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REVIEW

The treatment of mild upper respiratory tract infections – a position paper with recommendations for best practice

Andrew Smith¹, Peter Kardos², Oliver Pfaar³, Winfried Randerath^{4,5}, Guillermo Estrada Riobos⁶, Fulvio Braido^{7,8}, Laura Sadofsky⁹

¹School of Psychology, Cardiff University, Cardiff, UK; ²Centre of Allergy, Respiratory and Sleep Medicine, Maingau Clinic of the Red Cross, Frankfurt am Main, Germany; ³Department of Otorhinolaryngology, University Hospital Marburg, Philipps University Marburg, Marburg, Germany; ⁴Institute of Pneumology, University of Cologne, Cologne, Germany; ⁵Bethanien Hospital, Clinic of Pneumology and Allergology, Centre for Sleep Medicine and Respiratory Care, Solingen, Germany; ⁶Spanish Society Clinical Family and Community Pharmacy (SEFAC), Paseo de las Delicias, Madrid, Spain; ⁷Istituti di Ricovero e Cura a Carattere Scientifico, Ospedale Policlinico San Martino, Genova, Italy; ⁸Università di Genova, (DIMI), Genova, Italy; ⁹Hull York Medical School, University of Hull, Hull, UK

Abstract

Following the waning severity of COVID-19 due to vaccination and the development of immunity, the current variants of SARS-CoV-2 often lead to mild upper respiratory tract infections (MURTIs), suggesting it is an appropriate time to review the pathogenesis and treatment of such illnesses. The present article reviews the diverse causes of MURTIs and the mechanisms leading to symptomatic illness. Different symptoms of MURTIs develop in a staggered manner and require targeted symptomatic treatment. A wide variety of remedies for home treatment is available, including over-the-counter drugs and plant-derived substances. Recent pharmacological research has increased the understanding of molecular effects, and clinical studies have shown the efficacy of certain herbal remedies. However, the use of subjective endpoints in these clinical studies may suggest limited validity of the results. In this position paper, the importance of patient-centric outcomes, including a subjective perception of improved well-being, is emphasized. A best practice approach for the management of MURTIs, in which pharmacists and physicians create an improved

multi-professional healthcare setting and provide healthcare education to patients, is proposed. Pharmacists act as first-line consultants and provide patients with remedies, considering the individual patient's preferences towards chemical or plant-derived drugs and providing advice for self-monitoring. Physicians act as second-line consultants if symptoms worsen and subsequently initiate appropriate therapies. In conclusion, general awareness of MURTIs should be increased amongst medical professionals and patients, thus improving their management.

Keywords: common cold, coronavirus, cough, COVID-19 pandemic, holistic health, mild upper respiratory tract infections, pharmacist, rhinitis, rhinovirus, sleep.

Citation

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Introduction

This position paper addresses the treatment of mild upper respiratory tract infections (MURTIs) and provides recommendations for best practice. When the SARS-CoV-2 pandemic hit, infectious respiratory diseases were brought into an unprecedented, generalized

focus, with COVID-19 dominating news, politics and our daily lives. COVID-19 is a potentially life-threatening disease, affecting many organ systems and requiring intensive care in many patients.^{1,2} However, patients may also experience milder forms of COVID-19 with flu-like symptoms^{1,3,4} and the evolution of the virus as well as increased immunity of general populations have led to a decline in hospitalizations and deaths during the year

2022.² Today, SARS-CoV-2 variants often lead to MURTI, suggesting that a review of our knowledge of MURTI is desirable and a reassessment of treatment options is required. Unmet needs and appropriate healthcare provision will also be evaluated. Background information on the cause and outcomes of MURTI provides the context for discussion of treatment.

MURTI are complex viral diseases of the upper airways caused by a diversity of viruses, including multiple strains of rhinovirus, coronavirus, influenza virus, parainfluenza virus, respiratory syncytial virus, adenovirus, enterovirus and other viruses (Table 1). In total, it is estimated that >200 viral strains are causative for MURTI.¹⁵ Viral incubation typically lasts 2–4 days.⁶ Depending on the viral trigger, MURTI can manifest as a common cold – a self-limiting disease in immunocompetent patients, usually lasting about 2 weeks. The multiple symptoms related to MURTI (Table 2) are not directly caused by the viruses but by an immune-mediated response to them,^{7,8} and include typical nasal congestion, cough, sore throat and malaise, which causes a strong negative effect on general well-being.⁹

Sleep is a vital process for maintaining homeostasis and the quality of human life.¹⁰ Nasal congestion and cough often affect a patient's ability to sleep well.^{11,12} Lack of sleep has been found to increase the susceptibility to infectious diseases and stressors, including pathogens altering sleep patterns or disrupting sleep.^{13–19} Considering the above-listed symptoms, the quality of life (QoL) of affected persons is often severely impaired, leading them to self-medicate or seek medical attention.

Table 1. Common cold-causing viruses.

| Virus | The estimated annual proportion of cases |
|-----------------------------|--|
| Rhinoviruses | 30–50% |
| Coronaviruses ^a | 15–30% |
| Influenza viruses | 5–15% |
| Respiratory syncytial virus | 5% |
| Parainfluenza viruses | 5% |
| Adenoviruses | <5% |
| Enteroviruses | <5% |
| Metapneumovirus | Unknown |
| Unknown | 20–30% |

^aThere are four human coronaviruses known to cause symptoms of the common cold: 229E, NL63, HKU1 and OC43; this does not include SARS, MERS and SARS-CoV-2.¹¹⁹

Based on data from Heikinnen and Järvinen.⁵

The large number of viral strains involved in MURTI means that the development of effective vaccines is complex as respiratory viruses frequently mutate to escape immunity⁸ but important public health messages can help prevent or reduce infections.^{20,21} In most cases, antibiotics are inappropriate, as they do not influence the natural history of viral MURTI but contribute to antibiotic resistance^{22–27} and possible side effects such as gastrointestinal symptoms and allergies. Drugs for symptomatic treatment of different manifestations of MURTI are available, including analgesics, decongestants, antihistamines, herbal remedies or essential oils for inhalation, oral and transdermal application.^{28,29} Many of these over-the-counter (OTC) drugs have proven efficacy in improving symptoms and QoL in both randomized controlled trials (RCTs)³⁰ and clinical use.³¹

In summary, MURTI are amongst the most widespread infectious diseases.^{5,32,33} On average, adults have two to four MURTI, whilst children have six to eight MURTI per year,⁵ accounting for millions of lost working and school days⁵ and relevant direct costs per episode.³⁴

Pathophysiology and current management of MURTI

Clinical symptoms of the common cold, flu and other MURTI are caused by an immune response to the viruses^{7,8,35,36} (Figure 1). Typically, the onset of symptoms is staggered (Figure 2).³⁷ Symptoms of MURTI include sore throat, nasal congestion, nasal discharge, sneezing, headache, cough and general malaise (Table 2).³⁸ Symptom triggers include bradykinin release into the pharyngeal area as a cause for sore throat;³⁹ cytokine release causing breakdown of muscle tissue to facilitate protein release to support responsiveness leading to general aches, headaches and pain as well as fever;^{40–44} bradykinin and histamine release cause nasal congestion due to vasal dilation;^{39,45,46} and excess mucus production and inflammatory mediators^{47,48} sensitize and stimulate sensory nerve endings, inducing cough, which starts around 48 hours after the onset of symptoms and usually persists well beyond all other symptoms (Table 2).³⁷ Because the viruses do not directly cause the symptoms, it is difficult to distinguish the common cold, influenza and mild COVID-19 based on clinical presentation only, though some differences are observed (Table 2).^{1,3,4,49}

In addition, patient QoL is often severely affected by sleep disturbances caused by MURTI symptoms.⁵⁰ Immunity and sleep are bi-directionally related. Sleep increases lymphocyte proliferation and neutrophil function, whilst sleep deprivation increases complement activation and inflammatory gene expression. In a study with 22,726 participants, lack of sleep (i.e. <5 hours per day)

Table 2. Common symptoms of common cold, influenza and COVID-19.

| | Common cold | Influenza | COVID-19 ^a | Seasonal allergies |
|------------------------|---------------------------|--------------------------|------------------------------------|--------------------------|
| | Gradual onset of symptoms | Abrupt onset of symptoms | Symptoms range from mild to severe | Abrupt onset of symptoms |
| Length of symptoms | <14 days | 7–14 days | 7–25 days | Several weeks |
| Sneezing | Common | No | No | Common |
| Runny or stuffy nose | Common | Sometimes | Rare | Common |
| Sore throat | Common | Sometimes | Sometimes | Sometimes (mild) |
| Cough | Common (mild) | Common (dry) | Common (dry) | Rare (dry) |
| General aches, pains | Common | Common | Sometimes | No |
| Loss of taste or smell | Sometimes | Sometimes | Common | Rare |
| Fever | Rare | Common | Common | No |
| Shortness of breath | No | No | Sometimes | No |
| Wheezing | No | Sometimes | Rare | Sometimes |

^aInformation is still evolving.^{1,3,4,49}

Note: Some symptoms of the common cold and COVID-19 overlap, and testing may be required for a correct diagnosis. Symptoms for seasonal allergies without asthma.

or diagnosed sleep disorders increased the susceptibility to infectious diseases by 1.8-fold to 2.2-fold.¹³ Vice versa, stressors like pathogens alter sleep patterns or disrupt sleep,¹⁴ contributing to a vicious circle in patients with MURTI. Despite the high socio-economic burden,^{5,34} awareness towards MURTI was low prior to the COVID-19 pandemic, and significant patient information gaps and concerns have been identified.⁵¹ Self-medication, though common, is typically not discussed with general practitioners. Furthermore, as discussed in greater detail later, the use of antibiotics is still widespread despite not being indicated in uncomplicated acute viral diseases. Therefore, awareness towards improved management of MURTI should be raised.

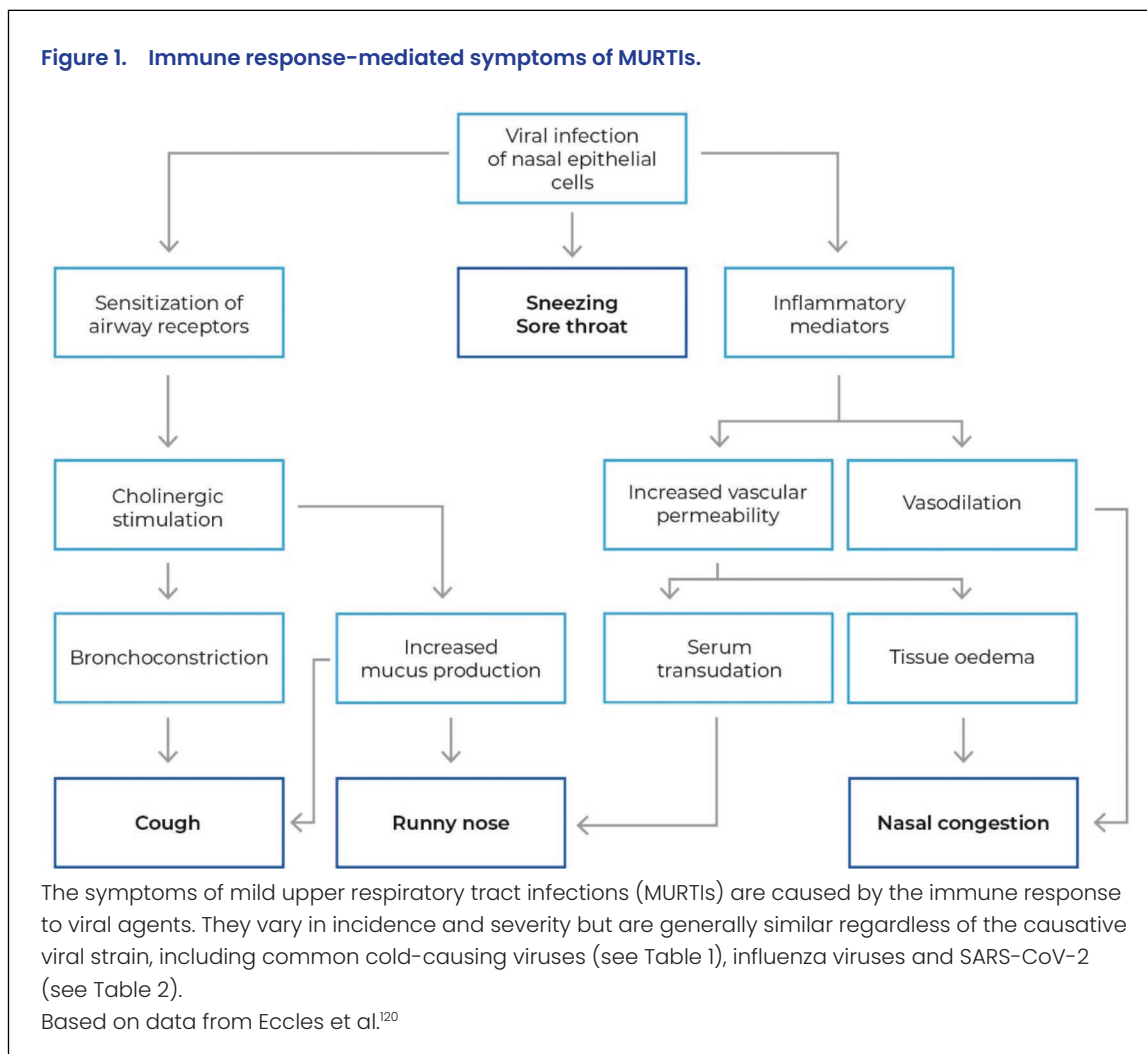
Treatment of MURTI is purely symptomatic and can speed up recovery^{52–54} and mitigate symptoms. A variety of OTC solutions, home remedies, food supplements or plant-derived substances, which can be taken orally, topically or via inhalation, are available^{28,29,55} and proven to soothe symptoms by influencing different functional triggers within the molecular network of symptom development (Figures 1 and 2). Intense research over the last decades has not only led to a better understanding of these triggers but also of the molecular processes of a diversity of pharmacologically active substances, thus allowing for more holistic approaches with adapted and well-targeted therapies.

Nasal decongestants, mainly sympathomimetics, constrict nasal blood vessels;⁵⁶ antitussives centrally or topically

reduce the frequency and/or intensity of coughs and include opium alkaloids and derivatives;⁵⁷ expectorants increase the production of fluid in the lungs to reduce the viscosity of mucus, whilst mucolytics break down disulfide bonds in the mucus.⁵⁵ First-generation antihistamines block both histaminic and muscarinic receptors and, in contrast to second-generation antihistamines, pass the blood-brain barrier, exerting their effects on the cough centre located in the brainstem. With their anticholinergic properties, they disrupt nerve signals that trigger mucus secretion and sneezing.⁵⁸ Analgesics can provide relief from pain-associated common cold symptoms and may be antipyretic.³¹

In addition, pharmacologically active plant-based molecules are also treatment options, including systemic use, topical application or inhalation of aromatics such as menthol, eucalyptus, camphor, thyme, ivy, primrose, African geranium, gentian root, elderflower and vervain herb, which have long been well-established treatments for respiratory tract illnesses. As an example, so-called inhaled therapeutic vapours are widely used to improve breath, reduce cough, improve alertness and improve sleep during a common cold.³⁶

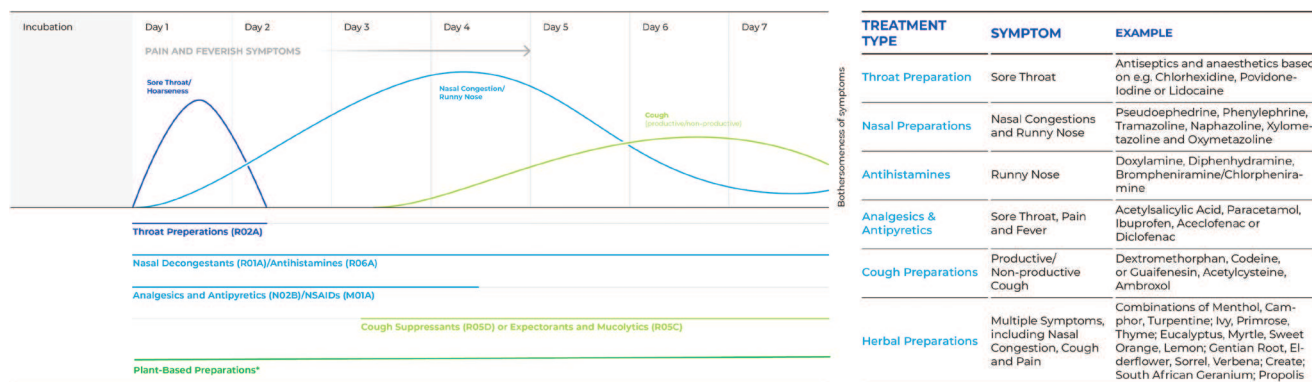
In this respect, a recent systematic review⁵⁹ provided an overview of pharmacological studies showing that aromatic compounds derived from natural plant extracts, such as menthol, eucalyptus or camphor, have multifaceted modulating effects on transient receptor potential channel (TRP) 'cough' receptors and/or

Figure 1. Immune response-mediated symptoms of MURTI.

the nasal TRP channels, such as TRPM8 and TRPA1,^{59,60} and therefore have the potential to target multiple symptoms during the course of MURTI (Figure 2).^{38,59,61} Clinically, the modulation of TRP receptors results in a significant reduction of coughing, as shown in three single-blind crossover studies (total $n=104$ with induced cough),⁶² where a combination of menthol, camphor, eucalyptus, turpentine oil, cedar leaf oil, myristica oil and thymol significantly reduced the frequency of coughing more effectively than single components. Further, the application of this combination significantly reduced the time taken for the feeling of nasal cooling and, importantly, the time to nasal decongestion compared with a petrolatum control (reviewed in detail by Smith and Matthews³⁶). Nasal airflow also influences TRP channels,^{38,61} and the absence of nasal airflow is associated with the feeling of stuffiness. Interestingly, as recently described in a systematic review by Stinson et al.,⁵⁹ some of these plant-derived aromatic substances have been shown to have a diversity of medicinal properties not restricted to the management of MURTI, including antipyretic, analgesic, anti-inflammatory or antibacterial effects (Table 3).^{59,63,64}

The clinical efficacy of a combination of cowslip, gentian root, black elder, sorrel and common vervain was tested in patients with acute viral rhinosinusitis ($n=386$)⁶⁵ in a placebo-controlled, double-blind, randomized trial and led to a significant and clinically relevant improvement of the investigator-assessed symptom score on day 15.⁶⁵ Furthermore, a combination of gentian root, primula flower, sorrel, elderflower and common vervain was shown to be safe and efficacious in patients with acute rhinosinusitis in phase IIb/III and phase III placebo-controlled clinical trials (total $n=589$).⁶⁶

Wagner et al.⁶⁷ and Kardos⁶⁸ provided summaries of the efficacy of plant-based cough remedies. A preparation of *Andrographis paniculata* (creat or green chiretta) was tested against placebo in five RCTs and versus echinacea and bromhexine in a sixth study (total $n=807$),⁶⁷ and was shown to significantly improve cough-related symptoms in all but one small pilot study.^{67,69} Four RCTs using a preparation based on ivy, primrose and thyme (total $n=1428$)⁶⁷ showed strong evidence for the beneficial effect of this combination, which not only reduced the frequency and severity of cough but also facilitated secretolysis.^{67,70} Furthermore, oral treatment with a syrup

Figure 2. Phases of common cold and suitable therapeutic agents.

Sore throat, nasal congestion and cough are the most burdensome symptoms of mild upper respiratory tract infections. Symptoms develop in a staggered manner (left panel). Targeted symptomatic treatment may require staggered use of drugs from different therapeutic classes (R02A, R01A, R06A, N02B, M01A, R05D, R05C based on the WHO ATC classification system). The use of single or combined plant-derived substances may provide a (co)treatment option with overlapping effects, decreasing the number of different pharmaceutical products required for the treatment of a common cold episode (list of examples, right panel). *See refs.^{36,38,53,59,61,62,65–68,70–73,81,115} Adapted from Witek et al.³⁷

containing thyme and ivy was shown to significantly reduce the Bronchitis Severity Score and cough severity and to improve health-related QoL in an observational, prospective, uncontrolled study ($n=730$).⁷¹ A meta-analysis of randomized, placebo-controlled trials assessing the effects of a *Pelargonium sidoides* extract (South African geranium), including 11 trials and 2195 patients,⁷² showed a reduced burden, earlier remission of cough and an increase in disease-associated QoL. Furthermore, patients treated with the geranium extract felt able to resume normal daily routines sooner than those treated with placebo.⁷² Several studies on the effect of a mixture of eucalyptus oil, sweet orange oil, myrtle oil, and lemon oil on coughing have been published. For example, Gillissen et al. reported significantly superior effects to placebo in coughing-related endpoints and sleep disturbances ($n=413$).⁵³ Fürst et al. reviewed clinical trials conducted with this mixture in China and confirmed its efficacy in the treatment of respiratory tract diseases in a Chinese patient population.⁷³

In this light, an oral spray based on propolis, traditionally used to maintain oral cavity and upper respiratory tract health due to its antimicrobial and anti-inflammatory properties, was tested in a randomized, double-blind, placebo-controlled clinical study in adults with MURTI ($n=122$). Resolution from MURTI was observed 2 days earlier in propolis extract-treated patients versus placebo-treated patients.⁷⁴

Not all studies successfully demonstrated the efficacy of essential oils in objective endpoints or lasting superiority over placebo controls, but they still reported efficacy in subjective endpoints, including the nasal

sensation of airflow and quality of sleep.^{38,75–77} Assessment of patient-centric outcomes is part of evidence-based medical research and should thus not be disregarded; symptomatic relief perceived by the individual patient is considered beneficial for well-being, stress reduction, and sleep quality^{9,78} and is considered the most important endpoint in a self-limiting disease. Even in RCTs of asthma, interstitial lung disease and chronic obstructive pulmonary disease, the FDA and EMA require patient-related outcomes (i.e. QoL Questionnaires) as coprimary or secondary endpoints. Given the importance of sleep for overall survival and individual well-being, treatment of sleep disorders and increasing quality of sleep are essential to improving immunity^{15,78}; thus, further studies and focus are required on holistic health approaches in the therapy of MURTI.

In conclusion, relief of nasal congestion and cough is key to breathing appropriately, which is not only important for sleep quality but also relevant for well-being. This may further lead to reduced susceptibility to infection and faster recovery, highlighting the importance of these therapeutic targets and holistic approaches, and acknowledging the significance of patient-centric efficacy outcomes.

Unmet needs in public health messages

Despite the high number of patients affected by and costs associated with MURTI, many have regarded these diseases as nothing more than a slight nuisance, adding to

Table 3. Medicinal properties of plant-based substances.

| | Menthol | Camphor | Eucalyptus oil | Turpentine oil | Thymol | Cedar leaf oil | Nutmeg oil |
|---------------------------------------|---|--|---|---|-------------------------------|---|--|
| Plant | <i>Mentha x piperita</i> (Peppermint) and other members of the mint family | <i>Cinnamomum camphora</i> (Camphor laurel) | <i>Eucalyptus globulus</i> (Tasmanian blue gum) and other members of the eucalyptus family | <i>Pinus Pinaster</i> (Maritime pine) and other members of the pine family | <i>Thymus vulgaris</i> | <i>Thuja orientalis</i> (Arbor vitae) and other members of the Cupressaceae family | <i>Myristica fragrans</i> (Fragrant nutmeg) |
| Medicinal properties described | | | | | | | |
| Antibacterial | ✓ | – | ✓ | – | – | ✓ | – |
| Analgesic | ✓ | ✓ | ✓ | – | – | – | ✓ |
| Anti-inflammatory | – | ✓ | ✓ | ✓ | – | – | ✓ |
| Antioxidant | – | – | ✓ | ✓ | – | ✓ | ✓ |
| Antiviral | – | – | – | ✓ | – | ✓ | – |
| Antimicrobial | – | – | ✓ | ✓ | ✓ | – | ✓ |
| Antitussive | ✓ | ✓ | – | – | ✓ | – | – |
| Antipyretic | – | – | – | – | ✓ | – | – |
| Expectorant | – | ✓ | – | ✓ | ✓ | – | – |
| Sedative | – | – | – | – | ✓ | – | – |
| Cooling effect | ✓ | – | – | – | – | – | – |
| Counter irritant | – | ✓ | – | – | – | – | – |

✓ = Medicinal properties most relevant to the management of cold symptoms.

Adapted from Stinson et al.⁵⁹

the somewhat neglected status of MURTI. With the pandemic, a new public and medical focus towards MURTI has developed. As previously stated, clinical symptoms may overlap between the common cold, influenza and mild COVID-19, making identification of the infecting agent difficult (Table 2). Diagnostic testing may be required depending on local regulations or at the health professional’s recommendation based on risk factors.

Whilst MURTI are usually not severe or life-threatening diseases in immunocompetent patients, immunocompromised patients are at risk of developing lower respiratory tract infections, including potentially fatal conditions like bronchiolitis obliterans syndrome in transplant patients¹⁵ and pneumonia.⁷⁹ Viral MURTI may also cause exacerbation of pre-existing respiratory conditions such as asthma,⁸⁰ chronic obstructive pulmonary disease,⁸¹ allergic rhinitis,⁸⁰ chronic rhinosinusitis,⁸² interstitial lung diseases⁸³ and breathing disturbances during sleep.⁸⁴

In the paediatric patient population, the use of OTC cough and cold medications often lacks support from well-designed, contemporary research and proof of efficacy.⁸⁵⁻⁸⁸ However, OTC products for the treatment of MURTI are widely used, increasing the trend of abuse and potential toxicity,^{85,86,88} which may even cause fatalities if used in very young children and/or in overdose.⁸⁹

Vaccine development is complex due to the sheer number of and frequent mutations in the viral strains involved, the latter making it impossible to develop complete natural immunity.⁸ It is unlikely that effective vaccines will become available in the near to mid-term future for the majority of common cold-causing viral strains. Effective prophylactic measures, for example, wearing masks,^{90,91} strongly depend on the individual’s compliance and capability and may not be suitable for some patient populations.

Finally, yet importantly, a holistic medical approach allows for centring the attention of medical professionals on the individual patient's needs, preferences and well-being, thus triggering compliance, increasing security, and reducing psychosocial stress and chronic disease.⁹² Stress, as described, can negatively influence immunity and could contribute to the worsening or prolongation of the symptoms of MURTI.⁹³

In summary, awareness towards MURTI has increased, but the pandemic has also increased people's insecurity about how to behave and where to seek medical attention and fear of viral infection.^{94,95} Thus, new guidance from medical professionals, including a holistic, patient-centric approach, is needed to guide treatment that is medically justified as well as endorsed by the patient.

Recommendations for best practice

The pandemic has put a new focus on MURTI in the general population as well as in politics, media and medical professionals. However, does this imply a lasting paradigm shift in the management of MURTI?

Prophylactic measures recommended or required by regulations to fight the COVID-19 pandemic included testing, public measures such as curfews, lockdowns and reduced crowd densities in shops and events, as well as personal measures such as wearing masks and improved hand hygiene. Whilst these measures were in place and/or still voluntarily endorsed by many, the incidence of the common cold and influenza as well as of bacterial respiratory infections and chronic obstructive pulmonary disease exacerbations was significantly reduced.^{96–98} Prior to the pandemic, the use of face masks to prevent the spreading or catching of diseases was uncommon in Europe and the United States. It will be interesting to study if there is a lasting effect on the general population's behaviour once incidences of the common cold and influenza rise to pre-pandemic levels. Such a lasting change in awareness regarding the effectiveness of personal hygiene measures against common infectious diseases might include the voluntary use of face masks as well as further embracing a shift in attitudes towards working places and educational institutions: will people return to a habit of going to work or school sick? Will colleagues accept the presence of team members suffering from (and potentially spreading) respiratory infections?

The pandemic has also put a new focus on the importance of pharmacists as first-line health consultants. MURTI are the main cause of consultation in both primary

care and community pharmacy. With long opening hours and short anticipated waiting times, pharmacies provide low-threshold access to medication advice and play an important role as the primary point of contact with a healthcare professional as patients consult the pharmacist for health advice, health literacy and social support.^{99,100} During the COVID-19 pandemic, a wide range of pharmaceutical interventions was provided, and expanded powers were granted to pharmacies, enhancing their role in a multi-professional healthcare setting.¹⁰¹ Furthermore, approximately 20% of consultations with doctors could be dealt with by other professionals like pharmacists, which would save 1 out of every 5 hours of medical doctor time that could be devoted to other activities or patients.¹⁰²

Enhancing the role of pharmacists as first-line consultants within applicable local legal boundaries could further reduce the use of antibiotics in patients with the common cold. Pharmacists are highly educated, giving advice regarding symptomatic treatment for viral upper and lower respiratory tract infections. Patients may erroneously believe that antibiotics could aid in the fast relief of symptoms. However, antibiotics were shown to be ineffective in changing the natural history of common colds and are not indicated in uncomplicated MURTI, as shown in a number of RCTs and observational studies.^{22–27,103} Still, 41% of all antibiotic prescriptions are for respiratory conditions,¹⁰⁴ which is one of the most important contributions to antibiotic resistance, whilst several scientific societies advise against antibiotic use in MURTI.^{105–107}

Symptomatic therapies versus subjective endpoints?

Despite accumulating clinical evidence and a better understanding of the mode of action of available pharmacotherapies, the availability of data, especially regarding the efficacy of plant-based substances, may often be considered limited due to study designs or endpoints used in clinical trials.

With patient-centred research becoming more important in medical care and research, patient-reported outcomes should not be disregarded because, beyond contagiousness, this is the cause of absenteeism from work or school. Although there is a gradual decline in cases per person per year over the lifespan, the common cold accounts for millions of days lost at school and work.⁵ Symptomatic relief perceived by the individual patient is the aim of the therapy and is considered beneficial for well-being, stress reduction and sleep quality. Based on the importance of sleep for individual

well-being,¹⁰ increased quality of sleep is essential to improve immunity.^{13–19} Data on subjective efficacy endpoints should thus not only be given serious consideration³⁶ but should also become the focus of attention and action in holistic health approaches in the therapy of MURTI in general and of SARS-CoV-2-related MURTI in particular.

With various OTC products available, including plant-based medicines, patients can benefit from tailored treatment approaches when experiencing MURTI. The scheme in Figure 2 summarizes chemical and plant-based actives as classified by World Health Organization Anatomical Therapeutic Chemical/Defined Daily Dose (WHO ATC/DDD) Index Codes¹⁰⁸ and by the latest research findings described earlier, and presents available treatment options for the therapy of MURTI symptoms over the illness time course. Treatment options include throat preparations to treat sore throat at the beginning of the illness (day 1); analgesics, non-steroidal anti-inflammatory drugs and antipyretics to treat pains and fever as well as nasal decongestants to treat nasal congestion (days 2–5); and cough suppressants and expectorants to treat cough (days 6–7). Plant-based medicines are often provided as either single substances or as combinations of various essential oils (e.g. inhaled therapeutic vapours), potentially covering all phases of MURTI with one pharmaceutical product. Therefore, (co)treatment with plant-based combinations is considered suitable to treat multiple symptoms throughout the course of the illness (Figure 2), as shown by *in vitro* data and/or clinical trials.^{37,59}

Overall, plant-based medicines and honey may provide a safer alternative to synthetic OTC products in a paediatric patient population,^{87,109,110} with similar or improved efficacy.^{111,112} Safety and tolerability endpoints for plant-derived substances are reported in the literature^{66,67,75,113} but are also limited in children,¹¹⁴ with reported adverse events being of a mild irritant nature.¹¹⁵

An estimated one-third of patients in the United States prefer and use 'natural alternatives' to chemical drugs in the treatment of the common cold and influenza, including plant-derived essences. Consideration of integrative therapies could thus increase patient compliance and positive patient care experiences.¹¹⁶

Best practice recommendations

The first pillar on which our best practice recommendations to manage MURTI are based is health literacy. Educated patients can understand and crosslink the interdependency and general importance of a healthy

lifestyle, good sleep quality, and their immune system. In the case of MURTI, healthcare professionals should educate and advise patients about treatment options, facilitating patients to make an educated decision to comply with the selected therapy. Most importantly, patients and caregivers should become aware that antibiotics are inappropriate and ineffective in the treatment of MURTI,^{22–27} and vaccines are not available, except for COVID-19, influenza and, most likely soon, respiratory syncytial virus.

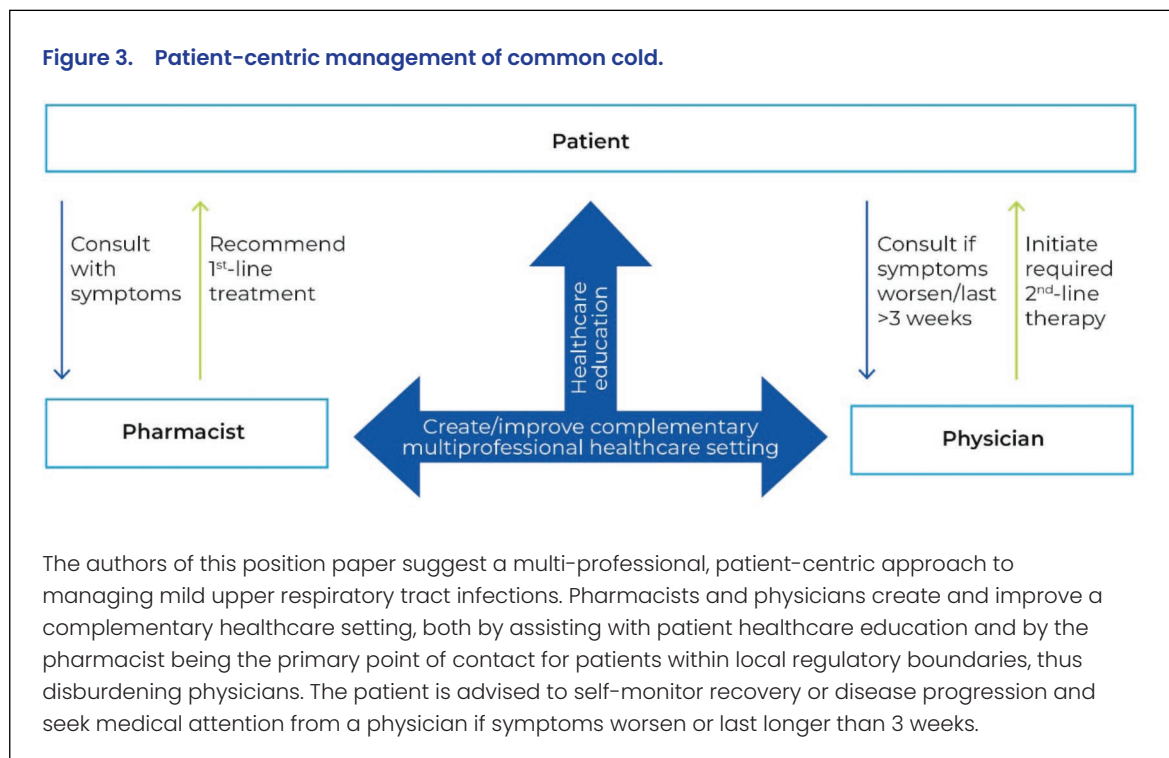
The second pillar consists of healthcare professionals creating and improving a complementary multi-professional healthcare setting. Pharmacists play a fundamental role not only in dealing with MURTI symptoms but also in health promotion and education. They can effectively reach patients and disburden medical doctors.¹⁰² Ideally, the patient's initial consultation is with the pharmacist (Figure 3), who advises the patient to closely monitor a potential worsening of symptoms and may recommend suitable OTC or plant-based drugs.

If symptoms worsen, a physician is to be consulted (Figure 3). Home assessment of oxygen saturation could increase patient safety and shorten response times in complicated cases of URTI. Pulse oximeters have been successfully used for self-monitoring in patients with mild COVID-19;¹¹⁷ they are inexpensive and easy to use¹¹⁸ and could be included in common medicine cabinets like fever thermometers in the future.

Furthermore, home tests for influenza A and B, SARS-CoV-2, and respiratory syncytial virus are available. Thus, acute testing should be advised to monitor for possible post-COVID-19 cases.

The proposed guide for the treatment of patients with MURTI and/or mild fever includes the following steps:

- Help increase self-awareness for symptoms and symptom development: consider signs of infection and illness, for example, by home assessment of fever and monitoring oxygen saturation using a pulse oximeter as appropriate.
- Focus on optimization of symptomatic treatment: use adapted continuous (co)treatment(s) targeting multiple symptoms of the natural history of MURTI, considering the patient's preferences between plant-derived remedies and chemical drugs, and avoiding initial antibiotic treatment.
- If relevant, use appropriate rapid tests (e.g. influenza, SARS-CoV-2): this is important for the identification of viruses during endemics and pandemics where targeted causal therapies are available and to monitor contagiousness.



- Advice to seek professional medical attention immediately if symptoms worsen or last longer than 3 weeks.

Conclusion

The COVID-19 pandemic highlighted unmet needs in the management of MURTI. Antibiotics are still inappropriate for MURTI, and vaccines are available only

for a few viruses, mainly mitigating the symptoms rather than preventing the diseases. Relevant prophylactic measures may include testing and reduced crowd densities in shops and events as well as personal measures such as wearing masks and improved hand hygiene. A strong advancement of patient-centred approaches is required, including the improved appraisal of subjective treatment outcomes within adapted holistic therapies.

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Correspondence: Andrew Smith; School of Psychology, Cardiff University, 63 Park Place, Cardiff, CF10 3AS, UK. Email: smithap@cardiff.ac.uk

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