Viral Upper Respiratory Tract Infections

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Abstract

The upper respiratory system is one of the most common sites of infection for adults, but even more so for children. Several viruses, from variable families, cause upper respiratory infections which, although generally underestimated due to their typically self-limiting nature, underlie enormous healthcare resource utilization and financial burden. Such, otherwise “benign” infections, can have very significant sequelae both in the form of bringing about local complications but also inducing asthma attacks, thus greatly increasing morbidity. Their enormous prevalence also indicates that rigorous research should be undertaken in order to tackle them, in both the prevention and treatment field.

1.1 Introduction

The upper respiratory tract is the site of infection for several viral and bacterial pathogens. The term “upper respiratory tract infection” (URTI) encompasses a number of conditions that have a variable and diverse range of presentations, due to the
URTI is therefore a nonspecific term used to describe acute infections involving the upper respiratory tract (nose, paranasal sinuses, ear, pharynx, and larynx) (Fig. 1.1). It is, however, rather imprecise as it incorrectly implies an absence of lower respiratory tract pathology, when clearly such pathology may often co-exist with upper respiratory tract disease [1]. Acute URTIs are an important part of general practice visits: A national study suggested that they comprise roughly 10% of all GP consultations [2]. Viral URTIs cause considerable financial burden, also in association to their comorbidities [3]. Often regarded as trivial, URTIs do not receive the attention they merit if their enormous incidence, morbidity and occasionally serious sequelae are taken into consideration [4].

Most URTIs have viral origin, with human rhinoviruses (RV), parainfluenza viruses (PIV), coronaviruses, adenoviruses, respiratory syncytial virus (RSV), enteroviruses, human metapneumovirus, and influenza being the main culprits (Table 1.1) [5]. Human metapneumovirus (hMPV) has been recently identified in samples from RSV-negative children with bronchiolitis [6], while human bocavirus (BoV) was discovered by large-scale molecular virus screening of pooled respiratory tract samples [7]. The importance of each viral agent in early life is not clear but RSV, RV, PIV, and influenza virus are predominant in the literature. However, several factors limit our understanding regarding the relative importance of each pathogen, including differences in study design (e.g. PCR versus immunoassay or other detection methods [8]), in recruitment criteria, and in the investigated viruses (e.g. RSV has been considerably easier to detect in-vitro, as compared to RV).

**Fig. 1.1** (a) The nasal cavity, pharynx and larynx are part of the upper respiratory system. (b) Sinusitis (rhinosinusitis), pharyngitis, laryngitis and otitis comprise the URTIs.
Transmission of viruses causing URTIs occurs by dispersal of small-particle aerosols (droplets), large-particle aerosols that are briefly suspended in air, and by direct contact with infectious secretions on skin/environmental surfaces (e.g. direct hand-to-hand contact), with subsequent passage to the nares or eyes [9]. Hence, transmission occurs easier in crowded spaces. However, transmission dynamics are not identical between different viruses.

1.2 Viruses

Respiratory viruses are genetically and antigenically distinct. Orthomyxoviridae are enveloped, segmented viruses that include influenza and Paramyxoviridae are enveloped, non-segmented viruses that include parainfluenza [10]. The Picornaviridae are non-enveloped viruses with a single-stranded genome, and include rhinoviruses and enteroviruses (e.g. coxsackie virus). Viruses from the family Coronaviridae are single-stranded RNA, enveloped viruses including human coronaviruses [11]. DNA viruses include the family Adenoviridae of non-enveloped double-stranded DNA viruses (i.e. adenoviruses), and the recently-discovered family of single-stranded DNA viruses Parvoviridae (e.g. bocavirus). In this chapter focus will be on the agent that is by far the most common cause of URTIs in children, the human rhinovirus (Table 1.1). Other agents such as influenza and RSV are described in detail in other chapters.

1.2.1 Human Rhinovirus

Studies using molecular methods have shown that RV is behind up to 80% of common colds [14] The only known host of RV is human, although primates may also host the virus as a non-symptomatic infection [15]. Historically, enteroviruses (EVs) and RVs

| Virus                     | Proportion of URTI cases | Predominant months of circulation (temperate climates, Northern Hemisphere)               |
|---------------------------|--------------------------|-------------------------------------------------------------------------------------------|
| Rhinovirus                | 30–50% (adults)          | Year round with a peak in September and a smaller peak around April                        |
|                           | Up to 80% (children)     |                                                                                            |
| Influenza viruses         | 5–15%                    | Winter months with a peak in February                                                    |
| Coronaviruses             | 5–15%                    | November to February                                                                     |
| Respiratory syncytial virus | 5%                      | Late fall and early spring, with a peak prevalence in winter                             |
| Parainfluenza viruses     | 5%                       | September to January                                                                     |
| Adenoviruses              | <5%                      | September to May                                                                          |
| Respiratory enteroviruses | <5%                      | Winter and spring months                                                                  |
| Metapneumovirus           | Unclear                  | Late winter-early spring                                                                  |

Table 1.1 The viruses most commonly causing URTIs, their frequency and main months of their circulation in the community [8, 12, 13]
were classified into separate genera, but due to their related genome structure they were merged into a single genus, the enteroviruses, which include three RV species (RV-A to RV-C) and four non-RV EV species (EV-A to EV-D) [3] (Fig. 1.2). These viruses have different phenotypic characteristics, with RVs mainly being restricted to the respiratory system, whereas EVs cause diverse multisystem clinical manifestations (e.g. myopericarditis, encephalitis, and quite often viral meningitis [16]). However, some EVs cause RV-like respiratory symptoms (respiratory EVs, e.g. species C and D).

RVs and EVs are small, non-enveloped, RNA viruses with a genome of about 7.2–7.5 kb packed in a 30 nm icosahedral capsid which, in turn, is composed of 12 pentamers, each composed of 5 protomers. The protomers contain four capsid proteins: VP1, VP2, VP3 and VP4 [17]. The major group of RVs which includes RV-A and RV-B, typically needs intercellular adhesion molecule (ICAM)-1 as a receptor, whereas the minor group needs low density lipoprotein receptor (LDL-R) [18]; RV-C uses a different receptor (cadherin-related family member 3—CDHR3) [19]. Regarding recognition by the innate immune system, after ssRNA internalization the genome is recognized by endosomal toll-like receptor (TLR)7 and TLR8 [20]. Once double-stranded RNA is generated, the type I interferon (IFN) response ensues leading to pro-inflammatory cytokine gene expression, including RANTES, inducible protein (IP)-10, interleukin (IL)-6, and IL-8 [21, 22]. The latter (IL-8), is a potent neutrophil chemotactic/activation agent, and is an important determinant of the clinical outcome of RV infection. IL-8 production has been shown after RV infection in both upper and lower airway epithelial cells [23]. An antibody response to RV infection occurs after viral clearance, with the development of neutralizing serum antibodies (IgG) and secretory antibodies (IgA) in the respiratory tract. These are detectable 1–2 weeks after infection and maintained for at least 1 year [24], protecting from
reinfection from the same type of virus [25]. Although this humoral response appears to offer some cross-serotype protection [26], we have shown that, generally, protection is sub-optimal [27]. As opposed to influenza virus and respiratory syncytial virus, RV is rarely associated with significant cytopathology of the upper respiratory tract. The structure of the epithelial cell (EC) lining usually remains intact, and viral shedding is relatively limited when considering the severity of the symptoms [28]. However RVs do disrupt the function of the epithelium, facilitating exposure of epithelial cells to bacteria, allergens and irritants [29].

Children are considered as the major reservoir for RVs and could experience up to 12 common cold infections per year [30]. The average incubation period is 2 days with symptom duration of 7–10 days [31, 32]. There are two main peaks of infection, the first being around April/May and the second around September/October in the Northern Hemisphere, although infections can generally be seen all year round [33]. The RV URTI typically induces nasal congestion and rhinorrhea, cough, sneezing, sore throat and malaise, but no or low-grade fever.

1.2.1.1 Transmission
The airway epithelium is the primary site of infection of RV. Viral transmission occurs mainly via direct contact or through a fomite, typically with inoculation in the nasal mucosa or the eye conjunctiva, from where it is transported via the lachrymal duct to the nasal cavity; transmission by large particle aerosols is less common and probably less efficient [34]. RVs survive on surfaces and skin for several hours, which allows for easy transmission in the absence of adequate hygiene [35]. In one classic study, viral inoculum to the right conjunctival sac [36] led to positive cultures for RV initially from the nasopharynx and afterwards from the inferior turbinates, where it presumably spread via nose blowing.

1.2.1.2 RV in the Lower Airways
About two decades ago it was believed that RV could not infect the lower airways as it grows best at 33 °C (91.4 °F), hence virus replication was thought to be reduced at the core temperature found in the lungs [3]. However, we have shown that RV can replicate in lower airway epithelial cells [29], and that the difference in replication capacity at higher temperatures is minimal [37]. This was shown for eight different RV strains whose titers at 37 °C (98.6 °F) were significantly higher than those required to initiate infection [37]. This provided conclusive evidence to the infection-related mechanism underlying the epidemiological link between common colds and asthma exacerbations. Up to two-thirds of virus-induced asthma attacks are due to RV, probably as a result of local and systemic immune responses. Local cytopathology in bronchial epithelial cells can only be observed after the use of high viral inocula [29], suggesting a potential dose-response relationship, to which patients with asthma may be particularly susceptible. It is now well recognized that RV is not a strictly upper respiratory pathogen [38], but is in fact one of the most powerful early factors associated with asthma throughout childhood [39]. The dynamics of RV infection are affected in atopic individuals, although it is still not clear to what extent there is increased susceptibility to the virus and/or a differential response to it. In this
context we have shown that atopic children with asthma have a higher rate of symptomatic cold and asthmatic episodes than non-atopic children [40, 41].

### 1.2.1.3 RV Triggering Asthma Exacerbations

For a long time clinicians had suspected that upper respiratory infections were a major cause of asthma exacerbations. Their seasonality and the strong peaks in asthma morbidity in September in temperate climates, shortly after children returning to school, [42] corresponded closely to patterns of RV identification. In the mid-1990s, using the novel, at that time, PCR-based viral diagnostics, viral presence was detected in up to 85% of exacerbations of pediatric asthma, with approximately two-thirds of these associated with RV. Although normal steady-state viral presence—rather than infection—cannot be excluded for some of these cases, it was shown that 60–80% of children presenting with asthma exacerbations were positive for viral genetic material versus only 10–40% of healthy controls [43, 44]. RV was detected in 65% of cases, coronaviruses in 17%, influenza and parainfluenza viruses in 9%, and RSV in 5% [43]. It is now well established that RV is a potent trigger of asthma exacerbations. Reduced interferon responses in asthmatic children are thought to be a potential mechanism underlying RV-induced asthma attacks [21].

### 1.2.1.4 RV Causing Asthma

Numerous longitudinal studies have demonstrated that RV infections precede the development of asthma [45–47], and a birth cohort of high-risk infants (Childhood Origins of ASThma, or COAST) has shown that wheezing-associated illness with RV is probably the most important risk factor for future asthma [46, 48]. Other birth cohort studies also demonstrate a dose–response relationship between infant RTI severity and asthma risk [49]. Among infants with LRTI, the prevalence of RV was approximately 20–30% [50] and RV infection conferred a much higher risk for future asthma development than allergen sensitization or RSV infection alone [51]. Insofar as certain strains of RV can directly infect and activate CD4+ and CD8+ T cells, the early-life altered immune response to RV could be strain specific rather than illness severity specific [52].

Taken together, these data suggest that either early RV infections cause future asthma, or that they may simply reveal a pre-existing tendency for asthma. If the latter is true then early wheezing-associated illnesses due to rhinovirus are essentially viral-induced asthma exacerbations. In support of this hypothesis, it was recently shown that children with asthma at age seven had a lung function deficit and increased bronchial responsiveness as early as the neonatal age [53]. However, currently there is no consensus, and details are unclear regarding the direction of the relationship between early rhinovirus infection and future asthma [51].

### 1.2.1.5 RV-Induced Changes

It has been shown that RV is not considerably cytotoxic and, even though its replication causes cell lysis (which is the principal method for releasing progeny virus), most RVs Infect a small subset of cells and their lysis is not extensively damaging
of the epithelium [54]. There could instead exist mechanisms whereby early-life RV infections might permanently alter lung and immune development and airway physiology. RV infections appear to induce immune responses such as interferon release which can cause malaise and myalgia, neural activation which can promote sneezing/sore throat/cough as well as mediator release from infected cells and leucocytes. RV-infected epithelial cells release a variety of chemokines [21, 55], which promote the recruitment of neutrophils and mononuclear cells. In neonatal mouse models, RV infection resulted in prolonged asthma-like responses that were dependent on IL-13 and IL-25 [56, 57]. Furthermore, extracellular matrix collagen deposition was increased in RV-infected, cultured human bronchial ECs. We have shown local induction of proinflammatory mediators by RV infection [29], namely, an increase in mRNA expression and subsequent release of IL-6, IL-8, IL-16 and RANTES, a C-C chemokine with chemoattractant activity for eosinophils, monocytes, and T lymphocytes. Produced IL-1 can enhance airway smooth muscle contraction and attenuate smooth muscle dilation responses to bronchodilators [58].

Pre-existing asthma may hinder antiviral responses. Studies of experimental RV inoculation have demonstrated that asthma is associated with increased neutrophil production [59]. The asthma phenotype, which is associated with increased ICAM-1 expression, the principal receptor for RV, might also be associated with increased susceptibility and complications from RV infection [60]. Chronic allergen exposure can also increase epithelial ICAM-1 expression, as is also true for RV infection itself, through production of IL-1 [60, 61].

1.2.1.6 Prevention-Treatment
There are currently no approved antiviral agents for the prevention or treatment of RV infections. Vaccine development has been traditionally hindered by the existence of over 150 RV serotypes [62], while treatment remains primarily supportive and focused on symptom relief.

To date, no RV vaccines are being used in the clinic. Alongside the considerable serotype variability, vaccine development is hindered by the incomplete understanding of antigenic differences between the recently discovered RV-C species and the RV-A and -B species; It is also only recently that an animal model of experimental RV infection has been developed [18, 63], due to RV being a dedicated human pathogen in its wild form [64]. Recent research work has focused on deriving antigenic peptides to be recognized by cross-neutralizing antibodies from viral capsid proteins, VP1 [27, 65] and VP2 [66], but a clinically-applicable vaccine is still far down the road.

Regarding medication for prevention and treatment (as opposed to vaccination), investigational approaches to date have included interferons (IFNs), inhibitors of viral attachment and entry, and inhibitors of viral protease. Intranasal recombinant IFN-2b was used several decades ago, and modest efficacy was shown for prophylactic use [67], but safety-wise, long-term administration was associated with nasal irritation and mucosal histologic changes [68]. For treatment of already established infection, intranasal IFN was ineffective [69]. Regarding attachment and entry inhibitors, intranasal Tremacamra (Boehringer Ingelheim, Ridgefield, CT), a
soluble form of ICAM-1 designed to interfere with the attachment of RV on target host cells demonstrated small effects on symptom scores [70]. However, when given more than 12 hours after viral challenge, efficacy was unclear. Regarding capsid binding agents, Pleconaril (WIN63843) was developed and submitted for approval to the U.S. FDA after having succeeded in reducing symptom duration by 1.5 days. However, side effects and presumed drug resistance led the FDA to decline approval in 2002 [71]. Up to now none of the several agents investigated in research trials has found its way into the clinic [72].

1.2.1.7 RV-C
New molecular diagnostic tools allowed the discovery in 2006 of a new species of RV (RV-C) [73]. Since its discovery, RV-C is reported to have a high prevalence, resembling RV-A rather than RV-B [74]. Its seasonality seems to differ from the other RV species, with a peak during the winter months [75]. In temperate or subtropical countries it reaches its peak in the early fall and late spring, and in tropical countries in the rainy season [74]. Limited research has been conducted on RV-C so far, due to the lack of a human experimental model and the virus’s inability to grow in standard cell lines. However the reports so far portray a predominant species with high virulence associated with acute, and occasionally severe, respiratory illness [74].

Young children who experience a wheezing illness due to RV-C are more likely to develop recurrent wheezing compared to other viruses [59]. Three types of RV-C (C2, C15, and C41) were shown to grow equally well at 33, 35, and 37 °C (91.4, 95, and 98.6 °F) [8]. This could facilitate development of lower respiratory tract infections (LRTI) and wheezing illnesses after RV-C infection [76].

1.3 Viral URTIs

Respiratory virus infections are often confined to the upper respiratory tract. Rhinitis and pharyngitis are frequently associated with some conjunctival and ear pathology. In infants, URTIs are often accompanied by fever and may lead to lethargy and poor feeding.

1.3.1 Diagnosis

Various techniques including nasal swab, aspirate, brush, and wash can be used to collect nasal specimens, and they are all effective [77]. Respiratory viruses are generally diagnosed by either of the following ways: virus culture, serology, immunofluorescence/antigen detection, and nucleic acid/PCR-based tests. In virus culture, cell lines are infected with viruses, whereas in serology, blood is tested for virus-specific antigen/antibodies [1]. Both methods are onerous and slow to produce results, therefore, they are not used in routine clinical work, but do have a role in an epidemiological context [1]. Antigen detection by antigen specific monoclonal
antibodies is the basis of a variety of rapid diagnostic tests. However, they demonstrate relatively low sensitivity in adults, where the viral load may be low [78]. Nucleic acid-based tests are increasingly being used and they have opened new avenues in research, especially for RV for which other methods were suboptimal [79]. Also, they are now being multiplexed, allowing the rapid concurrent detection of many viruses including RV, influenza virus, adenovirus, RSV, human metapneumovirus and PIV [8, 80–82]. Several rapid antigen tests have also been developed for certain viruses such as IFV [83], and RSV [84]. There are recommendations regarding the use of such tests, especially for influenza, where WHO has produced specific guidelines based on various criteria; e.g. for institutional outbreaks, for travelers, and when surveillance systems indicate that influenza is circulating in the community (“WHO recommendations on the use of rapid testing for influenza diagnosis”). URTIs are not an indication for the use of rapid antigen test in the clinic. Diagnostic tests for viral URTIs are generally not recommended in routine clinical practice unless there are special circumstances (e.g. complications, differential diagnosis issues, immunocompromised individuals etc.). We are currently developing a new chip to detect antibody responses to different RV subtypes in the context of the “PREDICTA” EU project. Such a tool may be able to be used for URTIs in the future. Although the role of radiologic studies in viral URTIs is limited, potential intracranial sequelae should be evaluated by computed tomography (CT) or magnetic resonance imaging (MRI).

### 1.3.2 Treatment

Currently, the only drugs for respiratory viruses used in everyday practice are for influenza, and only for lower respiratory infection. Several other drugs with antiviral activity, which mainly act as nucleoside analogues by inhibiting DNA/RNA polymerases, have been used up to now, but they are not generally used for URTIs. Brief mention will be made here of the most important of them, but not the detail as they are mainly being developed for lower respiratory tract infections, which is beyond the scope of this chapter.

*Ribavirin* was developed as an influenza drug with promising results in animal models several decades ago [85] but unclear results in humans [86], forcing the FDA to decline approval for influenza. It has been used off-label to treat RV and RSV infections in the immunocompromised host and hospitalized infants with severe lower respiratory infection [87], but because of its poor safety profile it’s generally no longer used. For influenza infection of the lower airways Oseltamivir (Tamiflu) or zanamivir (Relenza), two neuraminidase inhibitors, have been historically used; currently, the former is the main medication used for influenza. They are active against both influenza A and B, and don’t typically induce viral resistance. These agents have replaced the adamantanes (amantadine and rimantadine), M2 channel blockers only active against influenza A, which also caused widespread resistance and are not currently recommended for clinical use [88]. Currently, there are no licensed vaccines for parainfluenza, but various agents are
being evaluated in clinical trials (e.g. HPIV3 cp45 [89]). Regarding adenovirus, oral vaccines have been used for decades in USA military training installations [90]. Regarding treatment and/or prevention of RSV infection, several compounds are currently in clinical development: novel oral benzodiazepines, fusion inhibitors, F-protein inhibitors, siRNAs, and others [91, 92]. Furthermore, Palivizumab has reduced RSV hospitalizations by 50% in high-risk infants [93], and Motavizumab, was shown to be more effective [94, 95]. These agents are described in detail in other chapters of this book.

1.4 Specific Conditions

1.4.1 The Common Cold

The common cold is a mild, self-limiting illness of viral origin generally characterized by upper respiratory tract symptoms [31]. It is essentially a syndrome as it can be caused by several different viruses: most common culprit is RV, but it can also be caused by coronavirus, RSV, influenza virus, PIV, adenovirus, metapneumovirus and BoV. Occasionally, EVs are implicated in the summer. The common cold occurs year-round, but less so in warmer months. Cold temperatures may facilitate symptomatic presentation as has been shown in an important animal study where temperature changes directly impacted virus-host interaction and weakened the innate immune response to infection [96].

1.4.1.1 Symptomatology

The common cold is a clinical syndrome of rhinitis and other upper respiratory signs and symptoms, including rhinorrhea, sore throat, sneezing, cough, and watery eyes. Symptomatology is not pathognomonic for any specific viral agent, although there can be differences in the severity of specific symptoms between distinct viruses [10]; e.g. conjunctivitis is characteristically seen with adenovirus infections. Commonly, nasal congestion, sneezing and rhinorrhea form the initial presentation, while cough, sore throat and occasionally low-grade fever follow. Symptoms, usually peak at day 2–3 after the onset, decrease around day 5 and usually resolve spontaneously after 7–14 days. The incubation period could vary significantly depending on the virus: 1.5 days for influenza A, 12 hours for influenza B, 3 days for coronavirus, 4 days for RSV, 5.5 days for adenovirus, and 24–48 hours for RVs [31].

1.4.1.2 Diagnosis

Laboratory tests are not required for the diagnosis of the common cold: the clinical picture is diagnostic. Although large-scale PCR-based molecular screening for viral genome sequences continues to identify new causal agents, such testing is not needed in general practice as it does not alter management. Knowledge of the infecting agent does not offer significantly to treatment apart from potentially reducing excess use of antibiotics, and allowing more appropriate cohorting of hospitalized
patients to reduce nosocomial infection [1]. Rapid testing for bacteria may be, however, indicated when there is concern about differential diagnosis of microbial infection.

1.4.1.3 Treatment–Prevention
Generally, treatment is symptomatic only. Common cold is a syndrome and development of antivirals for specific viral agents will offer little relief to the majority of patients [10]. Furthermore, antibiotics have no role in treatment, consistent with the illness’s viral etiology [97]. Increasing oral fluid intake does not appear to be of any benefit [98] and there is not sufficient evidence for the use of complementary or alternative therapies [99]. Anti-inflammatory drugs may relieve some of the discomfort but do not significantly control the symptoms or alter the course of the disease [100]. As opposed to second generation antihistamines which are ineffective, first-generation antihistamines improve rhinorrhea due to their antiholinergic properties, but should not be given to children [101]. In combination with decongestants, they are more effective, but with further compromise of the safety profile of the formulation [102]. Topical ipratropium reduces rhinorrhea and sneezing but has no effect on nasal congestion [103]. Probiotics have a marginal effect on prevention and duration of colds [104].

1.4.1.4 Sequelae
Common complications include acute otitis media and sinusitis due to the culprit virus or to bacterial superinfection which can occur in a range of up to 60% [105]. Patients with superimposed bacterial rhinosinusitis may experience symptoms for several weeks after a common cold including facial pain, headache and purulent nasal discharge [106]. In young children, viral pneumonia could be a severe complication of parainfluenza and RSV [105], bacterial pneumonia could be a sequela of influenza infection, while RVs have been isolated in up to 25% of children hospitalized with community-acquired pneumonia [107]. Also, laryngotracheobronchitis and bronchiolitis usually start with an URTI. Postviral olfactory disorders including parosmia, hyposmia, or anosmia are not frequently seen in children, but can be seen in around 10–40% of adult cases, presumably due to the increased impairment of olfaction that is seen with age [108]. Immunocompromised children with primary immunodeficiencies, organ transplantations, malignancies, HIV-infection, diabetes and auto-immune diseases are susceptible to increased morbidity (including ICU admission), and of increased mortality from viral URTIs [109].

1.4.2 Acute Viral Rhinosinusitis
Sinusitis is one of the three most common health care complaints and although it is typically a self-limiting disease, it ranks among the top 10 most costly conditions in the US [106]. It is defined as inflammation of the mucous membranes of the paranasal sinuses (Fig. 1.3), which may be triggered by viral, bacterial, or fungal infections, and often starts in, and always involves the nasal cavity [110]; hence the term rhinosinusitis is widely accepted and used. Acute rhinosinusitis (ARS) is divided
into acute *viral* rhinosinusitis and acute *bacterial* rhinosinusitis although only about 2–4% of cases of community-acquired acute rhinosinusitis are due to bacteria, with the vast majority being of viral origin [111]. ARS is usually preceded by a viral rhinitis such as the common cold. In fact, the common cold would by itself often induce both rhinitis and sinusitis as detected by CT and MRI reports [112, 113].

### 1.4.2.1 Symptomatology
Common symptoms include nasal congestion, a reduced sense of smell, facial pressure/pain, rhinorrhea and fever/malaise. Symptoms peak within 2–3 days of onset, decline gradually thereafter, and resolve within 7–14 days.

### 1.4.2.2 Diagnosis
If symptoms of a common cold worsen after 5 days, or persist for longer than 10 days, and are more prolonged and/or severe than normally expected, the diagnosis of ARS, either viral or bacterial, is probable. The diagnosis of ARS is based on symptoms and their duration, and also on endoscopic or radiologic tests as seen in Table 1.2. Standard sinus radiographs may be useful for the diagnosis of acute frontal or maxillary sinusitis, but are not necessary.

Once ARS is diagnosed, the next step would be to distinguish acute bacterial rhinosinusitis from cases of viral rhinosinusitis, based on the patient’s medical history and the physical examination [114]. In general, the illness course appears to be longer in bacterial RS [111]. Guidelines regarding the course of disease vary. The SAHP guidelines support the diagnosis of acute bacterial rhinosinusitis in a patient whose URI has not resolved after 10 days, or has worsened after 5–7 days [115].
The AAAAI-ACAAI guidelines apply a longer time-frame for the persistence of URI symptoms, 10–14 days, before suspecting acute bacterial rhinosinusitis [114].

In clinical research, sinus puncture is used to confirm acute bacterial rhinosinusitis, but this procedure is not warranted in general practice except for patients with infections resistant to treatment, immunocompromised hosts and/or those with intracranial/orbital complications [116].

In chronic sinusitis, clinical manifestations generally are the same as in acute disease but last more than 12 weeks. Detailed discussion of chronic rhinosinusitis is beyond the scope of this chapter.

1.4.2.3 Treatment

Viral rhinosinusitis needs only support treatment focusing on symptom relief as the condition is self-limiting. Patients with symptoms persisting for ≥10 days without improvement, or those with severe symptoms (fever ≥ 39 °C (102.2 °F), purulent nasal discharge, facial pain), and those with a “double sickening” illness characterized by initial improvement of a typical viral URI, followed by deterioration, possibly have acute bacterial—rather than viral—rhinosinusitis [117]. Empiric antimicrobial therapy should be initiated. Treatment of acute bacterial sinusitis aims to eradicate bacterial growth in the sinuses, restore ventilation and drainage, and decrease the inflammatory process. First-choice antibiotics include amoxicillin, second- or third-generation cephalosporins, or amoxicillin plus clavulanic acid. The use of topical corticosteroids may be considered for better control of the symptoms in specific cases [118].

1.4.2.4 Sequelae

Viral rhinosinusitis induces local changes which increase the risk for bacterial superinfection (e.g. epithelial damage, mechanical/humoral/cellular alterations etc.). However, bacterial superinfection is seen in no more than 2% of cases of viral

| Table 1.2 | EPOS [111] guidelines for the diagnosis of rhinosinusitis |
|-----------------|----------------------------------------------------------|
| EPOS definition of rhinosinusitis | Inflammation of the nose and the paranasal sinuses characterized by two or more symptoms, one of which must be |
| i. Nasal blockage/obstruction/congestion or ii. Nasal discharge (anterior/posterior nasal drip) and any of: iii. Facial pain/pressure iv. Reduction or loss of smell | And one of the following |
| • Endoscopic signs (either of i. polyps, ii. mucopurulent discharge mainly from the middle meatus or iii. edema/mucosal obstruction primarily from the middle meatus) or • Computed tomography changes (mucosal changes within: i. the ostiomeatal complex or ii. the sinuses) | These guidelines are applicable both for adults and children. In *chronic* RS, symptoms last for >12 weeks (intermittently or continuously) |
rhinosinusitis. The bacteria usually involved are in descending order of frequency *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Staphylococcus aureus* and *Moraxella catarrhalis* [119]. Other complications may rarely occur in nearby structures, such as the orbit, e.g. orbital cellulitis, or the brain, e.g. cerebral abscess. Persistent or repeated acute sinusitis may lead to chronic sinusitis (symptoms >12 weeks). CRS is often linked to chronic lung disease, especially severe asthma.

### 1.4.3 Pharyngitis-Tonsillitis

Acute pharyngitis is defined as an infection of the pharynx and/or tonsils and describes a syndrome of sore throat, fever and pharyngeal inflammation. It is very common among children and adolescents. Viruses cause most acute pharyngitis episodes with RV, coronavirus and adenovirus accounting for roughly 33% of pharyngitis cases, while Epstein-Barr, influenza and PIV for about 5% [120] (Table 1.3). Many microbes also cause pharyngitis, with group A Streptococcus (also known as *Streptococcus pyogenes*) causing 37% of total cases in children older than 5 years. Other culprit bacteria are Group C Streptococcus (5% of total cases), *Clamydophila pneumoniae*, (1%) and *Mycoplasma pneumoniae* (1%) (Table 1.3).

#### 1.4.3.1 Symptoms

The disease is characterized by pharyngeal soreness, or irritation. Common symptoms are shown in Table 1.3. *Pharyngoconjunctival fever* can be seen in adenovirus cases, 35–50% out of which may present with conjunctivitis, a characteristic finding for this virus. *Acute lymphonodular pharyngitis* may be caused by coxsackie virus and is distinguished by characteristic nonvesicular eruption on the uvula, soft palate, anterior tonsillar pillars, and posterior pharynx. The lesions consist of multiple, raised, discrete papules surrounded by an erythematous halo. *Herpangina* is also caused by coxsackie viruses and is characterized by diffuse erythema and a vesicular eruption of the posterior oral mucosa and oropharynx which rupture, leaving painful ulcers. In young children, the typical *infectious mononucleosis* syndrome is caused by Epstein-Barr virus and is clinically characterized by sore throat, fever and lymphadenopathy, occasionally with characteristic palatal petechiae.

### Table 1.3 Viruses and bacteria causing pharyngitis, and symptoms of each condition

| Viral etiology                | Bacteria                                                                 |
|-------------------------------|--------------------------------------------------------------------------|
| Conjunctivitis                | Sudden onset Vomiting                                                   |
| Cough                         | Sore throat Patchy exudate                                               |
| Coryza                        | Fever Cervical lymphadenopathy                                           |
| Diarrhea                      | Nausea Winter presentation                                               |
| Viruses                       | Rhinovirus, coronavirus, adenovirus, herpes simplex virus types 1 and 2,|
|                              | parainfluenza virus, coxsackie virus A, Epstein-Barr virus, influenza A  |
|                              | and B virus                                                             |
| Bacteria                      | *Strep. pyogenes*, *Streptococci group C and G*, mixed anaerobes, Neisseria|
|                              | *gonorrhoeae*, *Corynobacterium diphteriae*, *Arcanobacterium haemolyticum*|
1.4.3.2 Diagnosis
It is important to identify those cases of acute pharyngitis caused by *Strep. pyogenes* as this is the main agent that requires specific antibiotic therapy. Clinically, few signs can help tell apart a viral from a bacterial case, as they show considerable overlap and no single element of the patient’s history or physical examination reliably detects etiology [121]. Subtle signs can help, however, including the diseases course, as onset of viral pharyngitis may be more gradual and symptoms more often include rhinorrhea, cough, diarrhea, and hoarseness. Bacterial culture of throat swabs is useful for the diagnosis of streptococcal pharyngitis but is not practical for routine use. Rapid antigen detection tests (RADTs) are highly specific, and provide an immediate result, thus being often used in routine daily practice. Where the clinical picture is suggestive of infectious mononucleosis (IM), diagnosis may be aided by a positive heterophile antibody test (Paul-Bunnell or “spot” test) which has a high sensitivity in the second week of illness. Investigations are rarely required for other causes of viral pharyngitis and the diagnosis is a clinical one.

1.4.3.3 Treatment
There is no management required for viral pharyngitis other than supportive measures. For *Strep. pyogenes* pharyngitis, penicillin V. and amoxycilin are the treatment of choice [122].

1.4.3.4 Sequelae
Complications can be distinguished in suppurative and nonsuppurative. Suppurative complications are mainly due to the spread of the culprit agent to adjacent tissues: In the case of *Strep. pyogenes* this can include peritonsillar/retropharyngeal abscess, cervical lymphadenitis, otitis media, mastoiditis and sinusitis [123]. All these complications except for the abscesses can be seen with viral pharyngitis as well. Nonsuppurative, immune-mediated sequelae are mainly associated with *Strep. pyogenes* rather than viruses, and include acute rheumatic fever (ARF), and acute post-streptococcal glomerulonephritis [123].

1.4.4 Otitis Media

*Acute otitis media* (AOM) is pathology of the middle ear and mucosa of the tympanic membrane (behind the ear drum), which complicates approximately one third of cold-like viral URTIs in early childhood. In other cases RSV, adenovirus, cytomegalovirus, PIV, adenovirus, enterovirus, and influenza virus [124] are identified. RVs have been increasingly appreciated as causes of the condition, as otologic manifestations of RV infection include eustachian tube dysfunction and abnormal middle ear pressure [125, 126], the main causes thought to underlie AOM. RV was detected by real-time PCR in nasopharyngeal aspirate or middle ear fluid specimens in 41% of episodes of AOM in children nasally inoculated with the virus [47]. RSV is the cause of acute otitis media in approximately 15% of cases, and it accounts for one-third of viral causes [127].

Otitis media with effusion (OME) is a condition, which often follows a slowly resolving AOM. There is an effusion of glue-like fluid behind an intact tympanic membrane in
the absence of signs of acute inflammation. RV was the predominant virus recovered by our team in the middle ear cavities of children with asymptomatic OME [128].

1.4.4.1 Symptoms
AOM typically has a short history, and is commonly associated with fever, otalgia, irritability, otorrhea, lethargy, anorexia, and vomiting; the symptoms alone lack sensitivity and specificity for diagnosis.

1.4.4.2 Diagnosis
Otoscopy is vital in making the diagnosis, with sensitivity and specificity being 90% and 80%, respectively; this may be increased by using pneumatic otoscopy [129]. The clinical findings are variable, and include abnormal color (e.g. yellow/amber/blue), retracted/concave tympanic membrane, and air–fluid levels. Additional tests such as audiometry and tympanometry could be used, but are not necessary to set the diagnosis of AOM.

1.4.4.3 Treatment
Viral AOM does not need any specific treatment. Bacterial AOM generally follows a mild course without antibiotic treatment. Supportive measures (analgesia and antipyretics) are important in both cases. Approximately 80% of children have spontaneous relief of AOM within 2–14 days [130, 131] suggesting that simple monitoring may be sufficient. However this is not always the case and different societies have produced guidelines regarding when antibiotics should be administered [129, 132]. Acute mastoiditis is more serious than uncomplicated AOM, typically requiring hospital admission, intravenous antibiotics, and surgery if abscess has formed or mastoiditis has not responded to initial therapy [129].

1.4.4.4 Sequelae
Coinfection with bacterial pathogens is common during viral AOM episodes. In one study, bacterial-viral coinfection occurred in 66% of patients, with picornaviruses accounting for two-thirds of cases [133]. A relatively common complication of AOM is acute mastoiditis, defined as acute inflammation of the mastoid peristeum [134]; Patients usually present with the symptoms of AOM plus post-auricular swelling and mastoid tenderness. Other more severe complications are usually seen more often in microbial otitis and include meningitis, epidural/brain abscess, thrombosis of the lateral/cavernous sinus and others.

1.4.5 Obstructive Conditions of the Upper Respiratory Tract
Acute obstructions may present in the supraglottic, glottic, or subglottic regions. Edema developing in this area will reduce the radius of the airway lumen and, subsequently, the airflow. Because of their similar pathophysiologic background and the confined anatomical space wherein these conditions develop (Fig. 1.4), they share several signs and symptoms, regardless of the underlying cause [135]. Viral tracheitis (viral croup) is by far the commonest of these conditions.
Fig. 1.4 (a) Anatomy of the wider site, and localization of the larynx in relation to other landmarks. (b) More detailed description of the laryngeal site, where the obstructive conditions develop
1.4.5.1 Acute Viral Laryngotracheitis (Viral Croup)
Viral croup is a common illness characterized by inflammation of the larynx. It is defined as an acute clinical syndrome with inspiratory stridor, a barking cough, hoarseness and variable degrees of respiratory distress. About 12 million cases are diagnosed annually, accounting for one third of patients presenting with acute cough. Viral croup is the commonest form of croup and accounts for over 95% of laryngotracheal infections. Peak incidence is in the second year of life and most affected children are aged between 6 months and 5 years. Although typically caused by PIV (and especially type 1 PIV [136]), all respiratory viruses can cause croup: RV [137], RSV, adenovirus, hMPV, influenza virus [138], CoV NL63 and HBoV have been described as causes of croup with variable incidence [139]. RV is detected more often in samples obtained during the fall whereas influenza A and RSV are more common in the winter, and PIVs are mainly found in winter and spring [20].

1.4.5.2 Symptomatology
Symptoms develop mainly due to airway obstruction. After a short history of preceding viral illness (sore throat, coryza, and fever) the patient will present with characteristic “barking” cough, harsh inspiratory stridor and occasionally, variable degrees of respiratory distress as evidenced by increased effort of breathing (intercostal/subcostal recession, grunting, nasal flaring, etc.) [135]. Most often, however, the presentation is mild [20].

1.4.6 Diagnosis
Viral croup is a clinical diagnosis and no tests need to be conducted to diagnose uncomplicated croup. If undertaken, lateral neck films may show subglottic narrowing and the classic “steeple sign” (Fig. 1.5). Plain neck radiographs could help to differentially diagnose retropharyngeal abscesses, epiglottitis, and foreign body aspiration. Direct laryngoscopy is rarely indicated.

1.4.6.1 Management
The episodes are usually self-limiting. Racemic epinephrine nebulizations to reduce subglottic edema are helpful. However, it should be noted that the beneficial effect of nebulized epinephrine is transient. Current treatment is systemic dexamethasone preferably via the oral route [140]. Fewer than 5% of hospital admissions for croup will require intubation.

1.4.6.2 Spasmodic Croup
Spasmodic croup is not caused directly by viruses or bacteria and almost always occurs at night in children that were previously well, or had a mild URTI. It is occasionally indistinguishable from viral croup and possibly represents a condition within the same spectrum [135]. Classically, the child awakens with, a “barky” cough and inspiratory stridor; Fever is not present and exposure to the moist night air typically helps resolve the symptoms. The etiology of the airway edema is
unclear but it may be caused by an allergic reaction to viral antigens. However, there is no direct viral involvement and usually patients have a history of allergic diseases. Treatment is identical to that of viral croup.

1.4.7 Epiglottitis (Supraglottitis) and Bacterial Tracheitis

Acute epiglottitis (supraglottitis) is an infection of the epiglottis. This is a disease that was historically caused by *Haemophilus influenzae* type b (Hib); however the development of the Hib vaccine has altered this trend, and now the rare cases of epiglottitis in an immunized child are mostly due to *Haemophilus parainfluenzae*, *S. aureus*, and *Streptococcus pneumoniae*. This is a condition caused by bacteria rather than viruses and its detailed description is beyond the scope of this chapter. It is briefly discussed in this section, alongside bacterial tracheitis for purposes of differential diagnosis [135]. This is a condition that can easily escalate to complete airway obstruction. The classic clinical presentation is of a toxic-looking child with severe anxiety and sore throat, soft inspiratory stridor, dysphagia, high fever and drooling. There is usually minimal or no

![Fig. 1.5 “Steeple sign”](image-url)
cough. Radiology is not required to set the diagnosis but if undertaken, the inflamed and swollen epiglottis gives the characteristic “thumb” sign [135]. Antibiotics (usually cefotaxime or ceftriaxone) must commence promptly [135]. This condition can be easily told apart from viral croup because of the toxic appearance of the child, the high fever, the lack of cough, and a history of severe sore throat with dysphagia. Bacterial tracheitis, or pseudomembranous croup, is another condition characterized by bacterial inflammation. The tracheal mucosa is infected by *Staphylococcus aureus*, *streptococci* or *Haemophilus influenzae* B (HiB) and the patient appears toxic with a high fever and progressive upper airway obstruction [135]. As opposed to epiglottitis, the characteristic barky cough is prominent and there is typically no drooling. Intravenous antibiotics (typically flucloxacillin and cefotaxime) should be given.

### 1.5 Conclusions

URTIs are some of the most prevalent pathologic conditions, and a considerable cause of morbidity and increased financial burden to health systems and the society. Their most severe sequela, although rare, could be a cause of mortality and significant disability. The importance of these conditions is grossly underestimated, and they need to be acknowledged as a significant health problem, especially since the over prescription of antibiotics is steadily leading to dangerous, treatment-resistant forms of disease.

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