally into the paranasal sinuses during the postoperative period to restore immune balance and enhance reparative processes.

4.2. Immunotherapy in patients with acute and chronic sinusitis of chlamydial etiology

In the comprehensive treatment of patients with acute and chronic sinusitis of chlamydial etiology, the effectiveness of the modern immunomodulatory agent Derinat was evaluated using the following immunotherapy regimens.

In patients with chronic sinusitis of chlamydial etiology, during the postoperative period, Derinat was administered locally in combination with basic antibacterial therapy: 2 mg by inhalation for 10 minutes and 5 mg intranasally into the sinus cavity once daily for five consecutive days.

In patients with acute sinusitis of chlamydial etiology, immunotherapy was carried out by local administration of Derinat: 1 mg by inhalation daily, together with 3 mg injected into the sinuses every other day, for a total course of six days.

As the basic etiotropic therapy, patients with acute and exacerbated chronic sinusitis of chlamydial origin received:

- Sumamed (azithromycin) 500 mg twice daily, according to the following schedule: 1st, 7th, and 14th day – 1 g each;
- Ofloxacin 200 mg twice daily for 7–10 days.

The obtained results were compared with those from the control group, which included 30 patients with acute and 30 patients with exacerbated chronic sinusitis

of non-chlamydial etiology, who received traditional therapy (local antibacterial agents from the penicillin and cephalosporin series).

The efficacy of treatment was evaluated based on the following criteria:

- the duration of relief of clinical manifestations of sinusitis;
- the timing of elimination of chlamydiae and associated microorganisms from the sinuses;
- the period of normalization of immunological parameters in peripheral blood and sinus lavage samples.

As shown in Table 4.2, in the experimental group of patients, the resolution of clinical symptoms of sinusitis occurred:

- by days 3–5 in 26.6% of cases,
- by days 8–10 in 60.1%,
- and by days 15–20 in 13.3%.

In contrast, in the control group, normalization of the clinical picture was observed:

- by days 3–5 in only 14.3% of patients,
- by days 8–10 in 47.6%,
- and by days 15–20 in 38.1% of patients.

The results of the comparative analysis of clinical efficacy of the applied immunotherapy are presented in Table 4.2, based on the study of 25 patients with sinusitis of chlamydial etiology and 21 patients with non-chlamydial sinusitis.

Table 4.2

Comparative clinical efficacy of immunotherapy regimens in patients with chlamydial sinusitis

Main clinical symptoms of the disease	Timing of examination	Experimental group (n=25)	Contr group (n=21)
Cessation of mucopurulent discharge, relief of headaches, normalization of body temperature, restoration of nasal breathing, and normalization of the rhinoscopic picture.	3-5 8-10 15-20	26,6% 60,1% 13,3%	14,3% 47,6% 38,1%
Bacteriological clearance of *Chlamydia* and associated microorganisms (control assessment after completed therapy).	After 10 days; after 30 days	93,3% 86,7%	33,7% 19,0%
Development of disease recurrences	Within 3 months	13,3%	61,8%

Within three months after treatment, disease relapses were observed in only 13.3% of patients in the experimental group, whereas in the control group they occurred in 61.8% of cases. Bacteriological clearance of *Chlamydia* and associated microorganisms following therapy was achieved in 93.3% of patients with sinusitis in the experimental group, compared to 33.7% in the control group. These results indicate a considerably high therapeutic efficacy in the experimental group (86.7% of patients), while in the control group, positive clinical outcomes were observed in only 19.0% of cases.

Table 4.3

Comparative Parameters of the Immune System in the Lymphocytotoxic Test (LCTT) in Patients with Acute Chlamydial Sinusitis Before and After Treatment with Derinat

Parameters	Relative (%)		Absolute (bl/mcr)	
	Before treatment	After treatment	Before treatment	After treatment
Lymphocite	41,0±4,932	32±3,335*	1,05±0,481	1,06±0,370**
CD3+(T- lymphocite)	49,0±0,300	55,2±0,315*	0,44±0,167	0,84±0,064**
CD4+(T-xelper)	28,6±2,848	32±2,932*	0,25±0,115	0,48±0,012**
CD8+(T-supressor)	20,0±2,993	24±1,673*	0,19±0,074	0,36±0,036**
Ratio CD4/CD8 IRI	1,44±0,101	1,35±0,060		
CD20+(B-ymphocite)	18,6±4,573	16,5±3,979*	0,16±0,056	0,29±0,032**
CB25+(Ressidev -2)	20,5±8,482	12,7±6,673*	0,29±0,045	0,16±0,025**

Note: The values differ significantly from those obtained before immunotherapy; $p < 0.01$; $\mathbf{p} < 0.05$

Thus, the use of the etiopathogenetic and immunocorrective therapy regimens developed by us in patients with chlamydial sinusitis proved to be more effective than conventional treatment. This conclusion is supported by the observed positive dynamics of immunological parameters in these patients.

Under the influence of *Derinat*, normalization of the T-cell component of the immune system was observed in patients with acute chlamydial sinusitis. A statistically significant increase was recorded in both the relative ($p < 0.01$) and absolute ($p < 0.05$) numbers of lymphocyte subpopulations—$CD3^+$, $CD4^+$, and $CD8^+$—as shown in Table 4.3.

Table 4.4

Comparative Immune System Parameters in the Lymphocytotoxic Test (LCTT) in Patients with Chronic Chlamydial Sinusitis Before and After Immunotherapy with Derinat

Parameters	Relative (%)		Absolute (bl/mcr)	
	Before treatment	After treatment	до лечения	Before treatment
Lymphocite	30,0±5,235	46±3,203*	2,16±0,439	2,39±0,382**
CD3+(T- lymphocite)	53,0±4,131	57±5,015*	1,05±0,202	1,36±0,156
CD4+(T-xelper)	30,0±2,451	32±3,002*	0,46±0,026	0.77±0,038**
CD8+(T-supressor)	21,0±2,818	24±2,576	0,41±0,059	0,57±0,032
Ratio CD4/CD8 IRI	1,31±0,0059	1,33±0,098		
CD20+(B-ymphocite)	16,5±2,927	16,1±1,851	0,35±0,037	0,38±0,024
CB25+(Ressidev -2)	10,0±2,248	15±1,726*	0,15±0,010	0,36±0,064**

Note: Values differ significantly from those obtained before immunotherapy; $p < 0.01$; **p** < 0.05

Table 4.4 presents the comparative parameters of lymphocyte counts and their subpopulations in the peripheral blood of patients with chronic chlamydial sinusitis before and after immunotherapy with Derinat.

As shown in Table 4.4, following the administration of *Derinat*, patients with chronic chlamydial sinusitis exhibited an increase in both the relative (46.0 ± 3.203%, $p < 0.01$) and absolute (2.39 ± 0.382, $p < 0.05$) lymphocyte counts in peripheral blood. Similar positive dynamics were observed in the lymphocyte subpopulations: $CD3^+$ (relative — 57.0 ± 5.015%, absolute — 1.36 ± 0.156), $CD4^+$ (relative — 32.0 ± 3.002%, absolute — 0.77 ± 0.038), $CD8^+$ (relative — 24.0 ± 2.576%, absolute — 0.57 ± 0.032), and $CD25^+$ (IL-2 receptor) (relative — 15.0 ± 1.72%, $p < 0.01$; absolute — 0.36 ± 0.064, $p < 0.05$).

Thus, under the influence of *Derinat*, patients with chronic chlamydial sinusitis demonstrated a statistically significant normalization of the T-cell component of the immune system, as well as an increase in the expression of lymphocyte receptors for endogenous IL-2.

Furthermore, in these patients, *Derinat* immunotherapy resulted in normalization of spontaneous IL-8 production in the serum. However, the parameters of induced IL-8 production remained elevated (6,450 ± 545 pg/mL) despite ongoing therapy, indicating a prolonged inflammatory response in patients with chronic sinusitis.

Therefore, the residual elevation of local IL-8 production observed in patients with acute chlamydial sinusitis receiving conventional therapy apparently reflected the transition of acute inflammation into a latent phase and, in our opinion, could serve as early “markers” of subsequent disease relapses.

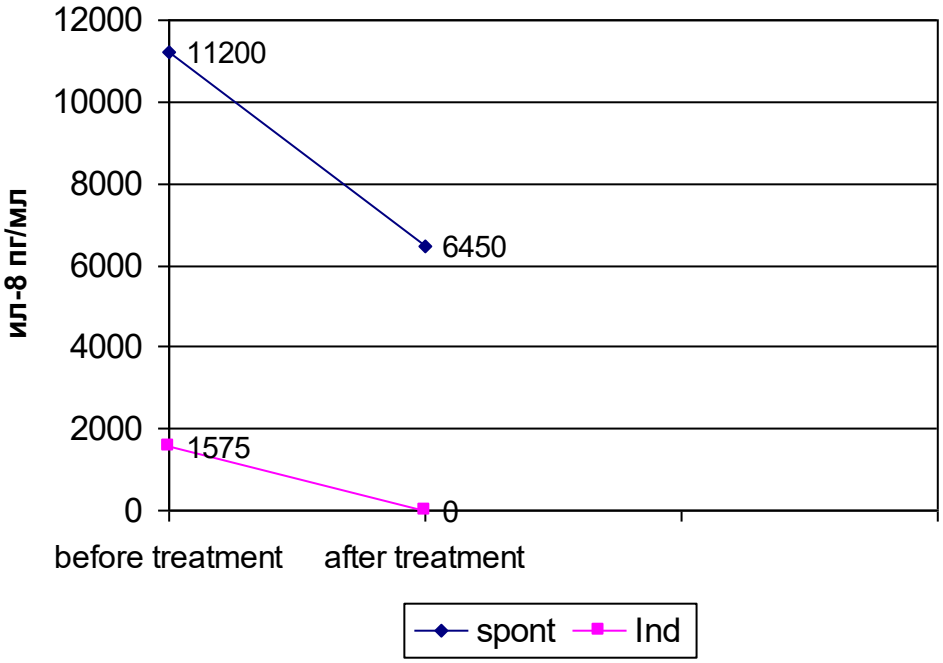

Fig. 4.2. Dynamics of spontaneous and induced il-8 production in patients with chronic chlamydial sinusitis during immunotherapy with derinat.

The high rate of exacerbations observed in these patients further confirmed the insufficient efficacy of conventional therapy for chlamydial sinusitis, as it did

not achieve complete pathogen elimination. The results of IL-8 dynamics analysis in inflammatory sinus exudates indicated a more favorable postoperative course in patients receiving anti-chlamydial and immunocorrective therapy, whereas in those treated conventionally, surgical trauma elicited a pronounced local inflammatory reaction, leading to an extended postoperative recovery period.

4.2.1. Clinical efficacy of derinat in patients with acute chlamydial sinusitis

A total of 43 patients with acute sinusitis were under observation. *Derinat* was administered to 27 patients, while the control group consisted of 16 patients who received standard therapy only.

In the group of patients with acute chlamydial sinusitis, combined therapy with *Derinat* and antibacterial agents led to clinical improvement in 90% of cases within 3–5 days after the start of treatment. The observed improvements included the resolution of intoxication symptoms, normalization of body temperature, disappearance of pain and tenderness in the projection area of the paranasal sinuses, and cessation of purulent discharge in the lavage fluid obtained during sinus puncture and probing.

In contrast, in the control group, clinical improvement was observed only on days 5–7 after the initiation of therapy.

4.2.2. Clinical efficacy of derinat in patients with chronic chlamydial sinusitis

A total of 41 patients with chronic sinusitis were under observation. *Derinat* was administered to 20 patients, while the control group consisted of 21 patients who received standard therapy only.

In the group of patients with chronic chlamydial sinusitis, combined therapy with *Derinat* and antibacterial agents led to clinical improvement in 90% of cases within 5–6 days after the start of treatment. The observed improvements included resolution of intoxication symptoms, normalization of body temperature,

disappearance of pain and tenderness in the projection area of the paranasal sinuses, and cessation of purulent discharge in the lavage fluid obtained during sinus puncture and probing. No disease relapses were observed during a one-year follow-up period.

In contrast, clinical improvement in the control group was noted only on days 10–12 after therapy initiation. In all patients receiving *Derinat*, a decrease in leukocytosis and a reduction in the band neutrophil shift were observed, accompanied by an increase in the percentage of monocytes in peripheral blood and a tendency toward earlier elevation of hemoglobin levels compared with the control group.

Thus, the etiopathogenetic therapy regimens we developed and applied for patients with acute and chronic chlamydial sinusitis — incorporating *Sumamed*, *Ofloxacin*, and the immunomodulator *Derinat* as part of comprehensive immunotherapy — proved to be more effective than conventional treatment. Moreover, these regimens contributed to a reduction in disease relapses, shortened hospitalization by 3–5 days, and were confirmed to be effective by bacteriological clearance of *Chlamydia* and associated microorganisms, normalization of immunological parameters, and improvement of overall clinical condition.

CONCLUSION

At present, diseases of the nose and paranasal sinuses (PNS) continue to occupy a leading position among upper respiratory tract pathologies [41]. The main etiological factor in both acute and chronic sinusitis remains the penetration of infectious agents into the paranasal sinuses. In recent years, among numerous infectious diseases in humans, *Chlamydia* infections have gained particular importance, becoming a significant public health concern.

Many authors regard *Chlamydia* as an etiological agent in the development of both acute and chronic diseases of the ear, nose, and throat, based on the detection of these pathogens in clinical materials from patients (lymphoid tissue of the Waldeyer's ring, nasal and pharyngeal mucosa, paranasal sinuses, tympanic cavity) [47,94,117,138,140,143,169,170,172,194]. However, data concerning the etiopathogenetic role of *Chlamydia* in the development of acute and chronic sinusitis are limited and often contradictory. Furthermore, diagnostic algorithms for *Chlamydia* infection in ENT pathologies and standardized therapeutic protocols for chlamydial sinusitis have not yet been developed in our country.

A review of the literature has shown that sinusitis is one of the most common human diseases [51]. Inflammatory diseases of the PNS are diverse in microbial etiology: acute sinusitis is typically caused by monoflora, whereas chronic sinusitis usually involves polymicrobial associations [34,77]. "Sterile" sinus aspirates obtained from patients with sinusitis are often due to anaerobic flora (such as *Bacteroides* spp.) [122,124] or possibly mycoplasmal infection [94]. The pathogenicity of these microorganisms is associated with their ability to survive penicillin therapy through capsule formation and β-lactamase production, which protects penicillin-susceptible pathogens from antibiotic exposure.

The pathogenesis of PNS mucosal inflammation in chronic sinusitis is based on persistent impairment of mucociliary transport, resulting from irreversible epithelial changes [171], and failure of the second line of local mucosal immunity

mediated by the phenomenon of resorptive cellular resistance involving granulocytic and macrophage systems, as well as cytokines. The cationic proteins released during this process can damage surrounding tissues when antigen elimination within the mucosa fails [56]. *Chlamydia* species are particularly relevant in this context, given their unique intracellular life cycle and ability to evade the host immune system, persisting within macrophages and epithelial cells of the upper respiratory and urogenital tracts, often leading to secondary immunodeficiency. Owing to multiple transmission routes (sexual, household, airborne, and others), *Chlamydia* infections are widely prevalent—affecting over 50% of the global population [134]. These infections may manifest as pneumonia or acute respiratory infections (*C. pneumoniae*), primarily affecting organized groups (including military units) and families, with diverse ENT complications such as sinusitis, tonsillitis, pharyngitis, and otitis, as well as systemic manifestations including meningitis, conjunctivitis, and others. *C. pneumoniae* has also been associated with atherosclerosis, bronchial asthma, and sarcoidosis, suggesting a potential negative impact on population longevity. Chronic chlamydial infections are implicated in trachoma, sexually transmitted genital diseases, atherosclerosis and arthritis. These infections are characterized by prolonged and chronic inflammation, scarring and fibrosis mediated by continuous stimulation of the host immune response. Multiple host and chlamydial factors contribute significantly to specific chlamydial chronic diseases. However, several characteristics of chlamydiae and chlamydial infection are especially relevant to the propensity of this organism to establish chronic disease in general: i) infection of multiple cell types and dissemination within the host, ii) the intracellular niche of the chlamydiae, iii) immune evasion allowing enhanced chlamydial survival by modulation of apoptosis, pathogen detection, and inflammatory and adaptive immune responses in the host , and iv) frequent asymptomatic infection which can make detecting chlamydiae difficult.

Additionally, recent findings have broad implications for diagnosis and treatment of chlamydial infections. First, although the importance of chlamydial persistence in vivo remains unclear, persistent growth forms (AB) can be found in the human endocervix (by electron microscopy) where the local microenvironment at infection is similar to the in vitro model of IFN gamma persistence induction . If the chlamydial persistent state is, in fact, present in vivo, both detection by culture (persistent chlamydiae are by definition non-cultivable) and treatment of chlamydial infection may be impacted. Persistent chlamydiae are resistant to killing by antibiotics in vitro; and a model of amoxicillin induced *C. muridarum* persistence in mice indicates persistent chlamydiae are resistant to killing by azithromycin in vivo as well. Furthermore, clinically relevant concentrations of commonly used penicillins induce *C. trachomatis* persistence in vitro . Second, tetracycline resistance in chlamydiae may be possible. Evidence of antibiotic resistance in human pathogenic chlamydiae is lacking, based on the observation that suspected tetracycline resistant strains lost the resistant phenotype during culture and failed to exhibit genomic evidence of resistance

Our own clinical observations revealed that conventional surgical and conservative treatments in patients with acute and chronic chlamydial sinusitis were often insufficient. Prolonged antibiotic therapy, guided by microbial sensitivity, necessitated extended bacteriological and immunological rehabilitation [9]. Among patients with systemic chlamydial infection, catarrhal inflammation of the upper respiratory mucosa was observed in 32%, and 65% of them had ENT diseases of chlamydial etiology, including sinusitis in 25.5% [87].

A total of 96 individuals were examined and divided into three groups: acute sinusitis (n=27), chronic sinusitis (n=39), and a control group (n=30). The primary diagnostic approach for chlamydial infection involved initial serological screening (ELISA, DFA), followed by comprehensive clinical, laboratory, and immunological assessment to develop individualized therapeutic regimens based

on antimicrobial susceptibility of associated microorganisms. Comparative analysis confirmed the diagnostic accuracy of these methods for *Chlamydia*-associated ENT pathologies and supported their implementation in otorhinolaryngological practice.

Distinct clinical features of acute chlamydial sinusitis were identified, including mild catarrhal (serous) inflammation, recurrent course, and poor response to conventional therapy. Patients with chronic chlamydial sinusitis exhibited prolonged postoperative rehabilitation characterized by frequent relapses. Acute *C. trachomatis*-induced sinusitis was often associated with chronic tonsillitis and pharyngitis, whereas chronic sinusitis commonly coincided with *C. pneumoniae* infection of the pharynx. Notably, *C. trachomatis* infections were more frequently isolated in the maxillary sinuses of patients with urogenital chlamydial forms. Additionally, recent findings have broad implications for diagnosis and treatment of chlamydial infections. First, although the importance of chlamydial persistence in vivo remains unclear, persistent growth forms (AB) can be found in the human endocervix (by electron microscopy) where the local microenvironment at infection is similar to the in vitro model of IFN gamma persistence induction. If the chlamydial persistent state is, in fact, present in vivo, both detection by culture (persistent chlamydiae are by definition non-cultivable) and treatment of chlamydial infection may be impacted. Persistent chlamydiae are resistant to killing by antibiotics in vitro; and a model of amoxicillin induced *C. muridarum* persistence in mice indicates persistent chlamydiae are resistant to killing by azithromycin in vivo as well. Furthermore, clinically relevant concentrations of commonly used penicillins induce *C. trachomatis* persistence in vitro. Second, tetracycline resistance in chlamydiae may be possible. Evidence of antibiotic resistance in human pathogenic chlamydiae is lacking, based on the observation that suspected tetracycline resistant strains lost the resistant phenotype during culture and failed to exhibit genomic evidence of

resistance. However, isolation of tetracycline resistant *C. suis* from pigs demonstrates an adaptive ability of chlamydiae to acquire antibiotic resistance under selective pressure, with implications for continued use of antibiotic treatment of chlamydial disease. Third, and finally, chlamydiae have long been known to colonize the gastrointestinal (GI) tracts of animal hosts, including poultry and sheep, without causing disease. And although humans can become rectally infected with *C. trachomatis*, long-term intestinal infection in humans has not yet been confirmed. Mouse model studies show chlamydiae infecting the GI tract can persist for up to 100 days with no pathology, and azithromycin treatment sufficient to cure genital infection did not similarly cure GI tract infection, despite drug levels in both anatomical sites. Thus, intestinal carriage of chlamydiae may not only allow auto- or re-inoculation of the genital tract, but may represent commensal association with the human host, providing a degree of incidental antibiotic resistance .

These findings indicate that future research in the areas of chlamydial persistence, mechanisms of protective immunity and immunopathology, and vaccine development is a priority. Given difficulties surrounding diagnosis and antibiotic treatment of chlamydial disease, development of an effective *Chlamydia* vaccine appears particularly advantageous in the context of chronic disease. Recent data from a non-human primate animal model demonstrated the efficacy of plasmid-deficient chlamydial strains as live attenuated vaccines against genital and ocular chlamydial infections, and vaccine development is underway. Continued study of the intricate biology of the chlamydiae will facilitate advances in prevention, diagnosis and treatment of chronic chlamydial disease.

Microbiological analysis revealed a high prevalence of *Chlamydia* (33.25%), *Mycoplasma* (31.5%), and *Bacteroides* (30.1%) among the control group. *Chlamydia* was detected in leukocytes in 6% of cases, *Mycoplasma* in 9.07%, and

Bacteroides in 10.23%. Asymptomatic carriage of *Staphylococcus* flora occurred in 33.12% and *Streptococcus* in 6.66%. Immunological testing revealed immune system tension and mild T-cell deficiency in the control group.

In acute sinusitis, *Chlamydia* was detected in 53% of sinus aspirates, *Mycoplasma* in 34.7%, and *Bacteroides* in 66% of cases, alongside pathogenic *Streptococcus* in 33.3%. Elevated antibody titers to *C. pneumoniae* (13.9%), *C. trachomatis* (18%), and *Bacteroides* (28%) were also found. These findings confirmed the polymicrobial nature of sinus infection, primarily comprising *Chlamydia–Mycoplasma–Bacteroides–Streptococcus* associations.

In patients with chronic chlamydial sinusitis, microbiota also had a polymicrobial profile dominated by *Chlamydia–Mycoplasma–Bacteroides–Staphylococcus* associations. *Chlamydia* was found in 63.8% of cases, *Mycoplasma* in 32.26%, *Bacteroides* in 48.21%, and *Staphylococcus* in 48.7%. Anti-bacteroidal antibodies (>1:160) were detected in 52.75%. The increase in *Chlamydia*-positive patients compared with the acute and control groups was notable.

Immunological testing in chronic chlamydial sinusitis revealed moderate decreases in $CD4^+$ and $CD8^+$ lymphocytes, reduced IL-2 receptor expression, and diminished neutrophil migratory activity. Surgical interventions further exacerbated immunodeficiency. Analysis of inflammatory exudate confirmed that local immune defense mechanisms largely depended on neutrophil migration under the influence of IL-8 and other chemokines. However, patients infected with *Chlamydia* exhibited marked impairment of neutrophil chemotaxis toward IL-8, especially in chronic cases, potentially contributing to disease chronicity via a “vicious cycle” of infection persistence.

These data justify the need for anti-chlamydial therapy in all patients with chlamydial sinusitis, including asymptomatic forms, taking into account antibiotic susceptibility of co-associated microorganisms and individualized immunotherapy

regimens. Our results demonstrated that in all patients with ENT pathology caused by *C. trachomatis*, the urogenital tract was also infected. The dissemination of *Chlamydia* through hematogenous spread by leukocytes to upper respiratory mucosa highlights the necessity of both systemic and local etiopathogenetic and immunomodulatory therapy.

Sensitivity analysis of sinus microflora to antibiotics supported the use of the following base therapeutic combinations: *Ofloxacin* + *Sumamed* for eradication of *Chlamydia–Mycoplasma–Streptococcus (Staphylococcus)* associations. Based on the immunological findings, immunotherapy regimens were developed for patients with acute and chronic chlamydial sinusitis. In chronic cases, postoperative local administration of *Derinat* was recommended to enhance $CD25^+$ lymphocyte counts (IL-2 receptor–expressing cells).

Local immunotherapy decisions were guided by analysis of IL-8 production in sinus exudate and cytograms of sinus contents. Acute chlamydial sinusitis was characterized by higher local inflammatory activity compared with non-chlamydial forms, as evidenced by significantly increased IL-8 production (2680 ± 203.5 pg/mL vs. 1636 ± 232.6 pg/mL, $p < 0.05$). In chronic cases, spontaneous IL-8 production was lower (11.5 ± 3.37 pg/mL vs. 37.7 ± 8.29 pg/mL), whereas induced IL-8 production remained significantly elevated (1073 ± 210 pg/mL vs. 170 ± 73.77 pg/mL, $p < 0.05$), indicating a less pronounced but prolonged local inflammatory response.

Cytological analysis of sinus exudates revealed an increase in the relative number of neutrophils, consistent with enhanced IL-8 production, and a concurrent decrease in lymphocytes, macrophages, and eosinophils. These findings substantiate the principle of local immunotherapy — intranasal administration of *Derinat* in patients with chronic chlamydial sinusitis is advisable.

In patients with acute chlamydial sinusitis receiving conventional therapy, residual elevation of local IL-8 production likely indicated a transition of acute

inflammation to a latent phase and may serve as an early marker of subsequent disease relapses. The high recurrence rate in these patients further confirmed the insufficient efficacy of standard therapy, which failed to achieve complete eradication of *Chlamydia*.

The obtained results on IL-8 dynamics in sinus exudate among patients with chronic chlamydial sinusitis demonstrated a more favorable postoperative course in the group receiving anti-chlamydial and immunocorrective therapy. In contrast, in conventionally treated patients, surgical trauma provoked an intense local inflammatory reaction, prolonging postoperative recovery.

Thus, the etiopathogenetic therapy regimens developed and implemented in this study — incorporating *Sumamed*, *Ofloxacin*, and the immunostimulant *Derinat* as part of comprehensive immunotherapy — proved to be more effective than conventional treatments.

CONCLUSIONS

1. *Chlamydia*, particularly *C. pneumoniae*, is an important etiological factor in the development of both acute and chronic sinusitis. These pathogens are most frequently associated with pathogenic forms of *Bacteroides*, *Mycoplasma*, *Streptococcus*, and *Staphylococcus*.

2. *Chlamydia* infection induces pronounced immune system tension even in asymptomatic carriers. Patients with chlamydial sinusitis are characterized by suppression of the T-cell component of immunity, showing a 2.0–2.5-fold decrease compared with healthy individuals and the control group.

3. The etiopathogenetic therapy regimens developed and implemented in this study — incorporating *Sumamed*, *Ofloxacin*, and the immunomodulator *Derinat* as part of comprehensive immunotherapy — proved to be more effective than conventional treatment. These regimens reduced the frequency of disease relapses and shortened hospital stay by 3–5 days, while contributing to faster recovery and normalization of immunological parameters.

PRACTICAL RECOMMENDATIONS

1. In patients with acute and chronic sinusitis, as well as those with concomitant ENT pathologies (otitis, pharyngitis, tonsillitis), it is recommended to perform comprehensive diagnostic testing for *Chlamydia*, *Bacteroides*, *Mycoplasma*, and *Staphylococcus* infections using modern laboratory methods such as ELISA and direct immunofluorescence (DFA). It is essential to determine the antibiotic susceptibility of *Chlamydia* isolates to ensure effective targeted therapy.
2. Patients with acute and chronic chlamydial sinusitis should undergo an extended immunological assessment, including determination of lymphocyte counts and their subpopulations, as well as measurement of cytokine production in peripheral blood.
3. In patients with chronic chlamydial sinusitis during the postoperative period, in addition to basic antibacterial therapy, it is recommended to administer *Derinat* locally as follows:
    - 10 mg by inhalation for 10 minutes daily;
    - 25 mg intranasally (into the sinus cavity) once daily for 2 days;
    - followed by daily inhalations and intranasal administration every other day for 5 days.
4. As basic etiopathogenetic therapy for patients with acute or exacerbated chronic chlamydial sinusitis, the following regimen is recommended:
    - *Sumamed* (azithromycin) — 500 mg twice daily, according to the schedule: 1 g on day 1, 1 g on day 7, and 1 g on day 14;
    - *Ofloxacin* — 200 mg twice daily for 10 days.

To evaluate treatment efficacy, follow-up assessments should be conducted 10 days, 30 days, and 3 months after completion of therapy, including bacteriological analysis of sinus aspirates and monitoring of immunological parameters (in blood and sinus lavage fluid).

5. If laboratory findings remain positive, it is recommended that patients be referred for consultation with infectious disease specialists (chlamydiologists) to evaluate possible multi-focal infection and to determine the need for additional systemic therapy.

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