Thieme

Common Cold – an Umbrella Term for Acute Infections of Nose, Throat, Larynx and Bronchi

Erkältung – ein Sammelbegriff für akute Infektionen von Nase, Rachen, Kehlkopf und Bronchien

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ABSTRACT

Acute respiratory tract infections, i. e. rhinitis, sinusitis, pharyngitis, laryngitis, bronchitis, belong to the most common medical conditions with a high economic burden. Nonetheless, there is little agreement concerning their differential diagnosis.
This paper will discuss to what extent different anatomical sites of acute respiratory tract infections can be uniquely identified or whether the overlap and consecutive development in signs and symptoms renders these distinctions meaningless.
Acute respiratory tract infections are variable but definition of diagnostic categories based on the anatomical sites of the dominant complaints shows that signs and symptoms both overlap to a great extent and/or emerge successively. Thus, in common cold distinguishing between acute symptom-based diagnoses arising from different anatomical sites of the aerodigestive system remains elusive. Therefore, preferred symptomatic treatments should foster a resolution of all possible symptoms as opposed to an isolated treatment of a single symptom (e. g. mucus hypersecretion) according to the presumed anatomical site (i. e. acute bronchitis).

ZUSAMMENFASSUNG

Akute Atemwegsinfektionen wie Rhinitis, Sinusitis, Pharyngitis, Laryngitis und Bronchitis sind weit verbreitet und belasten das Gesundheitswesen mit hohen Kosten. Die Differenzialdiagnose ist dennoch umstritten.
Die vorliegende Arbeit diskutiert, in welchem Ausmaß akute Atemwegsinfektionen jeweils anatomisch genau lokalisiert werden können (z. B. Pharyngitis, Rhinitis etc.) oder ob eine solche Unterscheidung angesichts überlappender und ineinander übergehender Symptome ohne Bedeutung ist.
Akute Atemwegsinfektionen treten mit örtlich und zeitlich wechselnden Symptomen auf. Die diagnostische Einordnung (z. B. Laryngitis oder Bronchitis) basiert auf einer vermuteten anatomischen Lokalisierung der dominierenden Beschwerden. Es zeigt sich allerdings, dass sich die verschiedenen Symptome stark überlappen bzw. in zeitlicher Abfolge auftreten. Eine symptombasierte diagnostische Unterscheidung bei akuten Atemwegsinfektionen in Abhängigkeit von der jeweiligen anatomischen Lokalisation erscheint somit schwierig. Die symptomatische Behandlung sollte daher auf die Verbesserung aller in Frage kommenden Symptome und nicht auf die Behandlung eines einzelnen Symptoms, wie beispielsweise auf die vermehrte Schleimproduktion bei akuter Bronchitis, gerichtet sein.

Background

Acute respiratory tract infections are among the most common conditions seen in primary care. Despite being self-limited diseases they pose a high symptom burden for individuals and a high financial burden to society – mostly due to loss of productivity, healthcare costs and school absenteeism [1]. Moreover, they play an important role as a trigger for exacerbations of chronic respiratory diseases, such as asthma, chronic obstructive pulmonary disease (COPD) or idiopathic pulmonary fibrosis (IPF) [2 – 4].

The causative agents of these infections are typically viruses (rhinovirus in up to 50 % of cases) [5]. Acute respiratory tract infections almost always present with some combination of nasal congestion, rhinorrhea, sore throat, and cough. Sometimes one or another of these symptoms predominates [6]. Because of their diverse nature, terminology has arisen based on the anatomic site of the main symptoms of the infection, i. e. rhinitis, rhinosinusitis, pharyngitis, laryngitis, bronchitis. It is, however, largely recognized that distinguishing between them, based on the involvement of these anatomic sites, is clinically impracticable [7, 8]. The term common cold encompasses multiple anatomical-clinical entities [9]. In English several other names are

also used, e. g. acute respiratory tract infections, cold, head cold, flu (incorrectly), upper respiratory tract infection (URTI), viral respiratory tract infection (VRTI), acute coryza, nasopharyngitis and rhinopharyngitis. Colds are associated with different symptoms such as cough, runny nose, blocked nose, sore throat, and are sometimes accompanied by muscle ache, fatigue, headache, and loss of appetite [10]. Often one symptom is more dominant or more bothersome to the patient than other symptoms and the symptoms usually change over the course of the infection. The symptoms start typically with sore throat (angina) (50 % of patients [11]) and fatigue, progress to rhinitis with sneezing, runny nose or blocked nose and then cough (40 % of patients [11]). Similarly, but not identically, other authors report that usually, common cold starts with sore throat (acute pharyngitis) followed by rhinitis, rhinosinusitis and in some but not all cases acute otitis media (in children) or bronchitis with the main symptom dry cough [12]. It is therefore author's current position that the term common cold should be understood as an umbrella term: the first infection site usually being the pharynx, followed by coryza (rhinitis), sinusitis etc.

In terms of numbers and severity, symptoms typically peak two to four days after onset [13] and usually resolve in adults in seven to ten days, but acute cough can last for up to three weeks [5]. Subacute cough is defined by durations of 3 – 8 weeks. Symptoms lasting longer than 8 weeks are arbitrarily defined as chronic and are by definition not the consequence of common cold.

Dominant symptoms of the common cold change not only with time lapsed but they can be different from person to person even in otherwise healthy people, who have presumably infected themselves from the same source. Such a variation of appearance of very different symptoms in the course of common cold is a challenge for pharmaceutical management.

The Pathogens

The diversity of symptoms experienced is partly due to the fact that colds are caused by over 200 different virus strains; the rhinoviruses, with at least 99 different strains, are the most prevalent (50 % of cold pathogens), followed by coronaviruses. Frequently more than one virus is detectable, but often the infecting organism cannot be identified [11]. Comorbidities (e. g. COPD) and the host's immune response is a further contributor to the variance of symptoms in individual patients.

Transmission of cold viruses is via airborne droplets or more often, hand to hand contact with subsequent passage to the nostrils and eyes [11]. Although the mechanism of the immune response is virus-specific, the symptoms are not [13]; that is to say the type of symptoms experienced rather reflect characteristics of the host. Usually they do not allow conclusions about a specific viral pathogen. Sometimes a patient's medical and travel history alongside with the local endemic situation can suggest a certain viral pathogen. Identification of the pathogen is most important for public health services assessing the epidemiological situation; the particular pathogen needs to be confirmed by microbiological and/or serology studies. Identification of the pathogen should allow assessment of latency, contagiousness and public health threats. E.g. it is generally thought that rhinovirus colds are most infectious during the first 3 days and much less so after that.

In 2009 the entire genome of the known human rhinoviruses was mapped, resulting in knowledge about their commonalities and differences [14]. Therefore, it is now possible to generate complete genomes from patient isolates with high throughput analysis at relatively low costs. This allows predictions about structure/function relations to pathogenesis. However, this has not yet led to breakthroughs in either antiviral treatments or vaccinations.

Epidemiology

The common cold affects people all over the globe, in the northern hemisphere mostly between October and March. There is general agreement that children suffer from colds more frequently than adults. However, reported viral incidence rates vary substantially. Arroll reports that adults have two to three colds a year while children suffer up to 5 colds [11]. Other sources have reported that children may have up to 8 colds a year [15]. A systematic review of the body of literature showed that the duration of common cold in children is from 10 to 15 days, cough lasts on average as long as 25 days and therefore longer than generally thought [16].

Complications

In otherwise healthy people the common cold is a self-limiting disease. In contrast, in people with (respiratory) comorbidities the common cold is the most important cause of exacerbations of asthma in both children and adults. Moreover, a recently discovered and potentially more pathogenic group of human rhinoviruses, known as human rhinoviruses group C (HRVC), have been identified and found to be present in 59.4 % of children admitted to an emergency department with acute asthma [17]. The mechanism of action of virus-induced inflammation in asthma exacerbations is not fully understood, but atopic asthmatics may release less antiviral interferon-alpha if their peripheral blood mononuclear cells are cross-linked with specific IgE [18]. Rhinovirus induced steroid resistance might also play an important role [19]. Moreover, recurrent acute respiratory tract infections by viral pathogens are closely linked to the occurrence of exacerbations of COPD [3], and occult viral infection has been proposed as one possible cause of exacerbation of IPF [4].

Furthermore, colds can lead to secondary bacterial infections such as sinusitis, ear infections, bronchitis and pneumonia.

Those most at risk from complications are thought to be patients with suppressed immune systems, e. g. who

- are pregnant
- are over 60 years old
- are under 2 years old
- have chronic lung disease such as asthma, COPD or other conditions

- have chronic heart or kidney disease
- have diabetes or another metabolic disorder
- have hematologic disorders or malignancies
- have a suppressed immune system, either from a disease or its treatment.

The Economic Burden

The common cold and its consequent complications impose a major health care burden including visits to health care providers, costs of over-the-counter drugs for symptom relief, often inappropriate antibiotic prescriptions fostering global antibiotic resistance development and missed work and school days. In the United States, the common cold led to conservatively estimated costs of $40 billion per year in a survey performed in 2000/2001 [20]. It was estimated that 70 million workdays were missed by employees suffering from cold, 189 million school days were missed by children and 126 million work days were missed by parents caring for children with cold. Likewise, a study of American students found that colds and influenza-like illnesses are associated with substantial morbidity and impairment of academic and work performance and health care use [1]. Important sequelae in comorbid patients as mentioned above are not even included. In 2007 Americans spent $3.6 billion on over-the-counter drugs and £100 million were spent in 2005 in the United Kingdom on symptomatic relief [21]. In 2014 the total sales of over-the-counter cold and flu treatments in Germany were a huge €578 million, of which doctors prescribed €54 million. The sales for cough treatments were an additional €325 million, of which €65 million were prescribed by doctors [22].

The Debate

What is the Illness?

In sharp contrast to the subjective symptoms, findings on physical examination are minimal. Therefore, this paper will discuss to what extent acute bronchitis, acute rhinosinusitis, acute pharyngitis and other anatomically based diagnoses can be uniquely identified, or whether, on the whole, an overlap in signs and symptoms of the common cold renders the distinctions meaningless.

Overlap of signs and symptoms of the common cold and acute bronchitis/acute cough

Acute bronchitis is considered as an inflammatory disease of the tracheobronchial system, is caused largely by viruses (~50% rhinovirus infection) and frequently develops during the course of a common cold. The main symptom is cough. Acute bronchitis is arbitrarily defined as usually lasting three weeks. However, in some patients with heightened cough reflex sensitivity cough can be more intense and can last longer [23]. Cough in acute bronchitis is due to irritation of receptors by release of inflammatory mediators disrupting the intact respiratory epithelium thereby sensitizing superficial cough receptors and the afferent pathway of the cough reflex. In contrast, excessive secretions play a rather ancillary role, emerging only at the very beginning of the illness [24]. Over recent years, 5 major pulmonary societies have published guidelines on the diagnosis and management of cough, including cough in acute bronchitis [25–32].

Wenzel et al. define acute bronchitis as a clinical term implying a self-limited inflammation of the large airways of the lung that is characterized by cough without pneumonia [33]. Due to the overlap of symptoms, the empirical diagnosis of pneumonia, acute bronchitis and upper respiratory tract infections in an outpatient setting remains difficult [34]. It is also evident that acute bronchitis symptoms usually occur after an upper respiratory tract infection [35]. Only 50% of patients with acute bronchitis produce purulent sputum that represents detritus containing tracheobronchial epithelial and inflammatory cells [36] as well as mucus. As the cough is often not 'wet' but 'dry', mucolytic agents are not always helpful. During a normal cold it is not uncommon for the cough to start with a short dry phase, for it to become wet within the following 48 hours, then reverting back to a dry cough. Cough is also one of 5 typical symptoms of acute bronchitis assessed by the Bronchitis Severity Scale (BSS; comprising cough, sputum, rales on auscultation, chest pain on coughing and dyspnea), which is currently the only validated scale to measure the severity of acute bronchitis in the general population [37]. Because of the overlap of symptoms in acute bronchitis and common cold, this scale was also recommended as a reliable tool to assess therapeutic effects in the latter condition [38].

As for common cold in otherwise healthy adults, cough has a duration as the main symptom of less than 3 weeks in 50% of patients (i.e. acute bronchitis), but it can last more than one month in 25% of patients [39]. Also in children it was found that, based on the pooled results from 5 studies, cough had resolved in 50% of patients after 10 days and in 90% after 25 days [16]. Cough guidelines [25, 28, 40] define acute cough as lasting as long as up to eight weeks – under some circumstances, i.e. if elicited by adenovirus, mycoplasma pneumoniae or Bordetella pertussis infection. Some use the term subacute cough for symptoms lasting 3–8 weeks [41].

Up to now it has been conventional wisdom to consider a post-infectious "subacute" cough to be one that lasted 3 to 8 weeks. It is thought that during an infection, cough results from hypersensitization of the cough reflex that has been activated by an inflammatory stimulus. Beyond the post-infectious cough the etiology of subacute cough has been investigated recently [42]. The authors found that sputum eosinophilia is common in subacute cough following acute upper respiratory tract infection and is frequently due to three different conditions: eosinophilic bronchitis, cough variant asthma and acute postviral rhinosinusitis.

Thus, cough can arise during an infection in patients in whom bronchial hypersensitivity occurs (cough-variant asthma), which usually fades away after 6–8 weeks and appears again with the next infection. However, over time this pattern can result in genuine asthma. Moreover, acute viral rhinosinusitis usually lasts 10 days, but can worsen after 7 days if postviral rhinosinusitis occurs and last as long as 12 weeks, then trigger-

ing sensitivity of the cough reflex resulting in long lasting cough, yet the condition is self-limiting [43].

After eight weeks duration, however, cough is usually defined as chronic. In these cases, further diagnostic measures such as chest x-ray, lung function tests etc. must be done in order to exclude severe pulmonary conditions, e. g. bronchial carcinoma and tuberculosis.

According to the American College of Chest Physicians' (ACCP) cough guidelines, acute cough is not only the presenting symptom of acute bronchitis, but also one of the cardinal symptoms of common cold: 'the clinical syndrome of nasal congestion, nasal discharge, postnasal drip (PND), throat clearing, sneezing, and cough is common to all of these infections' [26].

Now, it seems to be widely recognized that distinguishing between acute cough due to acute bronchitis and/or common cold in most cases is not practicable. ACCP guidelines state that the prevalence of cough due to the common cold is as high as 83 % within the first two days of illness, and that – as the common cold and acute bronchitis share many of the same symptoms – the clinical distinction between acute bronchitis and the common cold is difficult, or at times impossible, to make [27].

Indeed, a retrospective study [7] using a case-control design explored whether any clinical signs and symptoms distinguish between acute bronchitis and viral upper respiratory tract infections/common cold. This study consisted of the review of 544 patients' records (409 with the diagnosis common cold and 135 with acute bronchitis). Examining the symptoms reported by the patients with acute bronchitis and common cold, respectively, revealed that the symptoms cough, runny nose, fever, sore throat, nausea, sleep disturbance, and sweats were present in differing proportions but in both groups of patients. Cough was present in the majority of both conditions but did occur somewhat more often in patients diagnosed with acute bronchitis. Furthermore, comparisons of the recorded physical findings showed the presence of erythematous throat, erythema of tympanic membrane, paranasal sinus tenderness and chest rales in both conditions. The authors concluded that there was considerable overlap between the two conditions, and cough only explained 37 % of the variation between the diagnoses in the logistic model [7].

Experimental studies of cough sensitivity have shown that any acute inflammation of the upper airways can enhance cough. A randomized study with healthy volunteers who had undergone capsaicin challenge reaching only the nerve endings in the nasal mucosa found that subsequent inhalation of a tussigenic aerosol enhanced cough intensity after nasal capsaicin challenge if compared with the control condition [44]. In a similar study of cough sensitivity in children either with allergic rhinitis (both in and out of pollen season) or children with URI the same enhancement of cough sensitivity was found if compared with controls. The authors concluded that pathological processes of the nasal mucosa of any etiology could cause a sensitization of the cough reflex [45] by trigeminus mediated central mechanisms. As was shown by Tatar and colleagues [23] as well as Buday et al. [46], cough sensitivity can be enhanced via nasal mucosa, irrespective the fact, that the nasal mucosa doesn't have vagal afferent cough reflex innervation. Therefore, although not every patient suffering from rhinosinusitis is coughing, in patients having a heightened cough reflex sensitivity cough can be elicited by rhinosinusitis (see below).

Overlap of signs and symptoms of the common cold and acute rhinosinusitis

Acute rhinitis and acute sinusitis usually coexist and are now commonly known as acute rhinosinusitis (ARS) occurring in conjunction with a common cold of viral origin. Common symptoms of both the common cold and ARS are nasal blockage/obstruction/congestion or nasal discharge, rhinorrhea, sleep disturbance, fatigue, and inflamed nasal mucosa. The sudden onset of 2 or more symptoms one of which is nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip) and either facial pain or pressure or reduction or loss of smell for less than 12 weeks usually leads to the diagnosis ARS [47]. Only a small percentage of post-viral rhinosinusitis is caused by bacteria [47]. In the EPOS Guidelines [47] and in several presentations during the American Cough Conference 2015 in Washington, DC (will be published in Lung), however, it was suggested that a prolonged duration of ARS of up to 12 weeks is not, in itself, a sign that the condition is of bacterial origin. In addition, results of a study addressing the question of possible bidirectional modulation of cough response in human healthy volunteers showed that, in addition to trigeminal afferents expressing TRP channels, olfactory nerve endings, trigemino-olfactoric relationships, the smell perception process and other supramedullar influences should be considered as potential modulators of the cough response in humans [46].

Overlap of signs and symptoms of the common cold and acute sore throat (acute pharyngitis, tonsillitis, tonsillo-pharyngitis, acute laryngitis):

The pharynx is the common portal to the human respiratory and digestive tracts and the unifying site of the gut and respiratory microbiota. It is exposed to multiple potential pathogens. Acute pharyngitis is predominantly viral in etiology, accounting for 85 % to 95 % of throat infections in adults and in children younger than 5 years; in those aged 5 to 16 years, viruses cause about 70 % of throat infections, with the other 30 % due to bacteria, mostly group A β-hemolytic streptococcus (GABHS) [48]. However, also in this case, the cardinal feature, sore throat, is also an early feature of the common cold. Furthermore, cough, runny nose, chills, nasal congestions, and hoarseness are further symptoms which are common in non-bacterial pharyngitis and common cold [49]. The symptom sore throat is most likely caused by the action of prostaglandins and bradykinin on sensory nerve endings in the airway and the sensation of pain is mediated by the cranial nerves supplying the nasopharynx and pharynx [13]. Likewise, acute laryngitis is considered to be an infection of the larynx that results in an inflammatory reaction and consequential symptoms and signs [50]. It usually presents as part of an upper respiratory tract infectious syndrome and may be caused by common cold viruses such as rhinovirus, influenza virus, adenoviruses, RSV, or parainfluenza viruses. Hoarseness, aphonia, and symptoms of rhinitis or pharyngitis may also accompany this condition.

SUMMARY

It can be summarized that common cold is a mostly virus elicited self-limiting inflammatory condition involving variable sites of the aerodigestive tract including trachea and bronchi. The tradition of defining clinical entities according to the anatomical site of the dominant complaint is misleading, because of the high degree of overlap of signs and symptoms. Hueston et al. [7] hypothesized that sinusitis, viral upper respiratory tract infections/common cold, and acute bronchitis are all variations of the same clinical entity and that a reconceptualization of acute viral respiratory infection as a single problem, rather than anatomically distinct disorders, is warranted. Therefore, effective and fast relief of the many different symptoms of common cold requires treatments with broad efficacy on different symptoms i. e. anti-inflammatory, antitussive, secretolytic, antiviral efficacy. Alternatively, sequential treatment of successively developing symptoms, i. e. first mucolytic, decongestant and anti-inflammatory, while later in the dry cough phase of the disease antitussive is necessary.

In conclusion, we see common cold in otherwise healthy people as a self-limiting clinical entity with variable and in the course of the disease changing manifestations on different sites of the aerodigestive tract. Accordingly, treatments fostering resolution of many different symptoms are needed.

Authors' contribution

PK and FAM outlined the content of and helped to draft and finalize the manuscript. Both authors read and approved the final manuscript.

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Competing interests

PK received honoraria from Dr. Willmar Schwabe GmbH & Co. KG. FAM is an employee of Dr. Willmar Schwabe GmbH & Co. KG.

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