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# Exploring the Viral Paradigm — Acute Cold Respiratory Syndrome: A Comparative Pathophysiological Analysis and Rationale for Nosological Differentiation in ICD-11 in Accordance with WHO Classification Reform

**За межами вірусної парадигми - гострий холодовий респіраторний синдром: порівняльний патофізіологічний аналіз та обґрунтування нозологічної диференціації у МКГ-11 з реформою класифікації ВООЗ**

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# ABSTRACT

**Background.** Acute respiratory illnesses, collectively referred to as the "common cold," represent one of the most prevalent conditions worldwide, affecting billions of individuals annually and imposing an enormous socioeconomic burden estimated at over $40 billion per year in the United States alone. Despite their ubiquity, the etiopathogenesis of these conditions remains insufficiently understood and scientifically contested. Contemporary medicine attributes all common cold episodes exclusively to viral infections — predominantly rhinoviruses (30–50%), coronaviruses (10–15%), and other respiratory viruses. However, this monocausal viral paradigm fails to explain several well-documented clinical and epidemiological inconsistencies: the onset of symptoms within minutes of cold exposure (far preceding any possible viral incubation period), the reversibility of symptoms upon rewarming, the absence of fever in a substantial proportion of cases, and the paradoxical age-related pattern of incidence in which elderly individuals — despite progressive immunosenescence — suffer fewer episodes than children or young adults. These unresolved contradictions call for a fundamental reassessment of the pathogenesis of cold-associated respiratory disease. The present review builds upon and extends the pathophysiological framework systematically introduced by Gozhenko et al. (2025, 2026), who first proposed a paradigmatic shift from a pathogen-centric to a host-response model of the common cold, and who first described the five interconnected pathophysiological mechanisms forming a self-sufficient symptom cascade independent of any viral agent.

**Objective.** This narrative review critically examines the role of cold exposure and cold stress in the pathogenesis of acute upper respiratory tract disorders and proposes a novel conceptual framework distinguishing two fundamentally different clinical entities: Acute Cold Respiratory Syndrome (ACRS) and Acute Viral Respiratory Syndrome (AVRS). The review introduces a three-phase model of ACRS in which cold-induced vascular dysfunction opens a "gateway" for endogenous microbiome activation, followed by neutrophilic inflammation as a second phase — a mechanism analogous to the ancient folk tradition of steam inhalation therapy (potato steam, warm dry air inhalation documented by British researchers approximately 20 years ago). The review further presents evidence supporting a paradigmatic shift from a pathogen-centric to a host-response model, as proposed by Gozhenko et al. (2025, 2026), and provides formal justification for WHO ICD-11 nosological reform.

**Methods.** A comprehensive narrative literature review was conducted across PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar databases, covering publications from 1946 to 2026 in English, Ukrainian, and Polish. Search terms included: cold stress, thermoregulation, upper respiratory tract, mucosal immunity, vasoconstriction, common cold pathophysiology, mucociliary clearance, cold air inhalation, HPA axis immune suppression, TRPM8, TRPA1, nasal mucosa cold, respiratory microbiome, neutrophilic inflammation, warm air inhalation therapy, geomagnetic disturbances immune, aromatherapy nasal. Artificial intelligence tools (large language models) were used exclusively for auxiliary tasks — initial literature sorting, grammatical proofreading, and reference formatting — with all scientific content, analyses, and conclusions being the sole intellectual product of the authors. Original thermodynamic calculations of metabolic energy expenditure during cold air breathing were performed and are presented in full within the manuscript.

**Results.** Convergent evidence from physiology, immunology, neuroscience, thermodynamics, and microbiology reveals a three-phase pathophysiological model of ACRS fundamentally distinct from AVRS. Phase I (Initiation, 0–30 min): Cold air activates TRPM8 (threshold <25–28°C) and TRPA1 (threshold <17°C) thermosensory receptors, triggering rapid sympathetically mediated vasoconstriction within seconds to minutes, followed by reactive vasodilation with ischemia–reperfusion injury, release of histamine, bradykinin, prostaglandins ($PGE_2$, $PGD_2$), leukotrienes ($LTC_4$, $LTD_4$), and substance P — producing the clinical triad of rhinorrhea, nasal congestion, and sneezing independently of any viral agent. Phase II (Microbiome Activation and Bacterial Phase, 2–24 h): Cold-induced vascular dysfunction, mucociliary paralysis, and local immunosuppression open a "gateway" for the resident upper respiratory tract microbiome. The shift from protective commensals (Lactobacillus spp., Dolosigranulum pigrum) toward opportunistic pathogens (Staphylococcus aureus, Streptococcus pneumoniae) triggers neutrophilic recruitment and the classical inflammatory response — explaining why "pure" ACRS, if untreated, progresses to purulent rhinitis and sinusitis without any external viral agent. Phase III (Resolution or Viral Superinfection, 6 h – 3 days): Upon rewarming, pure ACRS resolves spontaneously. However, cold-induced mucociliary dysfunction, reduced sIgA, and suppressed interferon signaling create a "window of vulnerability" (2–4 h) that maximally favors viral invasion — explaining the clinical phenomenon of "severe cold after chilling." The comparative analysis of ACRS versus AVRS (Gozhenko et al., 2025, 2026) demonstrates that these two entities differ fundamentally in trigger (cold stress vs. external viral agent), incubation period (absent vs. obligatory 12–72 h), pathogenetic mechanism (thermoregulatory vasospasm → microbiome activation → neutrophilic inflammation vs. viral cytopathic effect → interferon response → adaptive immunity), seasonality (strictly temperature-dependent vs. year-round, as demonstrated by the COVID-19 pandemic), and therapeutic target (rewarming, steam inhalation, saline rinses vs. antiviral agents, vaccines). Original thermodynamic calculations demonstrate that conditioning cold air (0°C) to tracheobronchial conditions (37°C, 100% relative humidity) requires approximately 14.2 W — equivalent to ~18% of basal metabolic rate at rest, rising to 40–50% under extreme cold (−20°C). Neuro-ecological modulation by geomagnetic disturbances and therapeutic neuromodulation by aromatherapy (menthol, eucalyptol, camphor as natural TRPM8/TRPA1 agonists) are identified as novel dimensions of ACRS pathophysiology and treatment not previously integrated into a unified clinical concept.

**Conclusions.** The "common cold" is not a purely infectious disease but a complex syndrome in which cold stress plays an independent and fundamental pathogenetic role through a three-phase cascade: neurogenic vascular dysfunction → microbiome-mediated bacterial activation → neutrophilic inflammation. The term Acute Cold Respiratory Syndrome (ACRS), as systematically described by Gozhenko et al. (2026), more accurately reflects this multifactorial etiology. The current ICD-10/ICD-11 classification leads to massive overdiagnosis of viral infections, irrational antibiotic and antiviral prescribing, and neglect of evidence-based preventive strategies. Formal recognition of ACRS as an independent nosological entity in ICD-11 is scientifically justified, clinically necessary, and economically imperative — with potential annual savings of $20–44 billion globally.

**Keywords:** acute cold respiratory syndrome, ACRS, acute viral respiratory syndrome, AVRS, cold exposure, cold stress, thermoregulation, upper respiratory tract, vasoconstriction, mucociliary clearance, mucosal immunity, TRPM8, TRPA1, HPA axis, thermodynamics, host-response model, respiratory microbiome, neutrophilic inflammation, steam inhalation, warm air therapy, geomagnetic disturbances, aromatherapy, ICD-11, WHO classification reform, common cold, narrative review.

# РЕЗЮМЕ

**Актуальність.** Гострі респіраторні захворювання, що колективно позначаються терміном «застуда», є одними з найпоширеніших патологій у світі, щорічно вражаючи мільярди людей та спричиняючи колосальний соціально-економічний тягар, що перевищує 40

мільярдів доларів на рік лише у Сполучених Штатах. Попри їх повсюдність, етіопатогенез цих захворювань залишається недостатньо вивченим і науково дискусійним. Сучасна медицина пояснює всі епізоди застуди виключно вірусними інфекціями — переважно риновірусами (30–50%), коронавірусами (10–15%) та іншими респіраторними вірусами. Однак ця моноказуальна вірусна парадигма не пояснює низки добре задокументованих клінічних та епідеміологічних невідповідностей: розвиток симптомів протягом хвилин після холодового впливу (задовго до будь-якого можливого вірусного інкубаційного періоду), оборотність симптомів після зігрівання, відсутність лихоманки у значній частині випадків та парадоксальна вікова закономірність захворюваності, за якої літні люди — попри прогресивну імуносенесценцію — страждають від менш частих епізодів, ніж діти або молоді дорослі. Ці невирішені суперечності вимагають фундаментального переосмислення патогенезу холодо-асоційованих респіраторних захворювань. Цей огляд спирається на патофізіологічну концепцію, систематично запроваджену Gozhenko et al. (2025, 2026), які першими запропонували парадигматичний зсув від патоген-центричної до хост-відповідної моделі застуди та першими описали п'ять взаємопов'язаних патофізіологічних механізмів, що формують самодостатній каскад симптомів незалежно від будь-якого вірусного агента, і розвиває цю концепцію далі.

**Мета.** Цей наративний огляд критично аналізує роль холодового впливу та холодового стресу в патогенезі гострих захворювань верхніх дихальних шляхів і пропонує нову концептуальну модель, що розрізняє дві фундаментально різні клінічні одиниці: Гострий холодовий респіраторний синдром (ГХРС) та Гострий вірусний респіраторний синдром (ГВРС). Огляд вводить трифазну модель ГХРС, в якій холодо-індукована судинна дисфункція відкриває «ворота» для активації ендогенного мікробіому з наступним нейтрофільним запаленням як другою фазою — механізм, аналогічний давній народній традиції парових інгаляцій (дихання над картоплею, вдихання теплого сухого повітря, задокументоване британськими дослідниками приблизно 20 років тому). Огляд також представляє докази на підтримку парадигматичного зсуву від патоген-центричної до хост-відповідної моделі, запропонованого Gozhenko et al. (2025, 2026), та надає формальне обґрунтування для реформи нозологічної класифікації ВООЗ МКХ-11.

**Методи.** Проведено комплексний наративний огляд літератури в базах даних PubMed/MEDLINE, Scopus, Web of Science та Google Scholar, що охоплює публікації з 1946 по 2026 рік англійською, українською та польською мовами. Пошукові терміни включали: холодовий стрес, терморегуляція, верхні дихальні шляхи, слизовий імунітет, вазоконстрикція, патофізіологія застуди, мукоциліарний кліренс, вдихання холодного повітря, імуносупресія осі ГГН, TRPM8, TRPA1, холод слизової носа, мікробіом дихальних шляхів, нейтрофільне запалення, терапія вдиханням теплого повітря, геомагнітні збурення імунітет, ароматерапія ніс. Інструменти штучного інтелекту (великі мовні моделі) використовувались виключно для допоміжних завдань — первинного сортування літератури, граматичної коректури та форматування посилань — при цьому весь науковий зміст, аналіз і висновки є виключним інтелектуальним продуктом авторів. Оригінальні термодинамічні розрахунки метаболічних енергетичних витрат під час дихання холодним повітрям були виконані та представлені в повному обсязі в рукописі.

**Результати.** Конвергентні дані з фізіології, імунології, нейронауки, термодинаміки та мікробіології розкривають трифазну патофізіологічну модель ГХРС, що принципово відрізняється від ГВРС. Фаза I (Ініціація, 0–30 хв): холодне повітря активує термосенсорні рецептори TRPM8 (поріг <25–28°C) та TRPA1 (поріг <17°C), запускаючи швидку симпатично-опосередковану вазоконстрикцію протягом секунд–хвилин, за якою слідує реактивна вазодилатація з ішемічно-реперфузійним пошкодженням, вивільненням гістаміну, брадикініну, простагландинів ($PGE_2$, $PGD_2$), лейкотрієнів ($LTC_4$, $LTD_4$) та субстанції P — що продукує клінічну тріаду ринореї, закладеності носа та чхання незалежно від будь-якого вірусного агента. Фаза II (Активація мікробіому та бактеріальна фаза, 2–24 год): холодо-індукована судинна дисфункція, мукоциліарний параліч та місцева імуносупресія відкривають «ворота» для резидентного мікробіому верхніх дихальних шляхів. Зміщення від захисних коменсалів (Lactobacillus spp., Dolosigranulum pigrum) до умовно-патогенних мікроорганізмів (Staphylococcus aureus, Streptococcus pneumoniae) запускає нейтрофільне рекрутування та класичну запальну відповідь — пояснюючи, чому «чистий» ГХРС без лікування прогресує до гнійного риніту та синуситу без будь-якого зовнішнього вірусного агента. Фаза III (Розрішення або вірусна суперінфекція, 6 год – 3 доби): при зігріванні чистий ГХРС розрішується спонтанно. Однак холодо-індукована мукоциліарна дисфункція, зниження sIgA та пригнічення інтерферонової сигналізації створюють «вікно вразливості» (2–4 год), що максимально сприяє вірусній інвазії — пояснюючи клінічний феномен «важкої застуди після переохолодження». Порівняльний аналіз ГХРС та ГВРС (Gozhenko et al., 2025, 2026) демонструє, що ці дві одиниці принципово відрізняються за тригером (холодовий стрес проти зовнішнього вірусного агента), інкубаційним періодом (відсутній проти обов'язкового 12–72 год), патогенетичним механізмом (терморегуляторний вазоспазм → активація мікробіому → нейтрофільне запалення проти вірусного цитопатичного ефекту → інтерферонова відповідь → адаптивний імунітет), сезонністю (суворо температурно-залежна проти цілорічної, що продемонстровано пандемією COVID-19) та терапевтичною мішенню (зігрівання, парові інгаляції, сольові розчини проти противірусних препаратів, вакцин). Оригінальні термодинамічні розрахунки демонструють, що кондиціонування холодного повітря (0°C) до трахеобронхіальних умов (37°C, 100% відносна вологість) вимагає приблизно 14,2 Вт — що еквівалентно ~18% базального метаболізму у спокої, зростаючи до 40–50% при екстремальному морозі (−20°C). Нейро-екологічна модуляція геомагнітними збуреннями та терапевтична нейромодуляція ароматерапією (ментол, евкаліптол, камфора як природні агоністи TRPM8/TRPA1) визначені як нові виміри патофізіології та лікування ГХРС, що раніше не були інтегровані в єдину клінічну концепцію.

**Висновки.** «Застуда» є не суто інфекційним захворюванням, а складним синдромом, в якому холодовий стрес відіграє незалежну та фундаментальну патогенетичну роль через трифазний каскад: нейрогенна судинна дисфункція → мікробіом-опосередкована бактеріальна активація → нейтрофільне запалення. Термін «Гострий холодовий респіраторний синдром» (ГХРС), систематично описаний Gozhenko et al. (2026), більш точно відображає цю мультифакторну етіологію. Поточна класифікація МКХ-10/МКХ-11 призводить до масової гіпердіагностики вірусних інфекцій, нераціонального призначення антибіотиків та противірусних препаратів і нехтування науково обґрунтованими профілактичними стратегіями. Офіційне визнання ГХРС як самостійної нозологічної одиниці в МКХ-11 є науково обґрунтованим, клінічно необхідним та економічно imperative — з потенційною щорічною економією 20–44 мільярди доларів у глобальному масштабі.

**Ключові слова:** гострий холодовий респіраторний синдром, ГХРС, гострий вірусний респіраторний синдром, ГВРС, холодовий вплив, холодовий стрес, терморегуляція, верхні дихальні шляхи, вазоконстрикція, мукоциліарний кліренс, слизовий імунітет, TRPM8, TRPA1, вісь ГГН, термодинаміка, хост-відповідна модель, мікробіом дихальних шляхів, нейтрофільне запалення, парові інгаляції, терапія теплим повітрям, геомагнітні збурення, ароматерапія, МКХ-11, реформа класифікації ВООЗ, застуда, наративний огляд.

# ABBREVIATIONS AND ACRONYMS

**ACRS** — Acute Cold Respiratory Syndrome; **AVRS** — Acute Viral Respiratory Syndrome; **HPA** — Hypothalamic–Pituitary–Adrenal axis; **CBF** — Ciliary Beat Frequency; **sIgA** — Secretory Immunoglobulin A; **ROS** — Reactive Oxygen Species; **CRH** — Corticotropin-Releasing Hormone; **ACTH** — Adrenocorticotropic Hormone; **NF-κB** — Nuclear Factor kappa-light-chain-enhancer of activated B cells; **MAPK** — Mitogen-Activated Protein Kinase; **TRPM8** — Transient Receptor Potential Melastatin 8; **TRPA1** — Transient Receptor Potential Ankyrin 1; **$PGE_2$** — Prostaglandin $E_2$; **$PGD_2$** — Prostaglandin $D_2$; **$LTC_4$** — Leukotriene $C_4$; **$LTD_4$** — Leukotriene $D_4$; **$LTB_4$** — Leukotriene $B_4$; **CGRP** — Calcitonin Gene-Related Peptide; **IL-8 / CXCL8** — Interleukin-8; **IFN-α, IFN-β** — Interferon alpha, beta; **TNF-α** — Tumor Necrosis Factor alpha; **AI** — Artificial Intelligence; **ICD** — International Classification of Diseases; **WHO** — World Health Organization; **RCT** — Randomized Controlled Trial; **ATP** — Adenosine Triphosphate; **CNS** — Central Nervous System.

# 1. INTRODUCTION

## 1.1. Global Burden of Cold-Associated Respiratory Diseases

Acute respiratory illnesses, collectively designated by the term "common cold," constitute the most prevalent infectious pathology in human populations, affecting billions of individuals annually and creating a significant socioeconomic burden (Allan & Arroll, 2014). Epidemiological data reveal striking age-related patterns: children experience 6–8 cold episodes per year, working-age adults — 2–4 episodes annually, while elderly individuals suffer fewer than 1 episode per year (Monto, 2002; Heikkinen & Järvinen, 2003). In developed countries, cumulative economic losses exceed billions of dollars annually due to absenteeism, reduced labor productivity, and healthcare expenditures. Bramley et al. (2002) calculated that the common cold leads to 75–100 million physician visits annually in the United States alone, with direct and indirect costs exceeding $40 billion per year. Fendrick et al. (2003) estimated the total burden of non-viral respiratory diseases at over $40 billion annually in the United States alone, making this pathology one of the most economically significant in medicine. Despite such prevalence and significance, the pathophysiology of the "common cold" remains a subject of debate. The dominant viral paradigm, which formed in the second half of the twentieth century, explains all manifestations of the common cold exclusively through the lens of viral infection. However, this concept leaves a number of fundamental clinical and epidemiological questions unanswered. Recently, Gozhenko et al. (2025, 2026) proposed a paradigmatic shift from a pathogen-centric to a host-response model, emphasizing thermoregulatory reactions as key determinants of disease development. This concept fits organically into the broader research direction of the authors, studying somato-regulatory imbalance as the pathophysiological basis of diseases of civilization (Gozhenko et al., 2025b) and integrated regulation of homeostasis (Gozhenko et al., 2025a).

## 1.2. The Viral Paradigm and Its Limitations

Contemporary medical doctrine regards the "common cold" as synonymous with acute viral upper respiratory tract infection. According to this concept, more than 200 different viruses — rhinoviruses (30–50% of cases), coronaviruses (10–15%), influenza virus, parainfluenza, respiratory syncytial virus, and others — are the sole causative agents of the disease (Eccles, 2002). This paradigm is supported by a substantial body of virological research and has become the foundation for the development of antiviral drugs and vaccines. However, the viral paradigm has significant limitations. First, virological testing detects a pathogen in only 50–70% of clinical cases of the "common cold" (Johnston et al., 1993), leaving a significant

proportion of illnesses without an established infectious cause. Second, this paradigm does not explain why symptoms often develop within minutes of cold exposure — long before any possible incubation period. Third, it does not answer the question of the mechanism of seasonality: why does incidence sharply increase in winter if viruses circulate year-round? Eccles (2002) proposed several hypotheses to explain this seasonality, including decreased nasal mucosal temperature, reduced UV radiation, and changes in human behavior, but none of them has achieved the status of a generally accepted explanation. Gozhenko et al. (2025, 2026) systematically analyzed these inconsistencies and proposed an alternative model based on host-response reactions.

### 1.3. Clinical Inconsistencies Challenging the Monocausal Model

A number of well-documented clinical observations contradict the exclusively viral concept of the "common cold." The first is a temporal inconsistency: symptoms of rhinitis, nasal congestion, and sore throat often appear within 15–30 minutes of going out into the cold, while the minimum incubation period of rhinovirus is 12–24 hours (Eccles, 2002). This phenomenon, which Gozhenko et al. (2025) termed the "cold paradox," is fundamentally incompatible with any known viral kinetics. The second is reversibility of symptoms: in a significant proportion of patients, symptoms diminish or completely disappear after returning to a warm room and rewarming — which is absolutely uncharacteristic of a viral infection, where symptoms progress regardless of the temperature regime. The third is the absence of fever: in "pure" ACRS, body temperature remains normal or subfebile, while viral infection is almost always accompanied by elevated temperature as a manifestation of the systemic immune response. The fourth is the age paradox: elderly individuals with less effective immunity (immunosenescence) fall ill less frequently than young adults with fully functional immunity — which is a direct contradiction of the infectious model, but is fully explained by the cold exposure model (Gozhenko et al., 2025, 2026). The fifth is the absence of contagiousness: a "cold" after chilling is not transmitted to other family members if they were not subjected to similar cold exposure — which is a key distinction from a true viral infection.

### 1.4. The New Concept: ACRS and AVRS as Two Separate Nosological Entities

The central thesis of this article is that the "common cold" is in fact an umbrella term covering fundamentally different pathological processes. We propose a clear delineation of two nosological entities, first systematically substantiated by Gozhenko et al. (2025, 2026). **ACRS (Acute Cold Respiratory Syndrome)** is an ecologically determined condition triggered by a physical trigger (cold stress), developing without an incubation period through neurogenic dysfunction and activation of the host's own microbiome, and progressing through three sequential phases: (1) neurogenic vascular dysfunction (activation of TRPM8/TRPA1 → vasoconstriction → ischemia–reperfusion → release of inflammatory mediators); (2) microbiome-mediated bacterial phase with neutrophilic inflammation (activation of opportunistic endogenous microbiome → neutrophilic response → transformation of rhinorrhea); (3) resolution or viral superinfection (upon rewarming — spontaneous recovery; with continued cold exposure — a "window of vulnerability" for viral invasion). **AVRS (Acute Viral Respiratory Syndrome)** is a disease with a proven or highly probable external viral agent, a mandatory incubation period (12 hours to 14 days depending on the pathogen), cytopathic effect, and systemic immune response (type I interferons, NK cells, cytotoxic T lymphocytes, specific antibodies), independent of temperature conditions — as was vividly demonstrated by the COVID-19 pandemic, which caused mass outbreaks in the tropics in the height of summer. A detailed pathophysiological justification of the concept of ACRS as an independent nosological entity, including five interconnected mechanisms, is presented in Gozhenko et al. (2026).

## 1.5. Objectives of the Review

The objectives of this narrative review are: (1) to critically analyze the available evidence regarding the role of cold stress in the pathogenesis of acute respiratory diseases; (2) to systematize the pathophysiological mechanisms of cold-induced airway injury in a three-phase model; (3) to describe the role of the upper respiratory tract microbiome as an intermediary between vascular dysfunction and neutrophilic inflammation in ACRS; (4) to conduct a comparative analysis of ACRS and AVRS across all key clinical, pathophysiological, and epidemiological parameters; (5) to justify the need for WHO ICD-11 classification reform by establishing ACRS as an independent nosological entity; (6) to formulate a research agenda for verification of the proposed hypotheses.

## 1.6. Research Problems

The concept of ACRS as an independent nosological entity raises a number of fundamental scientific problems requiring systematic resolution. Below are ten key research problems that define the agenda for future research in this field.

**Problem 1. Nosological uncertainty of ACRS.** Despite accumulated pathophysiological evidence, ACRS has not yet been recognized as an independent nosological entity in any of the international disease classifications (ICD-10, ICD-11). The absence of official nosological status makes it impossible to systematically record incidence, conduct comparative epidemiological studies, and develop standardized treatment protocols. The problem lies in defining valid, reproducible, and clinically meaningful diagnostic criteria that will allow a clear distinction between ACRS, viral cold, and allergic rhinitis in routine clinical practice (Gozhenko et al., 2025, 2026).

**Problem 2. Quantitative assessment of the contribution of cold stress to the structure of acute respiratory diseases.** The actual proportion of ACRS in the overall structure of acute respiratory diseases remains unknown. Since most clinical studies do not perform virological testing or do not collect a detailed history of cold exposure, it is impossible to determine what proportion of "cold" cases is pure ACRS, what proportion is pure viral infection, and what proportion is a mixed form. Resolving this problem requires large-scale population studies with mandatory parallel virological testing and standardized cold exposure assessment. Johnston et al. (1993) established that in 30–50% of clinical cases of the "common cold," a viral agent is not detected even with modern molecular methods — this is a key epidemiological argument in favor of the existence of a non-viral form of the disease.

**Problem 3. Threshold values of cold exposure for initiation of ACRS.** The quantitative threshold values of temperature, duration, and intensity of cold exposure that are sufficient to initiate the pathological cascade of ACRS are unknown. Answers to these questions are of fundamental importance for developing scientifically based preventive recommendations and occupational health standards. Brenner et al. (1999) showed that immune changes during cold exposure depend on its intensity and duration, but quantitative threshold values for the upper respiratory tract remain unestablished.

**Problem 4. Individual variability in sensitivity to cold stress.** Clinical experience indicates significant inter-individual variability in response to cold exposure: some people develop pronounced ACRS symptoms after minimal chilling, while others remain asymptomatic even with prolonged exposure to frost. The genetic, hormonal, metabolic, and behavioral determinants of this variability remain practically unstudied. In particular, the role of polymorphisms of the TRPM8 and TRPA1 genes in determining individual cold sensitivity is a promising but unstudied direction (Vašek, 2025).

**Problem 5. Mechanisms of thermal adaptation of the upper respiratory tract.** It is well known that regular cold hardening reduces the incidence of the "common cold." However, the molecular and cellular mechanisms of thermal adaptation of the upper respiratory tract remain unclear. Does adaptation occur at the level of thermosensory receptors (decreased sensitivity

of TRPM8/TRPA1)? At the level of vascular reactivity (reduced amplitude of vasoconstriction)? At the level of the mucociliary apparatus (increased resistance of CBF to temperature reduction)? Answers to these questions will allow the development of scientifically based hardening programs with optimal parameters of temperature, duration, and frequency of procedures.

**Problem 6. Interaction of ACRS and viral infection at the molecular level.** Although the synergistic model of interaction between ACRS and viral infection is pathophysiologically justified, the molecular mechanisms of this interaction remain unstudied. In particular, it is unknown: does cold-induced vasoconstriction increase the expression of viral receptors (ICAM-1 for rhinoviruses, ACE2 for coronaviruses) on the surface of epithelial cells? Does metabolic stress reduce the production of type I interferons — key antiviral cytokines? Answers to these questions are of fundamental importance for understanding the mechanisms of seasonal outbreaks of respiratory viral infections (Chen et al., 2026).

**Problem 7. Role of the upper respiratory tract microbiome in the pathogenesis of ACRS.** The upper respiratory tract microbiome is an important component of local immune defense. Cold stress can alter the composition and functional activity of the microbiome through changes in temperature, humidity, and pH of the mucosa. However, the relationship between cold-induced changes in the microbiome and the development of ACRS or increased susceptibility to viral infections is practically unstudied. This is a promising research direction that may reveal new mechanisms of pathogenesis and prevention of ACRS.

**Problem 8. Impact of climate change on the epidemiology of ACRS.** Global warming is changing the pattern of seasonal temperature fluctuations, which may significantly affect the epidemiology of ACRS. On the one hand, rising average annual temperatures may reduce the frequency of ACRS in temperate climate zones. On the other hand, increased frequency of extreme weather events (sudden cold snaps, cold waves) may increase the risk of severe forms of ACRS. Rijkers et al. (2026) point to the need to study the impact of climate change on the immune system, including cold-associated respiratory diseases.

**Problem 9. Pediatric and geriatric aspects of ACRS.** The age-related pattern of ACRS incidence (children > adults > elderly) requires detailed study taking into account age-related features of thermoregulation, anatomy of the upper respiratory tract, neuroendocrine regulation, and behavioral factors. In particular, it is unknown: are newborns and infants particularly vulnerable to ACRS due to the immaturity of thermoregulatory mechanisms? Opdal et al. (2025) point to a possible link between thermoregulatory disturbances and sudden infant death syndrome, which requires further study.

**Problem 10. Pharmacological targets for prevention and treatment of ACRS.** Despite clearly defined pathophysiological mechanisms of ACRS, no specific pharmacological agents for its prevention and treatment exist. Potential therapeutic targets include: TRPM8/TRPA1 antagonists (to block the initiation of vasoconstriction), local vasodilators (to correct mucosal ischemia), next-generation mucolytics (to restore mucociliary clearance), adaptogens and immunomodulators (to correct neuroendocrine immunosuppression). The development and clinical evaluation of these agents is a pressing scientific and practical problem requiring an interdisciplinary approach (Gozhenko et al., 2025, 2026).

## 1.7. Research Hypotheses

Based on the analysis of the pathophysiological mechanisms of ACRS and the formulated research problems, the following working hypotheses are proposed for empirical verification.

**Hypothesis 1. Nosological independence of ACRS.** Formulation: ACRS is an independent nosological entity that meets the criteria of a separate disease: it has a specific etiology (cold stress), clearly defined pathophysiological mechanisms, a characteristic clinical picture, and a predictable course — regardless of the presence or absence of a viral agent. Verification: a prospective cohort study with parallel virological testing and standardized cold exposure

assessment. The hypothesis is confirmed if ≥20% of "cold" cases meet the criteria for ACRS with negative virological testing. Rationale: Gozhenko et al. (2025, 2026) showed that the pathophysiological mechanisms of ACRS are sufficient for the development of clinical symptoms without the participation of a viral agent. Johnston et al. (1993) established that in 30–50% of clinical "cold" cases, a viral agent is not detected.

**Hypothesis 2. Temperature threshold of mucociliary dysfunction.** Formulation: there is a critical temperature threshold (approximately +10°C for nasal mucosal temperature) below which mucociliary clearance decreases by more than 50% from baseline, which is sufficient for a clinically significant impairment of the protective functions of the upper respiratory tract. Verification: a laboratory study measuring CBF and mucociliary transport at different nasal mucosal temperatures in healthy volunteers using the saccharin test and video microscopy. Rationale: Tufail et al. (2025) demonstrated a pronounced temperature dependence of CBF. Brenner et al. (1999) established that immune changes during cold exposure are dose-dependent.

**Hypothesis 3. Metabolic depletion of epithelial cells.** Formulation: the metabolic costs of conditioning cold air (heating and humidification) lead to a measurable decrease in ATP levels in ciliated epithelial cells of the upper respiratory tract, which correlates with the severity of ACRS clinical symptoms. Verification: biochemical analysis of nasal epithelial samples (obtained by brush biopsy) before and after standardized cold exposure with measurement of ATP, ADP, AMP levels, and cellular energy charge. Rationale: original thermodynamic calculations (Gozhenko et al., 2026) demonstrate that conditioning cold air requires 15–50% of basal metabolism.

**Hypothesis 4. TRPM8-mediated vasoconstriction as a therapeutic target.** Formulation: pharmacological blockade of TRPM8 receptors of the nasal mucosa using a selective antagonist prevents cold-induced vasoconstriction and significantly reduces the severity of ACRS symptoms during standardized cold exposure. Verification: a randomized double-blind placebo-controlled study with intranasal administration of a TRPM8 antagonist before cold exposure. Rationale: TRPM8 is the primary molecular cold sensor in airway mucous membranes. TRPM8 agonists (menthol, WS-12) modulate reflex reactions of the airways.

**Hypothesis 5. Synergism of cold and virus ("window of vulnerability").** Formulation: prior cold exposure (30–60 min at temperature ≤+5°C) increases susceptibility to rhinoviral infection by at least 2 times compared to the absence of cold exposure, due to cold-induced reduction in type I interferon production and impairment of mucociliary clearance. Verification: a controlled study on cell cultures (primary human nasal epithelial cells). Rationale: cold airflow disrupts antiviral immune defense functions of the mucosa; interferon signaling in nasal epithelium is a key determinant of antiviral protection.

**Hypothesis 6. Thermal adaptation through regular cold hardening.** Formulation: systematic cold hardening (daily brief cold air exposure of the upper respiratory tract for 8 weeks) leads to measurable adaptive changes in the nasal mucosa: reduced amplitude of the vasoconstrictive response to cold, increased baseline sIgA levels, and improved mucociliary clearance during cold exposure. Rationale: Brenner et al. (1999) showed that prior heating and physical exercise significantly modify immune changes during cold exposure. Vašek (2025) confirmed that thermogenic stimuli can modulate both innate and adaptive immunity.

**Hypothesis 7. The age paradox through differential cold exposure.** Formulation: the age-related pattern of ACRS incidence (children > adults > elderly) is explained exclusively by differences in quantitative indicators of cold exposure (time spent in the cold, degree of insulation, minute ventilation per kg of body weight), and not by differences in immune competence. Rationale: Gozhenko et al. (2025, 2026) proposed this hypothesis as an explanation of the age paradox. Rijkers et al. (2026) emphasize the importance of accounting

for behavioral factors when studying immune reactions, as well as age and sex differences in the protective function of the nose with respect to cold, dry, and polluted air.

**Hypothesis 8. Vitamin D deficiency as a modifying factor.** Formulation: vitamin D deficiency (25(OH)D <20 ng/ml) significantly potentiates cold-induced immunosuppression and increases the risk of ACRS by at least 1.5 times, while correction of vitamin D deficiency reduces ACRS incidence in the winter season. Rationale: Dogan et al. (2023) showed that acute cold stress (4°C, 2 h) reduces T-cell response in peripheral blood, and this effect is modulated by vitamin D levels. James et al. (2023) demonstrated that physiological stressors, including cold water, activate the HPA axis and increase cortisol levels.

**Hypothesis 9. Microbiome disruption in ACRS.** Formulation: acute cold exposure (≥30 min at ≤+5°C) causes measurable changes in the composition of the upper respiratory tract microbiome — in particular, a decrease in the relative proportion of protective commensals (Lactobacillus spp., Dolosigranulum pigrum) and an increase in the proportion of opportunistic pathogens (Staphylococcus aureus, Streptococcus pneumoniae) — which precedes the development of clinical symptoms of Phase II ACRS. Verification: a prospective study with sequential collection of nasopharyngeal swabs before, immediately after, and at 24 and 48 hours after standardized cold exposure. Microbiome analysis by 16S rRNA sequencing. Rationale: this hypothesis is the central new element of the three-phase model of ACRS, developing the concept of Gozhenko et al. (2026).

**Hypothesis 10. Neurogenic inflammation as the primary mechanism of symptom formation.** Formulation: neurogenic inflammation initiated by activation of TRPA1 receptors and release of substance P and CGRP from sensory nerve endings of the nasal mucosa is the primary and sufficient mechanism for the development of the full ACRS symptom complex (rhinorrhea, congestion, sneezing) independently of vascular and immunological changes. Rationale: Tekulapally et al. (2024) described in detail the dual role of TRPA1 in airway physiology, confirming that TRPA1 activation by cold (<17°C) leads to release of substance P and CGRP from sensory nerve endings. Chen et al. (2026) described neuroimmune circuits in airway pathophysiology.

# 2. METHODOLOGY

## 2.1. Study Design

This review was conducted as a narrative literature review in accordance with the methodological principles described by Ferrari (2015) and Green et al. (2006). The narrative design was chosen deliberately, as the aim of the work is not a systematic quantitative synthesis of homogeneous studies, but a conceptual integration of heterogeneous pathophysiological data from different fields of medicine and physiology — physiology of thermoregulation, mucosal immunology, neuroendocrinology, microbiology, thermodynamics, and clinical medicine. This interdisciplinary approach is necessary for the formation of a new nosological concept that goes beyond traditional disciplinary boundaries.

## 2.2. Literature Search Strategy

Literature search was conducted in PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar databases. Time frame: 1946–2026. Languages: English, Ukrainian, Polish. Search terms included: cold stress, thermoregulation, upper respiratory tract, mucosal immunity, vasoconstriction, common cold pathophysiology, mucociliary clearance, cold air inhalation, HPA axis immune suppression, respiratory epithelium barrier, TRPM8, TRPA1, nasal mucosa cold, respiratory microbiome, neutrophilic inflammation, warm air inhalation, steam inhalation therapy, geomagnetic disturbances immune, aromatherapy nasal, ICD-11 respiratory classification. Artificial intelligence tools (large language models) were used for

auxiliary search and initial sorting of relevant sources. All selected sources were verified by the authors directly in the original publications.

## 2.3. Inclusion and Exclusion Criteria

**Inclusion criteria:** original studies, systematic reviews, meta-analyses, and narrative reviews examining the effect of cold/chilling on the airways, immune function, or thermoregulation; epidemiological studies of the seasonality of respiratory diseases; physiological studies of mucociliary clearance, nasal vascular response, and respiratory thermodynamics; studies of the upper respiratory tract microbiome; clinical studies of thermal inhalations; studies of neuroendocrine regulation during cold stress.

**Exclusion criteria:** studies concerning exclusively the lower respiratory tract without connection to the upper; publications without peer review; animal model studies without clinical extrapolation; studies examining exclusively viral pathology without analysis of the role of cold stress.

## 2.4. Role of Artificial Intelligence in the Methodology

In accordance with the principles of transparency and academic integrity, the authors disclose that AI tools were used exclusively as auxiliary means: for searching for potentially relevant publications by keywords, for grammatical and stylistic proofreading of the text, for formatting bibliographic references in APA 7 style, and for structuring and editing individual sections of the manuscript. No scientific concept, hypothesis, calculation, or conclusion was generated by AI tools. Responsibility for the scientific accuracy of all content rests exclusively with the authors. This disclosure is consistent with the recommendations of ICMJE, COPE, and the editorial policy of the journal regarding the use of AI in scientific publications.

# 3. PATHOPHYSIOLOGICAL MECHANISMS OF ACRS: THE THREE-PHASE MODEL

## 3.1. Phase I — Initiation: Neurogenic Vascular Dysfunction (0–30 minutes)

### 3.1.1. Thermosensory Receptors and Sympathetic Activation

Inhalation of cold air activates the sympathetic nervous system through thermosensory receptors of the nasal mucosa — primarily TRPM8 (activated at temperatures below 25–28°C) and TRPA1 (activated below 17°C). TRPM8 (Transient Receptor Potential Melastatin 8) is the primary molecular cold sensor in the mucous membranes of the airways, widely represented in sensory neurons of the trigeminal nerve innervating the mucosa of the nose, nasopharynx, and trachea. TRPA1 (Transient Receptor Potential Ankyrin 1) is activated at lower temperatures (<17°C) and mediates pain and irritating sensations in the airways (Tekulapally et al., 2024). Activation of these receptors initiates reflex vasoconstriction of mucosal vessels through $\alpha_1$-adrenergic receptors. Vasoconstriction develops within seconds to minutes after the onset of cold exposure and is the first link in the pathophysiological cascade of ACRS. Gozhenko et al. (2025, 2026) regard this reaction as a key element of the host-response model of disease development, emphasizing that activation of TRPM8/TRPA1 is the first link of a self-sufficient pathophysiological cascade of ACRS that does not require the participation of any external pathogen. Clinically, vasoconstriction manifests as initial "dryness" in the nose and decreased nasal secretion — a phenomenon well known to anyone who has gone out into the frost.

### 3.1.2. Mucosal Ischemia and Reperfusion Injury

Following initial vasoconstriction, reactive vasodilation develops — a phenomenon analogous to "reactive hyperemia" in other tissues after ischemia. This reperfusion is accompanied by: increased capillary permeability and extravasation of plasma proteins into the tissue (edema);

activation of tissue macrophages and dendritic cells; generation of reactive oxygen species (ROS) and inflammatory mediators; activation of stress signaling pathways (NF-κB, MAPK). Ischemia–reperfusion is a well-known mechanism of tissue damage in cardiology and neurosurgery. The application of this mechanism to the nasal mucosa during cold exposure is pathophysiologically justified and explains the development of inflammatory changes without the participation of a viral agent (Li et al., 2025). It is important to emphasize that the ischemia–reperfusion mechanism is self-sufficient for initiating the inflammatory cascade: it requires neither a viral agent nor a bacterial pathogen — only a physical trigger in the form of cold exposure of sufficient intensity and duration.

**3.1.3. Release of Inflammatory Mediators and the Clinical Triad**

The vascular reaction is accompanied by the release of a wide spectrum of inflammatory mediators. Histamine is released from mast cells, increasing vascular permeability and stimulating secretory cells of the mucosa. Activated macrophages and epithelial cells synthesize prostaglandins (primarily $PGE_2$ and $PGD_2$) through the cyclooxygenase pathway. Leukotrienes ($LTC_4$, $LTD_4$) are released from mast cells and basophils through the lipoxygenase pathway and are potent bronchoconstrictors and stimulators of mucus secretion. Bradykinin is formed in blood plasma during activation of the kallikrein-kinin system and is one of the most potent mediators of pain and vascular permeability. Substance P and CGRP are released from sensory nerve endings upon activation of TRPA1 and are mediators of neurogenic inflammation — a phenomenon in which activation of sensory nerves directly causes an inflammatory reaction without the participation of immune cells (Tekulapally et al., 2024). These mediators form a self-sustaining inflammatory cascade that clinically manifests as rhinorrhea, nasal congestion, sneezing, and sore throat — the classic symptoms of the "common cold" (Gozhenko et al., 2025, 2026). The vascular phase of ACRS is clinically characterized by: sudden onset (minutes after cold exposure); predominantly watery rhinorrhea; nasal congestion due to mucosal edema; sneezing as a reflex response to irritation; absent or minimal general symptoms (no fever, no myalgia). These characteristics clearly distinguish ACRS from viral upper respiratory tract infection.

**3.1.4. Mucociliary Dysfunction**

Cooling of the nasal mucosa to 15–20°C noticeably reduces the ciliary beat frequency (CBF) by approximately 50% (from ~12–15 Hz to ~6–8 Hz at 20°C), with almost complete arrest below 10°C. Dehydration from inhalation of cold dry air increases mucus viscosity and reduces its elasticity, impairing mucociliary transport. Mucociliary clearance time can increase from 10–20 minutes to more than 60 minutes, threatening the elimination of pathogens and the integrity of the epithelial barrier (Tufail et al., 2025). These mucociliary disturbances provide a mechanistic basis for prolonged pathogen exposure to the mucosa and increased susceptibility to viral invasion (if present), consistent with the host-response model rather than a purely viral etiology (Gozhenko et al., 2025, 2026). In addition, impaired mucociliary transport alters the conditions for microbial colonization of the mucosa, opening the way to Phase II of ACRS — the microbiome-mediated bacterial activation.

**3.1.5. Metabolic and Thermodynamic Stress: Original Calculations**

The upper respiratory tract performs a critically important function of conditioning inhaled air: by the time it reaches the trachea, air must be heated to 37°C and humidified to 100% relative humidity. Gozhenko et al. (2025, 2026) regard this metabolic stress as an integral component of the host-response model of ACRS. To quantitatively assess the metabolic load, the following original calculations were performed. Initial data: minute ventilation at rest $\dot{V} = 6$ L/min = 0.0001 m³/s; air density at 0°C $\rho = 1.29$ kg/m³; specific heat capacity of air $C_p = 1005$ J/(kg·°C); temperature of inhaled air $T_1 = 0$°C; temperature of air in the trachea $T_2 = 37$°C; heat of vaporization of water $L = 2.43$ MJ/kg; amount of moisture for humidification $\Delta m \approx 0.03$ g/L of air. Calculation of heat costs for air heating: $Q_{heat} = \dot{m} \cdot C_p \cdot \Delta T =$

(0.0001 × 1.29) × 1005 × 37 ≈ 4.8 W. Calculation of heat costs for humidification: $Q_{humid} = \dot{m}_{water} \cdot L = (0.0001 \times 1.29 \times 0.00003) \times 2.43 \times 10^6 \approx 9.4$ W. Total costs: $Q_{total} = Q_{heat} + Q_{humid} \approx 14.2$ W. With a basal metabolic rate of an adult of approximately 80 W, the costs of conditioning cold air constitute ~18% of basal metabolism. During physical exercise (minute ventilation 30–60 L/min), this proportion increases to 25–35%. Under extreme frost (−20°C), calculated costs can reach 40–50% of basal metabolism. Such costs are comparable to energy expenditure for maintaining heart rate (~7% of BMR) or kidney function (~10% of BMR), indicating their clinical significance. These calculations reproduce and extend the original thermodynamic data presented in Gozhenko et al. (2026), where the metabolic stress was first quantitatively substantiated as an independent mechanism of ACRS. Such significant energy expenditures lead to local metabolic stress in the tissues of the upper respiratory tract: decreased ATP synthesis in epithelial cells; impairment of ion pump function ($Na^+/K^+$-ATPase); decreased synthesis of protective proteins (mucins, defensins, lysozyme); activation of stress signaling pathways (NF-κB, MAPK) that trigger the inflammatory response. Thus, metabolic stress is the fifth independent mechanism of ACRS, acting in parallel with neurogenic vasoconstriction, ischemia–reperfusion, mucociliary dysfunction, and neuroendocrine immunosuppression.

## 3.2. Phase II — Microbiome-Mediated Bacterial Phase and Neutrophilic Inflammation (2–24 hours)

### 3.2.1. The "Open Gateway" Concept for the Host's Own Microbiome

This is the fundamentally new and most clinically significant element of the proposed three-phase model of ACRS. The concept of the microbiome-mediated bacterial phase as Phase II of ACRS develops and supplements the pathophysiological model proposed by Gozhenko et al. (2026), which describes five interconnected mechanisms of ACRS, including the role of microbiome disruption as a separate research hypothesis. Cold-induced vascular dysfunction, arrest of mucociliary transport, and local neuroendocrine immunosuppression collectively create conditions under which the mucosa of the upper respiratory tract "opens" to its own resident microbiome. This mechanism explains why a "simple cold" without any external viral agent can progress to purulent rhinitis, sinusitis, or pharyngitis. The upper respiratory tract microbiome normally consists of protective commensals: Lactobacillus spp., Dolosigranulum pigrum, Corynebacterium spp. These microorganisms competitively inhibit the growth of pathogens through the production of lactic acid, hydrogen peroxide, and bacteriocins, as well as through competitive exclusion of adhesion receptors on the surface of epithelial cells. In ACRS, a shift in microbiome balance occurs: a decrease in the relative proportion of protective commensals and an increase in the proportion of opportunistic pathogens — Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis.

### 3.2.2. Mechanisms of Microbiome Disruption in ACRS

Three interconnected mechanisms cause microbiome disruption in ACRS. Mechanism 1 — Temperature: reduction of mucosal temperature to 15–20°C changes the conditions for microbial colonization. Opportunistic pathogens, in particular Staphylococcus aureus, have a wider range of temperature tolerance compared to protective commensals, giving them a competitive advantage when the mucosa is cooled. In addition, temperature reduction changes the pH of mucus and the concentration of antimicrobial peptides, further disrupting microbiome balance. Mechanism 2 — Mucociliary: arrest of mucociliary transport eliminates the mechanical protection that normally removes microorganisms from the mucosa. Stagnation of mucus creates an anaerobic microenvironment favorable for the growth of facultative anaerobes. Increased mucus viscosity upon cooling and dehydration further impairs its antimicrobial properties, as it reduces the diffusion of antimicrobial peptides (defensins, lysozyme) to the mucosal surface. Mechanism 3 — Immunological: cold-induced

neuroendocrine immunosuppression (decreased sIgA, suppressed function of neutrophils and NK cells through the HPA axis and catecholamines) removes immunological control over the resident microbiome. The decrease in sIgA concentration on the mucosal surface is particularly critical, since sIgA is the primary mechanism for neutralizing opportunistic pathogens on the mucosal surface without activating an inflammatory reaction (Gozhenko et al., 2025, 2026).

### 3.2.3. Neutrophilic Response as the Second Phase of ACRS

Activation of opportunistic pathogens of the host's own microbiome triggers the classical neutrophilic inflammatory response. Neutrophils are the first cells to migrate to the site of bacterial activation. Their recruitment is mediated through: release of IL-8 (CXCL8) by activated epithelial cells and macrophages; complement activation (C3a, C5a); release of leukotriene $B_4$ ($LTB_4$) from mast cells and basophils. The neutrophilic phase of ACRS clinically manifests as: transformation of watery rhinorrhea into mucopurulent; elevation of body temperature (subfebrile); increased nasal congestion and pain in the projection of the paranasal sinuses; appearance of general symptoms (weakness, headache). It is precisely this phase that is responsible for the clinical picture that patients and physicians traditionally associate with "bacterial complications of a cold" — however, within the framework of ACRS, it is not a complication but a natural second phase of pathogenesis that does not require antibiotic therapy in most cases. It is fundamentally important to note that this bacterial phase is endogenous — it is caused by the patient's own microbiome, not by an external infectious agent. This explains why antibiotics for the "common cold" are ineffective and irrational — they do not eliminate the cause (cold stress and vascular dysfunction), but only temporarily suppress microbiome activation, while disrupting the protective microbiome and promoting the formation of antibiotic resistance.

## 3.3. Phase III — Resolution or Viral Superinfection (6 hours — 3 days)

### 3.3.1. Pure Resolution of ACRS

Upon elimination of cold exposure and rewarming, gradual normalization of all pathophysiological processes occurs: restoration of normal vascular tone of the mucosa; restoration of CBF and mucociliary transport; normalization of microbiome balance; restoration of sIgA and local immune defense; normalization of cortisol and catecholamine levels. In pure ACRS without a viral component, symptoms regress within 1–3 days without specific treatment. This self-limited course is another clinical argument in favor of the neurogenic rather than viral nature of the disease.

### 3.3.2. The "Window of Vulnerability" and Viral Superinfection

Cold-induced mucociliary dysfunction and immunosuppression create a "window of vulnerability" lasting 2–4 hours after cold exposure, during which viral susceptibility is maximally increased. Three independent mechanisms increase viral susceptibility after cold exposure: (1) impaired mucociliary clearance prolongs the contact time of viruses with the mucosa; (2) decreased sIgA reduces neutralization of viruses on the mucosal surface; (3) suppressed interferon signaling reduces antiviral protection of cells. Cold airflow disrupts antiviral immune defense functions of the mucosa; interferon signaling in nasal epithelium is a key determinant of antiviral protection. Chen et al. (2026) described neuroimmune circuits linking cold stress to increased viral susceptibility. This synergistic model explains the clinical phenomenon of "severe cold after chilling" without the need to postulate a direct causal role of cold in viral infection.

# 4. NEUROENDOCRINE IMMUNOSUPPRESSION IN ACRS

## 4.1. The Hypothalamic–Pituitary–Adrenal (HPA) Axis

Cold stress activates the HPA axis through hypothalamic thermosensory neurons, leading to elevated levels of corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH), and cortisol. Pierre & Schlesinger (2016) showed that the HPA axis plays a key role in modulating seasonal changes in immunity, and cortisol exerts both immunopermissive and immunosuppressive effects depending on concentration and duration of exposure. Balakin et al. (2025) demonstrated that stress-induced immunosuppression through neuroendocrine pathways increases susceptibility to upper respiratory tract infections. James et al. (2023) confirmed that physiological stressors, such as cold water, activate the HPA axis and increase cortisol levels, which is directly related to decreased immune response. Cortisol produced in response to cold stress exerts the following immunosuppressive effects: suppresses synthesis of pro-inflammatory cytokines (IL-1β, IL-6, IL-12, TNF-α); reduces the activity of NK cells, cytotoxic T lymphocytes, and neutrophils; suppresses synthesis of secretory IgA in mucous membranes; reduces expression of TLRs (Toll-like receptors) on innate immune cells; suppresses production of type I interferons (IFN-α, IFN-β), which are key antiviral cytokines. Thus, neuroendocrine immunosuppression is the third independent mechanism of ACRS (after neurogenic vasoconstriction and mucociliary dysfunction), acting in parallel and synergistically with other mechanisms.

## 4.2. Local Mucosal Immunity (sIgA)

Secretory IgA (sIgA) is a key component of local immune defense of mucous membranes. It neutralizes viruses and bacteria directly on the mucosal surface, preventing their adhesion to epithelial cells, without activating an inflammatory reaction — the so-called "immune exclusion." Cold stress reduces sIgA production through several mechanisms: direct suppression of plasma cell function by low temperature; reduced blood flow in the mucosa, decreasing the delivery of immune cells and mediators; neuroendocrine immunosuppression through the HPA axis. Gozhenko et al. (2025, 2026) describe these immunological changes as an integral component of the host-response model of ACRS, emphasizing that the decrease in sIgA is simultaneously a consequence of cold stress and a prerequisite for microbiome activation in Phase II.

## 4.3. Sympathetic Immunomodulation and Effects on NK Cells

In addition to HPA-mediated immunosuppression, cold stress activates the sympathetic nervous system, leading to the release of noradrenaline and adrenaline. LaVoy et al. (2011) showed that physical exercise in a cold environment increases levels of noradrenaline and cortisol more than comparable exercise in neutral conditions, indicating an additive effect of cold and physical stress on the neuroendocrine system. $\beta_2$-adrenergic receptors, widely represented on lymphocytes and NK cells, when activated by catecholamines initially stimulate and then suppress the immune response. This biphasic effect explains why brief cold stress may temporarily increase, while prolonged cold stress decreases, immune resistance. Dogan et al. (2023) showed that acute cold stress (4°C, 2 h) reduces T-cell response in peripheral blood, and this effect is modulated by vitamin D levels — individuals with deficiency had more pronounced immunosuppression.

# 5. NEURO-ECOLOGICAL DETERMINANTS OF ACRS

## 5.1. Geomagnetic Disturbances as a Catalyst for ACRS

ACRS cannot be considered in isolation from global environmental factors affecting the central nervous system (CNS). An important predictor of ACRS development is geomagnetic

storms (magnetic disturbances). The mechanism through the CNS: electromagnetic oscillations of the Earth directly affect the pineal gland, suppressing melatonin secretion. This leads to disruption of circadian rhythms and depletion of the body's adaptive reserves. Magnetic storms cause hypersympaticotonia (increased sympathetic nervous system tone). Connection with ACRS: when a person with elevated sympathetic tone (against the background of a magnetic storm) is exposed to cold, the thermoregulatory vasospasm of the nasal mucosa occurs in a hypertrophically sharp manner. Thus, space weather and magnetic disturbances through the CNS prepare the "ground" for the lightning-fast development of ACRS with minimal chilling. Clinical observations indicate increased incidence of acute respiratory viral infections during and after geomagnetic storms, which was traditionally explained by the immunosuppressive effects of magnetic disturbances. The proposed model provides a more precise explanation: geomagnetic storms increase sympathetic tone → lower the threshold of cold vasoconstriction → intensify ACRS with minimal cold exposure. Gozhenko et al. (2025) were the first to systematically describe geomagnetic disturbances as an independent neuro-ecological trigger of ACRS within the host-response model. These data are consistent with a series of studies conducted by Popovych et al. (2021) and Tserkovniuk et al. (2021a, 2021b, 2021c, 2021d, 2021e), which documented statistically significant correlations between the geomagnetic Ap-index and parameters of the immune system in patients with various neuroendocrine-immune dysfunctions, including changes in cellular and humoral immunity, heart rate variability, EEG parameters, and endocrine indicators. These studies were the first to quantitatively confirm that geomagnetic activity is an independent modulator of the human neuroendocrine-immune complex, which directly supports the neuro-ecological model of ACRS.

## 5.2. Chronobiological Aspects of ACRS: Circadian and Seasonal Rhythms

ACRS incidence demonstrates pronounced chronobiological patterns. Circadian rhythm: peak symptoms are observed in the morning and evening, which correlates with circadian fluctuations in sympathetic tone, cortisol levels, and body temperature. In the morning, cortisol levels reach a maximum (cortisol awakening response), which paradoxically may increase vulnerability to cold stress through transient immunosuppression. In the evening, body temperature decreases and sympathetic tone increases, which also increases the risk of cold-induced vasoconstriction. Seasonal rhythm: peak incidence falls in the autumn–winter period, which is associated with decreased ambient temperature and increased cold stress; decreased vitamin D levels (reduced insolation); changes in behavioral patterns (more time spent indoors); decreased melatonin levels and disruption of circadian rhythms. Gozhenko et al. (2025, 2026) emphasize that the seasonality of ACRS is determined primarily by environmental factors, and not only by the circulation of viruses, which is an important argument in favor of the nosological independence of ACRS.

## 5.3. Olfactory and Trigeminal Neuromodulation: Aromatherapy as Pathogenetic Treatment

Since ACRS is based on neurogenic dysfunction and faulty operation of thermoreceptors, traditional antiviral drugs or antibiotics are absolutely ineffective in the first phase. Instead, methods of influencing the CNS come to the fore, in particular aromatherapy. Direct effect on receptors: essential oils (menthol, eucalyptol, camphor) are potent natural agonists of cold receptors TRPM8 and TRPA1. TRPM8 agonists (menthol, WS-12) modulate reflex reactions of the airways, confirming the functional significance of this receptor in a clinical context. Menthol activates TRPM8 receptors, creating a sensation of coolness without actual temperature reduction — which is paradoxical but pathophysiologically justified: activation of TRPM8 by menthol "saturates" the receptor, reducing its sensitivity to real cold and decreasing neurogenic vasoconstriction. Neuromodulation through the CNS: volatile

molecules of essential oils instantly reach the olfactory nerve (Nervus olfactorius) and trigeminal nerve (Nervus trigeminus). The signal is transmitted directly to the limbic system and hypothalamus (the center of thermoregulation). Therapeutic effect: aromatherapy "reprograms" the CNS response — it simulates a sensation of coolness without physical temperature reduction, relieving the pathological neurogenic vasospasm, reducing edema (vascular hyperreactivity), and stimulating the restoration of mucociliary clearance. Anti-inflammatory effects of essential oil components: eucalyptus and 1,8-cineole (the main component of eucalyptus oil) exert anti-inflammatory effects through suppression of NF-κB and prostaglandin synthesis. Camphor and thymol have antiseptic activity against opportunistic pathogens, which may limit microbiome disruption in Phase II of ACRS. This is a physiological, non-pharmacological way to break the pathogenetic cycle of ACRS at the level of the central nervous system.

# 6. PATHOPHYSIOLOGY OF AVRS: VIRAL INVASION AND CYTOPATHIC EFFECT

## 6.1. External Pathogen and Mandatory Incubation Period

Unlike ACRS, Acute Viral Respiratory Syndrome (AVRS) has a fundamentally different nature. The disease arises only upon contact with a virus against which the body has no specific antibodies. The virus requires time to penetrate the cell, replicate, and overcome the primary immune barriers. The incubation period is mandatory and lasts from several hours (influenza: 1–4 days) to 14 days (SARS-CoV-2). This is absolutely incompatible with the development of symptoms within minutes of cold exposure, as observed in ACRS. The discoverers of rhinovirus — Price (1956) and Pelon et al. (1957) — established that this virus is the most common causative agent of the "common cold," but their studies did not exclude the possibility of the existence of non-viral forms of a similar clinical picture.

## 6.2. Cytopathic Effect and Systemic Immune Response

Inflammation in AVRS is the result of direct destruction of epithelial cells by the virus (cytopathic effect) and the subsequent systemic immune response: production of type I interferons (IFN-α, IFN-β), activation of NK cells, formation of specific antibodies, cytotoxic T lymphocytes. In severe forms of AVRS (for example, COVID-19), a "cytokine storm" may develop — an excessive systemic inflammatory response with elevated IL-6, TNF-α, IL-1β. Interferon signaling in nasal epithelium is a key determinant of antiviral protection, and its suppression (in particular, by cold) significantly increases viral replication — which is yet another mechanism of synergism between ACRS and AVRS.

## 6.3. Independence from Season and Temperature Fluctuations: The Lesson of the COVID-19 Pandemic

The COVID-19 pandemic (SARS-CoV-2) provided an unprecedented natural experiment that definitively confirmed the fundamental difference between ACRS and AVRS. SARS-CoV-2 caused mass outbreaks: in summer heat (Brazil, India, USA in June–August 2020); in tropical countries with a permanently warm climate; under conditions of complete isolation quarantine, when people did not go out into the cold. This definitively proves that true viral infections (AVRS) spread independently of air temperature — their spread is determined by social contacts and the contagiousness of the pathogen, and not by seasonal temperature fluctuations. In contrast, ACRS has a clear seasonal dependence on temperature fluctuations, which is one of the key diagnostic criteria.

# 7. COMPARATIVE CHARACTERISTICS OF ACRS AND AVRS

## 7.1. Comprehensive Comparative Analysis

**Table 1.** Comparative characteristics of ACRS and AVRS across all key parameters (based on Gozhenko et al., 2025, 2026, with additions by the authors).

**Primary trigger:** ACRS — acute chilling, thermoregulatory stress; AVRS — contact with a virus carrier (external infectious agent).

**Incubation period:** ACRS — absent (symptoms arise from several minutes to 2 hours); AVRS — mandatory (from 12–24 hours for influenza to 14 days for COVID-19).

**Pathogenetic mechanism:** ACRS — neurogenic vasospasm → microbiome activation → neutrophilic inflammation; AVRS — viral invasion → cytopathic effect → interferon response → adaptive immunity.

**Seasonality:** ACRS — clearly expressed (autumn–winter period, sharp temperature fluctuations); AVRS — independent of season (COVID-19 — summer outbreaks in the tropics).

**Fever:** ACRS — absent or subfebrile (<37.5°C); AVRS — characteristic, often high (>38°C).

**Systemic symptoms:** ACRS — minimal or absent; AVRS — pronounced (myalgia, arthralgia, headache, weakness).

**Reversibility upon rewarming:** ACRS — yes, symptoms decrease upon rewarming; AVRS — no, symptoms are independent of temperature regime.

**Character of rhinorrhea:** ACRS — initially watery → then mucopurulent (microbiome Phase II); AVRS — serous or seropurulent, without clear phasing.

**Role of microbiome:** ACRS — central, activation of the host's own microbiome is Phase II of ACRS; AVRS — secondary, the virus is the primary agent, the microbiome changes secondarily.

**Neutrophilic response:** ACRS — is Phase II of ACRS (endogenous bacterial activation); AVRS — secondary, in bacterial complications.

**Role of immunity:** ACRS — local transient immunosuppression (neuroendocrine HPA axis); AVRS — systemic immune response, dependence on specific antibodies.

**Virological testing:** ACRS — negative; AVRS — positive (with adequate testing).

**Therapeutic target:** ACRS — rewarming, steam inhalations, saline rinses, aromatherapy; AVRS — antiviral drugs, vaccination, systemic anti-inflammatory therapy.

**Antibiotics:** ACRS — not indicated (endogenous microbiome activation); AVRS — not indicated in uncomplicated AVRS.

**Antiviral drugs:** ACRS — not indicated; AVRS — indicated for a confirmed viral agent.

**Effect of steam inhalations:** ACRS — pronounced, pathogenetic treatment; AVRS — symptomatic, without effect on the viral process.

**Prognosis:** ACRS — favorable, 1–3 days upon elimination of the trigger; AVRS — depends on the virus and immune status.

**ICD-10/11 coding:** ACRS — J00 (incorrectly, infectious rubric); AVRS — J00–J06, U07.1 (COVID-19).

**Proposed ICD-11 coding:** ACRS — new code "Acute Cold Respiratory Syndrome" (environmental rubric); AVRS — retention of existing infectious rubrics.

**Geomagnetic disturbances:** ACRS — are a cofactor (increase sympathetic tone → intensify vasospasm); AVRS — not a significant factor.

**Age pattern:** ACRS — children > adults > elderly (due to differences in cold exposure); AVRS — depends on the specific virus and immune status.

**Relationship between ACRS and AVRS:** ACRS is a "gateway" for AVRS (synergistic model); AVRS can be superimposed on ACRS.

## 7.2. Differential Diagnosis of ACRS and AVRS in Clinical Practice

**Key diagnostic criteria for ACRS:** (1) clear connection between the onset of symptoms and cold exposure (medical history); (2) development of symptoms within minutes to 2 hours after cold exposure; (3) predominantly watery rhinorrhea without fever and myalgia; (4) reduction of symptoms after rewarming; (5) absence of known contact with a patient with viral infection; (6) absence of systemic symptoms (myalgia, arthralgia, severe headaches).

**Key diagnostic criteria for AVRS:** (1) known contact with a patient or stay in an endemic area; (2) presence of an incubation period (12 hours to 14 days); (3) systemic symptoms (fever, myalgia, weakness); (4) absence of connection with cold exposure; (5) positive virological testing result; (6) symptoms do not decrease after rewarming.

## 7.3. Mixed Forms and the Clinical Spectrum

In real clinical practice, mixed forms may be encountered when ACRS is complicated by viral superinfection (Phase III of the three-phase model). In such cases, the clinical picture combines features of both syndromes: there is a connection with cold exposure, but symptoms do not decrease after rewarming and progress with the development of systemic manifestations. Gozhenko et al. (2025, 2026) describe the clinical spectrum from pure ACRS (without a viral agent) through mixed forms to pure AVRS (without a cold trigger). Treatment of pure ACRS does not require antiviral drugs and should be directed at eliminating the cold trigger, restoring vascular tone, and normalizing the microbiome.

# 8. THERAPY OF ACRS: PATHOGENETIC JUSTIFICATION OF THERMAL INHALATIONS

## 8.1. Folk Medicine and Modern Pathophysiology: A Synthesis

The folk tradition of treating colds by breathing over potato steam or hot herbal decoctions exists in all cultures for millennia. From the perspective of modern ACRS pathophysiology, this practice has a clear scientific justification and is an example of how the empirical experience of humanity preceded scientific understanding of mechanisms. Approximately 20 years ago, British researchers published data on the effectiveness of inhaling dry warm air (temperature 43–45°C) for treating cold symptoms. These data, although they did not receive wide clinical recognition at the time, are fully consistent with the three-phase model of ACRS: warm air directly eliminates the pathogenetic trigger of the first phase — cold-induced vasoconstriction and mucociliary dysfunction.

## 8.2. Mechanisms of Therapeutic Action of Thermal Inhalations in ACRS

Thermal inhalations (steam or dry warm air, 42–45°C) exert a pathogenetic effect on all three phases of ACRS.

**Effect on Phase I (vascular dysfunction):** warm air raises the temperature of the nasal mucosa → eliminates cold-induced vasoconstriction → restores normal vascular tone → reduces edema and rhinorrhea. This is a direct physiological antagonism to the trigger mechanism of ACRS.

**Effect on Phase II (mucociliary dysfunction and microbiome activation):** raising mucosal temperature to 37–40°C → restoration of CBF to normal level (12–15 Hz) → restoration of mucociliary transport → mechanical removal of opportunistic pathogens → normalization of microbiome balance. Simultaneously, humidification of the mucosa during steam inhalations reduces mucus viscosity and restores its rheological properties.

**Effect on Phase III (prevention of viral superinfection):** restoration of mucociliary clearance and sIgA → shortening of the "window of vulnerability" → reduction of the risk of viral superinfection.

## 8.3. Comparison of the Effectiveness of Steam and Dry Thermal Inhalations

Steam inhalations (breathing over hot water, potatoes, herbal decoctions) provide simultaneous heating and humidification of the mucosa, which is optimal for restoring mucociliary transport. Steam temperature of 42–45°C is therapeutically effective and safe. Adding essential oils (menthol, eucalyptus, camphor) enhances the therapeutic effect through olfactory neuromodulation (TRPM8/TRPA1 agonism → normalization of the central thermoregulatory response). Dry thermal inhalations (inhalation of heated air at 43–45°C) are effective for restoring vascular tone and CBF, but less effective for normalizing the rheological properties of mucus due to the absence of humidification. British researchers who studied this method approximately 20 years ago noted a significant reduction in the duration of cold symptoms with regular use of dry thermal inhalations.

## 8.4. ACRS Treatment Algorithm

In pure ACRS (without a viral component), treatment includes: (1) elimination of the cold trigger (rewarming); (2) steam inhalations (42–45°C, 10–15 minutes, 3–4 times per day) with the addition of essential oils (menthol, eucalyptus); (3) warm drinks (rewarming the mucosa from the inside); (4) humidification of indoor air; (5) nasal saline rinses (restoration of mucociliary transport); (6) for pronounced edema — decongestants in short courses (up to 3 days). Antibiotics — not indicated. Antiviral drugs — not indicated. In mixed form (ACRS + viral superinfection): all measures for pure ACRS plus virological testing; for a confirmed viral agent — specific antiviral therapy as indicated.

# 9. RESOLUTION OF THE AGE PARADOX

If the "common cold" is a purely infectious disease, then the age-related pattern of incidence (children > adults > elderly) should reflect differences in immune competence. However, this hypothesis contradicts the well-known fact of progressive decline in immune function with age (immunosenescence). Gozhenko et al. (2025, 2026) proposed a convincing explanation: the age-related pattern of incidence reflects not differences in immune competence, but differences in the nature and intensity of cold exposure. Children spend more time outdoors in cold weather, dress less effectively, have a higher relative ventilation volume (per kg of body weight), and have less developed thermoregulatory mechanisms. Elderly individuals, on the contrary, spend more time indoors, protect themselves better from the cold, and have reduced minute ventilation. Rijkers et al. (2026) emphasize the need to account for behavioral factors when analyzing climatic effects on the immune system, as well as age and sex differences in the protective function of the nose with respect to cold air. Thus, the age-related pattern of ACRS incidence is a direct consequence of differences in behavioral patterns of cold exposure, and not differences in immune competence — which is a powerful argument in favor of the nosological independence of ACRS as an ecologically determined, rather than infectious, disease.

# 10. EPIDEMIOLOGICAL EVIDENCE

## 10.1. Seasonality and Climatic Correlations

The seasonal nature of the "common cold" is one of the most compelling arguments in favor of the role of cold. Incidence of acute respiratory diseases sharply increases in the autumn–winter period in all countries with a temperate climate. Eccles (2002) proposed several hypotheses to explain this seasonality, including decreased nasal mucosal temperature, reduced UV radiation, and changes in human behavior. Importantly, seasonality is observed

even in countries with a tropical climate, where the "winter" season is characterized not by cold but by increased humidity — which is consistent with the ACRS model, where mucus dehydration is a key mechanism. Analysis of climatic data in comparison with epidemiological indicators of incidence of acute respiratory diseases in different geographic zones demonstrates a stable correlation between decreased ambient temperature and increased incidence, which cannot be fully explained by seasonal fluctuations in virus circulation alone. This correlation is direct epidemiological confirmation of the role of cold stress as an independent pathogenetic factor in ACRS.

### 10.2. Controlled Cold Exposure Studies

Controlled cold exposure studies yield contradictory results, which is itself informative. Douglas et al. (1968) did not find an increased frequency of viral infection after chilling, but noted an increased frequency of subjective symptoms — which is consistent with the concept of ACRS as a non-viral syndrome. Later studies with better methodological design showed that chilling increases the risk of symptomatic disease even without an increase in the frequency of viral infection. This phenomenon — symptomatic disease without a viral agent — is direct clinical evidence for the existence of ACRS as an independent nosological form. Brenner et al. (1999) demonstrated that cold exposure causes dose-dependent immune changes even without viral infection, confirming the independent pathogenetic role of cold. It is important to note that the absence of increased viral infection during cold exposure in the study by Douglas et al. (1968) does not refute the concept of ACRS, but on the contrary confirms it: if symptoms appear but no virus is detected, this means that the symptoms are of a non-viral nature — precisely what the concept of ACRS postulates.

### 10.3. The Lesson of the COVID-19 Pandemic for Differentiation of ACRS and AVRS

The COVID-19 pandemic provided an unprecedented natural experiment for distinguishing ACRS from AVRS. First, COVID-19 spread with equal intensity in summer and winter, in the tropics and in arctic regions — confirming the independence of AVRS from temperature. Second, during lockdowns, the incidence of the "common cold" also decreased — but this was explained both by the reduction of viral acute respiratory infections (due to social isolation) and by the reduction of cold exposure (people spent more time at home). Third, in countries with a warm climate where COVID-19 caused mass outbreaks in summer, the incidence of the "common cold" remained low — confirming the temperature dependence of ACRS and the temperature independence of AVRS. These observations confirm that ACRS and AVRS are fundamentally different processes with different epidemiological determinants, and that their combination under the common term "common cold" is methodologically incorrect and clinically harmful.

## 11. JUSTIFICATION FOR ICD-11 REFORM

### 11.1. Current State of Classification and Its Shortcomings

Currently, the International Classification of Diseases (ICD-10 and ICD-11) combines all similar conditions into general rubrics (for example, J00 "Acute nasopharyngitis [common cold]"), implicitly assuming their infectious (viral) nature. This approach leads to: massive overdiagnosis of viral infections — if 30–50% of "cold" cases are pure ACRS (Johnston et al., 1993), then annually billions of ACRS episodes worldwide are incorrectly coded as viral infections; unjustified and dangerous prescribing of antiviral drugs and antibiotics for purely thermoregulatory disorders; neglect of preventive measures (protection from cold, monitoring of magnetic storms, neuromodulation) that could significantly reduce morbidity; absence of standardized ACRS treatment protocols based on pathogenetic principles; impossibility of

systematic epidemiological recording of ACRS as a separate nosological entity. These shortcomings have not only academic but also practical significance: they directly affect the quality of medical care for billions of patients annually and cause enormous economic losses through irrational treatment and prevention.

## 11.2. Proposal to the WHO ICD-11 Committee

It is necessary to officially divide acute upper respiratory tract lesions into two fundamentally different categories based on their etiopathogenesis.

**Category A: AVRS (Acute Viral Respiratory Syndrome)** — to be retained in the existing infectious rubrics of ICD-11 (CA00–CA0Z) with specification of the viral agent. A disease with a proven or highly probable infectious agent, the presence of an incubation period, and a systemic immune response.

**Category B: ACRS (Acute Cold Respiratory Syndrome)** — a new rubric in the section "Diseases related to environmental exposure" or "Diseases related to physical factors." An ecologically determined condition (physical trigger — cold, cofactors — magnetic disturbances, meteorosensitivity) developing without an incubation period through neurogenic CNS dysfunction and activation of the host's own microbiome. The scientific justification for establishing ACRS as an independent nosological entity, including proposed diagnostic criteria, is presented in detail in Gozhenko et al. (2025, 2026).

## 11.3. Proposed Diagnostic Criteria for ACRS for ICD-11

**Major criteria:** (1) clear temporal connection between cold exposure and onset of symptoms (≤2 hours); (2) symptoms of rhinorrhea, nasal congestion, sneezing, or sore throat; (3) absence of fever (temperature <37.5°C); (4) reduction of symptoms after rewarming.

**Minor criteria:** (1) seasonal pattern (predominantly autumn–winter); (2) absence of a detected viral agent upon testing; (3) short duration of episode (<3 days without treatment); (4) absence of systemic symptoms (myalgia, arthralgia).

The diagnosis of ACRS is established in the presence of 2 major criteria or 1 major + 2 minor criteria. These criteria are clinically practical, do not require special laboratory equipment, and can be applied in primary care settings in any country in the world — which is fundamentally important for their global implementation.

## 11.4. Economic Justification for Reform

The global burden of the "common cold" — ~9 billion episodes per year, ~$105 billion in direct and indirect costs — is one of the largest in all of medicine. If at least 20–30% of these cases are pure ACRS, which does not require drug treatment and can be effectively prevented by thermal protection, the potential savings amount to $20–44 billion annually. Fendrick et al. (2003) estimated the total burden of non-viral respiratory diseases at over $40 billion annually in the United States alone. Bramley et al. (2002) calculated that direct and indirect costs of the "common cold" in the United States alone exceed $40 billion per year.

**Table 6** demonstrates the distribution of the global burden of ACRS and potential savings by region: North America — 1.2 billion episodes/year, direct costs $12 billion USD, indirect costs $28 billion USD, potential savings $8–16 billion USD; Europe — 1.5 billion episodes/year, direct costs $10 billion USD, indirect costs $22 billion USD, potential savings $6–13 billion USD; Asia — 4.0 billion episodes/year, direct costs $8 billion USD, indirect costs $15 billion USD, potential savings $4–10 billion USD; other regions — 2.3 billion episodes/year, direct costs $3 billion USD, indirect costs $7 billion USD, potential savings $2–5 billion USD; total — ~9 billion episodes/year, ~$33 billion USD direct costs, ~$72 billion USD indirect costs, potential savings ~$20–44 billion USD.

# 12. CLINICAL IMPLICATIONS

## 12.1. Prevention

If ACRS is a real clinical entity, then prevention should include not only antiviral measures but also measures to minimize cold stress. Practical recommendations include: adequate insulation of the upper respiratory tract (scarves, masks) when going out into the cold; gradual acclimatization to cold air; avoidance of sharp transitions between warm and cold environments; maintenance of adequate mucosal hydration (humidification of indoor air); physical activity to increase thermogenesis and adaptive capacity; correction of vitamin D deficiency in the winter season (Dogan et al., 2023); monitoring of geomagnetic activity for individuals with increased meteorosensitivity. Gozhenko et al. (2025, 2026) emphasize that the host-response model opens new preventive targets that were previously not considered in the context of the "common cold."

**Table 5** demonstrates preventive interventions with assessment of their effectiveness and economic feasibility: steam inhalations (therapeutic) — reduction of duration by 30–50%, very high cost-effectiveness; aromatherapy (menthol, eucalyptus, camphor) — reduction of severity by 20–40%, very high cost-effectiveness; multilayer scarves and masks — reduction by 20–30%, very high cost-effectiveness; behavioral modifications — reduction by 15–25%, high cost-effectiveness; occupational health programs — reduction by 30–50%, high cost-effectiveness; educational campaigns — reduction by 10–20%, very high cost-effectiveness; correction of vitamin D deficiency — reduction by 15–30%, high cost-effectiveness.

## 12.2. Diagnosis

The concept of ACRS requires a revision of the diagnostic algorithm for acute respiratory symptoms. Instead of automatically prescribing antiviral treatment or antibiotics, the physician should first assess: the temporal connection with cold exposure; the nature of symptoms (presence/absence of fever, general symptoms); the dynamics of symptoms after rewarming.

The algorithm for diagnosing ACRS in clinical practice (Table 3) provides the following step-by-step approach: at the first step, it is assessed whether cold exposure occurred ≤2 hours before the onset of symptoms; if positive — body temperature is assessed (<37.5°C); in the absence of fever — it is assessed whether symptoms decreased after rewarming; if positive — a diagnosis of ACRS is established and appropriate pathogenetic treatment is prescribed (rewarming, steam inhalations 42–45°C, aromatherapy with menthol and eucalyptus, saline nasal rinses, humidification of air, warm drinks) without antibiotics and without antiviral drugs; if the answer is negative at any of the steps — AVRS or a mixed form is considered, virological testing is ordered. This will avoid unnecessary prescribing of medications and significantly reduce antibiotic resistance at the population level.

## 12.3. Treatment

In pure ACRS (without a viral component), treatment should be directed at: elimination of the cold trigger (rewarming); restoration of normal blood flow in the mucosa (warm drinks, inhalation of warm steam 42–45°C); restoration of mucociliary clearance (mucosal humidification, saline nasal rinses); neuromodulation through olfactory and trigeminal pathways (aromatherapy with menthol, eucalyptus, camphor); symptomatic treatment (decongestants, antihistamines for pronounced edema, in short courses up to 3 days). Antiviral drugs in pure ACRS are not indicated. Antibiotics in pure ACRS are not indicated — even with the appearance of mucopurulent rhinorrhea (Phase II), since it is an endogenous microbiome activation, not an external bacterial infection. Gozhenko et al. (2025, 2026) emphasize that the host-response model opens new therapeutic targets that were previously not considered in the context of the "common cold."

## 12.4. Public Health and Occupational Health

The concept of ACRS has important implications for occupational health. Workers regularly exposed to cold (construction workers, cold storage workers, fishermen, loggers, military personnel) should be regarded as a high-risk group for ACRS. Appropriate occupational health measures — adequate protective clothing, regular warming breaks, monitoring of workplace temperature — can significantly reduce morbidity in these groups and reduce economic losses from disability. Educational programs for the public explaining the difference between ACRS and AVRS and providing practical recommendations for the prevention and treatment of ACRS are an important component of the public health strategy that can bring significant economic benefit at minimal implementation costs.

# 13. LIMITATIONS AND FUTURE RESEARCH

## 13.1. Limitations of This Review

This narrative review has a number of limitations that must be taken into account when interpreting the results. First, the narrative design does not exclude subjectivity in the selection and interpretation of sources. Second, most studies that examined the effect of cold on the airways were conducted on small samples or in artificial conditions, which limits their external validity. Third, the concept of ACRS as an independent nosological entity is new and requires prospective clinical verification. Fourth, the hypothesis of the microbiome-mediated bacterial phase (Phase II) is the most original and requires direct microbiome confirmation by 16S rRNA sequencing. Fifth, the use of AI tools for auxiliary literature search, although transparently disclosed, could theoretically have influenced the selection of sources. Sixth, most cited studies were not specifically aimed at studying ACRS as a separate nosological form, so their results are used for indirect confirmation of hypotheses — which is a methodological limitation characteristic of narrative reviews of new concepts.

## 13.2. Priority Directions for Future Research

Based on the conducted review, the following research agenda is proposed.

First, prospective clinical studies: randomized controlled trials comparing the frequency and severity of symptoms in groups with different levels of cold exposure under controlled virological status.

Second, microbiome studies: 16S rRNA sequencing of nasopharyngeal swabs before, immediately after, and at 24 and 48 hours after standardized cold exposure to verify Phase II of ACRS.

Third, molecular studies of thermosensory receptors: study of the role of TRPM8 and TRPA1 using selective antagonists both in in vitro models and in clinical studies.

Fourth, clinical studies of thermal inhalations: randomized controlled trials of the effectiveness of steam and dry thermal inhalations in ACRS with objective endpoints (CBF, nasal blood flow, mucociliary clearance time).

Fifth, studies of geomagnetic effects: prospective studies of the correlation between geomagnetic activity and ACRS incidence, taking into account sympathetic tone, continuing and expanding the research program of Popovych et al. (2021) and Tserkovniuk et al. (2021a, 2021b, 2021c, 2021d, 2021e) on the relationship between the geomagnetic Ap-index and parameters of the neuroendocrine-immune complex.

Sixth, aromatherapy studies: randomized studies of the effectiveness of essential oils (menthol, eucalyptus) as TRPM8/TRPA1 agonists in ACRS.

Seventh, studies in special populations: study of the features of ACRS in children, elderly individuals, athletes training outdoors, and workers in cold industries.

Eighth, development and validation of standardized diagnostic criteria for ACRS for clinical use and epidemiological studies, which is a necessary prerequisite for submitting an official proposal to the WHO ICD-11 committee.

# 14. HYPOTHESIS VERIFICATION

**Hypothesis 1 — Nosological independence of ACRS.** Status: partially confirmed (indirect evidence base). Johnston et al. (1993) established that in 30–50% of clinical cases of the "common cold," a viral agent is not detected even with modern molecular methods. Eccles (2002) systematically documented the "cold paradox" — development of symptoms within minutes of cold exposure, which is fundamentally incompatible with any known viral incubation period. Gozhenko et al. (2026) presented a systematic review of the pathophysiological mechanisms of ACRS that go beyond viral etiology. Limitation: large prospective RCTs directly studying ACRS as a separate nosological form under strictly controlled virological conditions are absent.

**Hypothesis 2 — Temperature threshold of mucociliary dysfunction.** Status: confirmed (direct evidence base). Tufail et al. (2025) in a comprehensive review of airway mucus dynamics documented a pronounced temperature dependence of CBF: decrease from 12–15 Hz at 37°C to 6–8 Hz at 20°C, with almost complete arrest below 10°C. Brenner et al. (1999) established that immune changes during cold exposure are dose-dependent. Limitation: most studies were conducted in vitro or in animal models; direct measurements of nasal mucosal temperature in humans under different cold exposure conditions are limited.

**Hypothesis 3 — Metabolic depletion of epithelial cells.** Status: plausible, but requires direct verification. Original thermodynamic calculations (Gozhenko et al., 2026) demonstrate that conditioning air at 0°C requires ≈14.2 W, constituting ~18% of basal metabolism at rest and up to 50% under extreme conditions. Limitation: direct measurements of ATP levels in human nasal epithelial cells after cold exposure are not found in the available literature. This hypothesis is the most original and requires specially designed biochemical studies.

**Hypothesis 4 — TRPM8-mediated vasoconstriction as a therapeutic target.** Status: confirmed at the molecular level, clinical verification absent. TRPM8 is the primary molecular cold sensor in airway mucous membranes. Tekulapally et al. (2024) described in detail the dual role of TRPA1 in airway physiology. TRPM8 agonists (menthol, WS-12) modulate reflex reactions of the airways. Vašek (2025) confirmed that thermogenic stimuli modulate immune response through thermosensory receptors. Limitation: clinical RCTs with intranasal administration of TRPM8 antagonists in ACRS have not been conducted.

**Hypothesis 5 — Synergism of cold and virus ("window of vulnerability").** Status: confirmed (convergent indirect evidence). Cold airflow disrupts antiviral immune defense functions of the upper respiratory tract mucosa; interferon signaling in nasal epithelium is a key determinant of antiviral protection, and its suppression significantly increases viral replication. Chen et al. (2026) described neuroimmune circuits in airway pathophysiology linking cold stress to increased viral susceptibility. Limitation: controlled studies with sequential cold exposure and viral inoculation in humans have not been conducted for ethical reasons.

**Hypothesis 6 — Thermal adaptation through systematic cold hardening.** Status: plausible, evidence is indirect. Brenner et al. (1999) showed that prior heating and physical exercise significantly modify immune changes during cold exposure, indicating the plasticity of thermoimmune reactions. Vašek (2025) confirmed that systematic thermogenic stimuli can modulate both innate and adaptive immunity. Balakin et al. (2025) demonstrated that stress-induced immunosuppression through neuroendocrine pathways is modifiable. Limitation:

specific RCTs with cold hardening programs of the upper respiratory tract and objective measurement of CBF, sIgA, and nasal blood flow have not been conducted.

**Hypothesis 7 — Age paradox through differential cold exposure.** Status: plausible, supported by indirect evidence. Monto (2002) and Heikkinen & Järvinen (2003) documented the age-related pattern of incidence that is incompatible with a simple model of "accumulated immunity." Rijkers et al. (2026) emphasize the importance of accounting for behavioral and climatic factors when studying immune reactions, as well as age and sex differences in the protective function of the nose with respect to cold, dry, and polluted air, which directly supports the hypothesis of differential exposure. Limitation: prospective studies with objective monitoring of cold exposure in different age groups are absent.

**Hypothesis 8 — Vitamin D as a modifying factor.** Status: confirmed (indirect evidence base). Dogan et al. (2023) directly showed that acute cold stress (4°C, 2 h) reduces T-cell response in peripheral blood, and this effect is significantly modulated by vitamin D levels. James et al. (2023) demonstrated that physiological stressors, including cold water, activate the HPA axis and increase cortisol levels. Limitation: specific RCTs with vitamin D supplementation in ACRS have not been conducted.

**Hypothesis 9 — Microbiome disruption in ACRS.** Status: theoretically justified, no direct evidence. This hypothesis is the central new element of the three-phase model of ACRS proposed in this article, developing the concept of Gozhenko et al. (2026). Limitation: direct studies of the effect of acute cold stress on the upper respiratory tract microbiome in humans by 16S rRNA sequencing have not been conducted. This is the least studied of all ten hypotheses and requires specially designed microbiome studies.

**Hypothesis 10 — Neurogenic inflammation as the primary mechanism of symptom formation.** Status: confirmed at the molecular level. Tekulapally et al. (2024) described in detail the dual role of TRPA1 in airway and gastrointestinal physiology, confirming that TRPA1 activation by cold (<17°C) leads to release of substance P and CGRP from sensory nerve endings. Chen et al. (2026) described neuroimmune circuits in airway pathophysiology, including neurogenic inflammation as a key mechanism of symptom formation. TRPM8 agonists (menthol, WS-12) modulate reflex reactions of the airways. Limitation: specific measurements of substance P and CGRP in nasal lavage in ACRS (as opposed to allergic rhinitis) have not been conducted.

**Summary table of hypothesis verification (Table 2):** Hypothesis 1 — nosological independence — partially confirmed, evidence level B (indirect); Hypothesis 2 — temperature threshold of CBF — confirmed, evidence level A–B (direct); Hypothesis 3 — metabolic ATP depletion — plausible, evidence level C (theoretical); Hypothesis 4 — TRPM8 blockade as prevention — confirmed at molecular level, evidence level B (preclinical); Hypothesis 5 — synergism cold + virus — confirmed, evidence level B (indirect); Hypothesis 6 — thermal adaptation through hardening — plausible, evidence level C (indirect); Hypothesis 7 — age paradox through exposure — plausible, evidence level B (indirect); Hypothesis 8 — vitamin D as modifier — confirmed, evidence level B (indirect); Hypothesis 9 — microbiome disruption (Phase II) — theoretical, evidence level D (absent); Hypothesis 10 — neurogenic inflammation (TRPA1) — confirmed at molecular level, evidence level A–B (direct). Evidence levels: A — direct clinical; B — indirect/preclinical; C — theoretical/analogical; D — absent.

# 15. CONCLUSIONS

**Conclusion 1. The three-phase model of ACRS is a fundamentally new contribution to the understanding of the pathogenesis of the "common cold."** The most important theoretical contribution of this work is the demonstration that ACRS develops through three

sequential, pathophysiologically distinct phases: (I) neurogenic vascular dysfunction, (II) microbiome-mediated bacterial activation with neutrophilic inflammation, (III) resolution or viral superinfection. This model for the first time integrates into a unified concept vascular physiology, microbiology of the upper respiratory tract, and neuroimmunology, explaining both the initial symptoms (watery rhinorrhea, sneezing) and their evolution (transformation into mucopurulent rhinorrhea) without the participation of an external viral agent. This three-phase model develops and deepens the pathophysiological concept of ACRS presented in Gozhenko et al. (2026), where five interconnected mechanisms of ACRS forming a self-sufficient symptom cascade of the "common cold" without the participation of a viral agent were first systematized.

**Conclusion 2. The microbiome-mediated bacterial phase explains "bacterial complications" of ACRS without an external pathogen.** Cold-induced vascular dysfunction opens a "gateway" for the host's own upper respiratory tract microbiome. The shift in balance from protective commensals (Lactobacillus spp., Dolosigranulum pigrum) to opportunistic pathogens (Staphylococcus aureus, Streptococcus pneumoniae) is an endogenous process that does not require an external infectious agent. This explains why antibiotics for the "common cold" are ineffective and irrational — they do not eliminate the cause (cold stress), but only temporarily suppress endogenous microbiome activation, while disrupting the protective microbiome and promoting the formation of antibiotic resistance.

**Conclusion 3. Thermal inhalations are pathogenetic treatment of ACRS, not symptomatic.** The folk tradition of breathing over potato steam and the treatment by inhalation of dry warm air documented by British researchers have a clear pathophysiological justification within the three-phase model of ACRS. Warm moist air (42–45°C) directly eliminates the pathogenetic trigger: raises mucosal temperature → restores CBF and mucociliary transport → normalizes microbiome balance → shortens the "window of vulnerability" for viral superinfection. This is pathogenetic, not symptomatic treatment, which fundamentally distinguishes thermal inhalations from decongestants or antihistamines.

**Conclusion 4. ACRS and AVRS are fundamentally different nosological entities.** The comparative analysis of ACRS and AVRS (Gozhenko et al., 2025, 2026) demonstrates their fundamental differences across all key parameters: trigger, incubation period, pathogenetic mechanism, seasonality, clinical picture, response to rewarming, therapeutic targets. The COVID-19 pandemic provided definitive proof of the independence of AVRS from temperature conditions, which is one of the key differentiation criteria. These differences are sufficient grounds for establishing ACRS as an independent nosological entity, separate from AVRS.

**Conclusion 5. The neuro-ecological model of ACRS opens new therapeutic and preventive opportunities.** The involvement of geomagnetic disturbances (through the CNS → increased sympathetic tone → intensification of cold vasospasm) and aromatherapy (through olfactory and trigeminal nerves → limbic system → hypothalamus → normalization of the thermoregulatory response) as new dimensions of ACRS pathophysiology and treatment makes this concept unique. No one has previously combined the epidemiology of COVID-19/AVRS, thermoregulation, space weather (magnetic storms), microbiology of the upper respiratory tract, and olfactory physiology into a unified clinical concept. The research program of Popovych et al. (2021) and Tserkovniuk et al. (2021a, 2021b, 2021c, 2021d, 2021e) provided the first systematic quantitative evidence base for the relationship between geomagnetic activity and parameters of the neuroendocrine-immune complex, which is the fundamental basis for the neuro-ecological model of ACRS.

**Conclusion 6. WHO ICD-11 classification reform is scientifically justified and economically necessary.** The current ICD-10/11 classification, which assigns all acute upper respiratory tract diseases to infectious rubrics, leads to massive overdiagnosis of viral

infections, irrational prescribing of antibiotics and antiviral drugs, and neglect of effective preventive strategies. Establishing ACRS as a separate nosological entity in ICD-11 will allow: systematic collection of epidemiological data, development of standardized protocols, reduction of irrational antibiotic prescribing, and savings of $20–44 billion annually globally. The scientific justification for this reform is presented in detail in Gozhenko et al. (2025, 2026).

**Conclusion 7. The paradigmatic shift is scientifically justified and clinically necessary.** The paradigmatic shift from a pathogen-centric to a host-response model of the "common cold" proposed by Gozhenko et al. (2025) and developed in Gozhenko et al. (2026) is scientifically justified and supported by convergent evidence from physiology, immunology, neuroscience, thermodynamics, and microbiology. This paradigm does not deny the role of viruses, but expands the understanding of pathogenesis, adding thermoregulatory, microbiome, and neuro-ecological dimensions. For full acceptance of this paradigm by the scientific community, direct clinical verification of key hypotheses is necessary — above all the microbiome hypothesis (Phase II) and the hypothesis of the effectiveness of thermal inhalations in randomized controlled trials.

# DISCLOSURES

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**Author Contributions.** A.I. Gozhenko: conceptualization, methodology, writing of the original text, scientific supervision, formulation of the three-phase model of ACRS and the concept of the microbiome-mediated bacterial phase. V.S. Biryukov: literature review, writing and editing of the text, clinical interpretation of pediatric aspects. I. Popovych: review and editing of the text, verification of pathophysiological data. O.A. Gozhenko: clinical interpretation, review and editing of the text. O.S. Vitiukov: clinical interpretation, review and editing of the text, data verification. W. Zukow: formal analysis, editing and reviewing, administrative support. All authors have read and agreed to the published version of the manuscript.

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**Artificial Intelligence Use Disclosure.** In the process of preparing this manuscript, the authors used artificial intelligence (AI) tools — in particular, large language models (LLMs) — exclusively for the following auxiliary tasks: initial search and sorting of scientific literature by key topics; grammatical and stylistic proofreading of the text; formatting of bibliographic references in APA 7 style; structuring and editing of individual sections of the manuscript. AI tools were not used for: generating scientific concepts, formulating conclusions, performing calculations, interpreting data, or making any scientific decisions. All scientific ideas, original thermodynamic calculations, analyses, and conclusions are exclusively the result of the intellectual work of the authors. The authors have fully verified all content of the manuscript and bear full responsibility for its accuracy and reliability. This disclosure is consistent with the recommendations of ICMJE, COPE, and the editorial policy of the journal regarding the use of AI in scientific publications.

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