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An Overview of Management of URTI and a Novel Approach Towards RSV Infection

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1. Introduction

Upper respiratory tract infection (URTI) is an acute infection involving nose, paranasal sinuses, pharynx, larynx, trachea, and bronchi. It is one of the commonest infectious disease affecting people of all age groups particularly children. In most of the cases it is of viral origin. Viruses like myxovirus, paramyxovirus, adenovirus, picornavirus, and coronavirus groups are some of the common viruses that cause cold and similar upper respiratory tract illnesses in adults (Hamre and Connelly, 1966; Mims et al., 1998). URTI are frequent as there are large numbers of different causative viruses and also re-infections may occur with the same type of virus because of its ability for antigenic drift/shift.

There are many different antigenic types in these viruses and new strains/immunotypes are being discovered newly especially in coronavirus group. With the use of currently available methods of detection, the cause of approximately one third to one fourth of colds in adults remains unknown (Makela et al., 1998). Some illnesses may be undiagnosed because of the low sensitivity of diagnostic methods currently in use for detection of known viruses (Monto, 1997).

The respiratory viruses have a worldwide distribution. An URTI epidemic usually tends to occur during rainy season in the tropics and colder months in the temperate regions. Some viruses have their own seasonality viz. rhinovirus infection has its peak in the autumn and coronaviruses in the winter. Apart from climate variation, relative humidity plays a vital role in survival of the viruses. Enveloped viruses survive better than non-enveloped virus in a low relative humidity (Gwaltney 1984).

The main reservoir of respiratory viruses is the upper airway in young children. Spread of URTI is most common in an enclosed surrounding like home, schools and daycare centers

(Frenck RW, Glezen, 1990). The mechanisms for the spread of URTI viruses have not been well established but possibly occur by direct contact with infectious secretions on skin and environmental surfaces or contact with airborne droplet/droplet nuclei of respiratory secretions suspended in the environment or its combinations. For some viruses, such as rhinovirus and RSV, physical contact is necessary for efficient spread. Respiratory viruses are produced primarily in the nose and are shed in highest concentrations in nasal secretions. Effective spread is achieved when these viruses are present in hands of adults/children (Gwaltney, 1980).

Bacterial origin of URTI is less common involving etiological agents such as beta-hemolytic streptococci, *Corynebacterium diphtheriae*, *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis* (Richard and Garibaldi, 1985).

2. Pathophysiology of RSV

Respiratory syncytial virus (RSV) is an enveloped single-stranded RNA virus belonging to family Paramyxoviridae (genus *Pneumovirus*) and is related to the parainfluenza, mumps and measles virus. RSV is a highly infectious, ubiquitous and is one of the most contagious human pathogens, comparable to measles virus. The RSV outbreak was first documented in 1964 in a neonatal intensive care unit (Berkovich, 1964). RSV is a significant cause of acute upper respiratory tract disease in individuals of all ages occurring both in normal and immunocompromised individuals (Hall et al., 2001).

Globally, the World Health Organization (WHO, 2009) estimates that RSV causes 64 million infections and 160,000 deaths annually. Approximately two-thirds of infants are infected with RSV during the first year of life, and 90% have been infected one or more times by 2 years of age (Karron et al., 1999). RSV infects patients earlier in life with greater consequences than other respiratory viruses. Rhinoviruses, influenza viruses, parainfluenza virus commonly infect children <6 months of age but RSV causes more frequent and severe infections because of their small size and narrow airways which is susceptible to obstruction. The ability to infect infants very early in life increases the impact of RSV.

The risk factors for severe RSV (Welliver, 2003)

- young age (<6 months)
- premature birth (<35 weeks of gestation)
- bronchopulmonary dysplasia
- congenital heart disease
- immunodeficiency or immunosuppression
- low birth weight
- low titer of RSV-specific serum antibodies
- old age increased exposure to infection in day care center, hospitalization, multiple siblings
- genetic predisposition (family history of asthma, genetic polymorphisms in genes encoding cytokines, chemokines)

The two major strains of RSV are A and B. The A strain is responsible for the majority of more severe forms of RSV bronchiolitis (Martinello et al, 2002; Walsh et al, 1997). Martinello et al. (2002) found that a subgroup of the A strain (GA3) was associated with more severe

disease. It is also important to know that the different strains of RSV often circulate at the same time, and season-to-season variation is found in the predominant strain (American Academy of Pediatrics [AAP], 2003; Martinello et al., 2002).

The virus is shed in nasopharyngeal secretions; infected patients can shed the virus for up to 21 days. The portal of entry of the virus is through the mucosal surfaces of the mouth, nose, and conjunctivae. The virus replicates in the nasopharynx with an incubation period of 2 to 8 days with replication cycle (*in vitro*) of 30 to 48 hours. G protein on the viral envelope mediates attachment of the virus to the superficial cells of the respiratory epithelium including type 1 pneumocytes in the alveoli which are major targets of infection in the lower airway and non-ciliated epithelium and intraepithelial dendritic cells (Beeler and van Wyke Coelingh, 1989)

RSV invades the bronchiolar epithelial cells causing inflammation and edema. The membranes of the infected cells fuse with adjacent cells to form a large, multinucleated cell creating large masses of cells or "syncytia" (McIntosh, 2000; Wong et al., 2003) formation due to F (fusion) viral envelope glycoprotein which facilitates URTI to spread to lower respiratory tract. There may be occasional proliferation of the bronchiolar epithelium, infiltrates of monocytes and T cells centered on bronchiolar and pulmonary arterioles, and neutrophils between vascular structures and small airways. Infection and tissue damage are patchy rather than diffuse. There are abundant signs of airway obstruction due to sloughing of epithelial cells, mucus secretion, and accumulated immune cells (Levine et al., 1987).

RSV URTI symptoms include coryza, cough, wheezing, low-grade fever (< 101°F), and loss of appetite. Symptoms of LTRI are common even in infants with mild disease. Clinical symptoms of bronchiolitis include increased airway resistance, air trapping, and wheezing.

Coryza (the prominent symptom) is the inflammation of the mucous membranes lining the nasal cavity which causes nasal congestion and anosmia. The 3 stages of coryza are;

- Dry Prodromal Stage (initial phase): nasal drying and irritation, low-grade fever, chills, general malaise, anorexia
- Catarrhal Stage (second stage): watery clear rhinorrhea, congestion, lacrimation, worsening of constitutional symptoms
- Mucous Stage: thickened rhinorrhea (greenish and foul smelling if secondarily infected), improved constitutional symptoms

Reinfection with RSV occurs at all ages; however, with recurrent infection and increasing age, RSV infections are more limited to the URT. RSV URTI is more severe in nature than the URTI caused by other common cold viruses. RSV can re-infect throughout life without considerable antigenic change in sharp contrast with the ability of influenza A virus requiring antigenic drift or shift (Falsey et al., 2005).

An uncomplicated URTI can also progress to complicated lower respiratory tract infection (LRTI). The pathogenesis of RSV-induced airway inflammation and hyperreactivity remain largely unknown. There is mounting evidence suggesting that young children who contract RSV infection are more likely to suffer from long-term respiratory complications like reactive airway disease later in life (Shaheen, 1995). It is also observed that severe infantile RSV and influenza virus LRT are characterized by inadequate adaptive immune responses.

There is no effective therapeutic option currently available for the management of acute and chronic clinical manifestations of RSV.

3. Treatment of acute URTI

Common cold is a self limiting illness and can resolve spontaneously. It has been rightly told that "treated cold lasts for 1 week and the untreated lasts for seven days". The treatment of common cold is directed for alleviating the symptoms associated with it and the infection can be taken care by body's own immunity

Acute rhinosinusitis is most often associated with common cold and can be treated by a first generation antihistamine and a decongestant like pseudoephedrine. Similarly acute cough associated with common cold may be resolved by first generation antihistamine like diphenhydramine and chlorpheniramine along with decongestants (Chest 2006). Patients suffering from common cold are reluctant to take first generation antihistamines because of fear of drowsiness and absence from their work and can be treated by second generation antihistamine like cetirizine or loratadine for relief of symptoms of rhinosinusitis and acute cough. Cough usually occurs due to viral inflammation of the throat and can also be managed by simple home remedies like warm saline gargling and taking honey which can reduce symptoms and improve sleep particularly in children. Other drugs which can be prescribed for cough are dexomethorphan and codeine but these drugs can cause drowsiness and constipation respectively.

Over the counter preparations for cough and cold has limited efficacy in relieving cough due to URTI (Braman 2006). They may have undesirable side effects like allergic reactions, sleep disturbances, hallucinations particularly in children and therefore they should be avoided in children. Rest is an important factor for treating URTI but usual activities such as working and light exercise may be advised as much as tolerated (Siamak, 2011). Increased intake of oral fluids is also encouraged to sustain the fluid loss from running nose, fever and poor appetite associated with URTI. (Siamak, 2011)

Other medications which can be helpful in relieving the symptoms of common cold (acute URTI) are as follows

- Acetaminophen or Paracetamol – It is a safe drug to be used in both adults and children to reduce fever and body ache which are often associated with acute URTI
- NSAIDs – Non Steroidal Anti Inflammatory Drugs like ibuprofen can be used for fever and body ache
- Nasal secretions can be reduced by using nasal ipratropium (topical)
- Many cough medications like dextromethorphan, guaifenesin and codeine are also commercially available and can be used to relieve cough, if it is not reduced by saline gargling or antihistamines and decongestants. However, these medications can cause drowsiness and codeine can cause constipation.
- Oxymetazolin nasal drops can be used to reduce nasal stuffiness but for a short period. It can cause after congestion. Very young children and infants may be relieved from nasal stuffiness by saline drops instilled into both the nostrils.
- Other groups of drugs indicated are bronchodilators like short acting $\beta_2$agonists and ipratropium bromide administered by metered dose inhaler (MDIs) which help reduce

mucous in lungs and relax smooth muscles of large and medium bronchi, if URTI is associated with wheeze and bronchospasm.

Antibiotics are not advised if the patient is otherwise healthy because the immune system can clear the viral infection. No benefit has been demonstrated in terms of overall improvement from the use of antibiotics compared to placebo in patients with acute URTI. (Arroll et al., 2008).

Treatment with antibiotics neither shortens the duration of illness nor prevents bacterial rhinosinusitis and patients with purulent green or yellow secretions do not get benefit from antibiotic treatment (Gonzales et al., 2001)

The following complications may need a course of antibiotics

- Acute bacterial rhinosinusitis - Acute bacterial rhinosinusitis may develop in only 2% of cases (Hickner et al., 2001). Bacterial sinusitis may be present if symptoms persist for more than 7 days and pus is localized to the maxillary sinus (Hansen et al., 1995). Patients with mild symptoms need only symptomatic treatment with topical and oral decongestants. Patients with moderate or severe symptoms may be benefited by the use of narrow spectrum antibiotic like amoxicillin which can cover *Streptococcus pneumoniae* and *Hemophilus influenzae*. Alternatively Amoxicillin-clavalunic acid combination, third generation cephalosporins and for penicillin allergy, cotrimoxazole and extended spectrum macrolide or respiratory fluroquinolone may be considered if no improvement or worsening of symptoms after 72 hours.
- Pharyngitis may occur due to infection by group A beta hemolytic streptococci (GABHS) and routine respiratory viruses. Antibiotics are indicated if the symptoms persist for more than 7 days or there is increased severity particularly with GABHS infection manifested by sore throat, fever, head ache, tonsilopharyngeal erythema and exudates, palatal petecheae and anterior cervical lymphadenopathy and absence of cough (Cooper et al., 2001). The diagnosis of GABHS may be confirmed by throat culture and rapid antigen testing before using antibiotics.
  First line therapy includes penicillin V or benzathine penicillin G
  Alternative therapy may be instituted by amoxicillin, oral cephalosporins and erythromycin incase of patients allergic to penicillin.

Duration of treatment with suitable antibiotics is usually 10 days and the treatment guideline is same for adult as well as pediatric patients.

- Otitis media in children – another indication for the use of antibiotics complicating URTI. In case of non severe illness, high dose of amoxicillin is the first line therapy. If this treatment fails, the combination of amoxycillin and clavulanic acid in high doses may be tried. Alternative therapy includes oral third generation cephalosporins and in penicillin allergic patients macrolides. Bacterial agents complicating URTI with
- Acute bronchitis - Bacterial agents complicating are *Bordetella pertussis, Mycoplasma pneumoniae* and *Chlamydia pneumonia*e. Uncomplicated acute bacterial bronchitis does not need treatment with antibiotics even if the patient complains of purulent sputum. 95% of patients with purulent sputum do not have pneumonia (Diehr et al., 1984). The evaluation and treatment of the patient should be focused on excluding severe illness particularly pneumonia (Metlay et al., 1997). Treatment with antibiotics is reserved for

patients having acute bacterial exacerbation of chronic bronchitis and COPD most often in smokers. Antibiotics preferred in this group are amoxicillin, cotrimoxazole or doxycycline. In case of *B. pertussis, C. pneumoniae* and *M. pneumoniae* erythromycin or doxycycline can be given. (Smucny et al., 2004).

In children less than 8 years suffering from acute bronchitis and presenting with prolonged unimproving cough lasting for more than 14 days and after exclusion of pneumonia, macrolides may be preferred but for older children tetracyclines are preferable. Bronchiolitis or non specific URTI characterized by sore throat, sneezing, mild cough, fever less than 102ºF for less than 3days, rhinorrhea, nasal congestion, self limited typically 5-14days needs only symptomatic treatment with adequate fluid intake, rest and humidifier.

URTI arising due to influenza and RSV needs special mention. The diagnosis of influenza may be done by abrupt onset of fever, myalgias, headache, rhinitis, severe malaise, non productive cough and sore throat. The mainstay of treatment is supportive care to relieve symptoms. But antiviral drugs like oseltamivir and zanamavir can decrease the duration of illness if administered within first 36hours of onset of illness (Montalto et al., 2000)

Recently a number of studies have established RSV as a potential pathogen in certain adult population, particularly very elderly with underlying cardiopulmonary disease and immunocompromised individuals. But the disease remains undiagnosed in many situations because diagnosis is difficult during acute illness. Antibiotics may be used in selected RSV infected persons having bacterial pathogens isolated from their sputum. At present aerosolized ribavarin is the only approved treatment for RSV infection (AHRQ 2003, Falsy and Walsh 2000). But the use of ribavarin is controversial in case of infants and is indicated only in high risk patients. Two immunoglobulin preparations i.e., polyclonal high titred RSV immunoglobulin and a humanized F-specific monoclonal antibody can be used along with ribavarin. The treatment must be instituted promptly at the onset of the illness to effectively inhibit the replication of the virus. (Malhotra and Krilov 2000). But regular and wide spread use of immunoglobulins is not encouraging due to their high cost of each monthly dose and only high risk infants can get benefits from prophylactic treatment (Cooper , 2011).

Development of RSV vaccine has been unsuccessful and previously developed vaccine using inactivated whole virus caused infection in infants. Recently it was understood that RSV can invade or even alter immune system. Therefore, better understanding of the immunological role of the virus and development of either immunomodulatory drugs or a vaccine remains the challenge for the future for the effective prevention or treatment of RSV infection (Sorrentino et al., 2000).

4. A new strategy of management: Immunomodulation

With the traditional knowledge available in the literature of the Siddha system of medicine (an ancient system of complementary medical practice in India) and the intense research on medicinal herbs done at Dr JRK Siddha Research and Pharmaceuticals Pvt Ltd, Chennai, India, a unique polyherbal formulation (trade named as SIVA syrup) was made with the following herbs.

Indigofera aspalathoides
Celastrus paniculates
Corallocarpus epigaeus
Solanum trilobatum
Wrightia tinctoria
Bacoba monnieri
Piper longum
Piper nigrum
Zingiber officinale
Tinospora cordifolia
Leucas aspera
Piper betle

5. Plant details

Indigofera aspalathoides Vahl ex DC. (Papilionaceae)

Vernacular names: *Tamil* – Shiva malli, shivanarvembu.

Habit – Undershrubs, leaves digitately compound, flowers red, pods straight, turgid.

Distribution – South India, Sri Lanka.

Uses – Leaves, flower and tender shoots demulscent; their decoction used in cancerous lesions and leprosy. Leaves also applied in abscesses.

Celastrus paniculatus Willd. (Celastraceae)

Vernacular names: *Sanskrit* – Jyothismathi; *Tamil* – Vaaluluvai.

Habit – Scandent shrubs with lenticellate branches. Leaves crenate-serrate. Flowers yellow or greenish-white, in terminal panicles. Capsules sub-globose, yellow with scarlet fleshy aril closing the seeds.

Distribution – South Asia to Australia.

Uses – Bark – Abortifacient. Seeds tonic and aphrodisiac. Seed oil used as nerve stimulant and brain tonic; also used in rheumatic pain.

Chemical constituents – Plant contain sesquiterpene ester malkanguniol, malkangunin, celapanine, etc. and alkaloids celastrine and paniculatine.

Corallocarpus epigaeus (Rottl. ex Willd.) Cl. (Cucurbitaceae)

Vernacular names: *Sanskrit* – Shukanaasa; *Tamil* – Agasagarudan.

Habit – Prostrate or climbing herb with tuberous roots. Leaves sub-orbicular. Flowers unisexual; female flowers usually solitary. Fruits ellipsoid, pulpy; seeds with a reddish margin.

Distribution – Tropics.

Uses – Roots used in chronic mucous enteritis and dysentery. It is also used as liniments for rheumatism.

Chemical constituents – Roots contains bitter principle bryonin.

Solanum trilobatum Linn. (Solanaceae)

Vernacular names: *Sanskrit* – ; *Tamil* – Thoothuvalai.

Habit – Much branched spiny scandent shrubs. Leaves deltoid or triangular, irregularly lobed. Flower purplish blue, in cymes. Berry globose, red or scarlet.

Distribution – Peninsular India and Malaysia.

Uses – Roots used for consumption in the form of electuary, decoction or powder. Berries and flowers used to relief cough.

Chemical constituents – Fruits and leaves contains alkaloid solasodine.

Wrightia tinctoria (Roxb.) R.Br. (Apocynaceae)

Vernacular names: *Sanskrit* – Svetakutaja; *Tamil* – Vetpalai.

Habit – Small deciduous tree with light grey, smooth, scaly bark. Leaves elliptic-lanceolate. Flowers fragrant white, in lax, dichotomously branched terminal cymes. Follicle cylindrical, acute, cohering when young.

Distribution – India, Sri Lanka.

Uses – Bark and seeds used in flatulence and bilious troubles. Seed aphrodisiac and anthelmintic.

Chemical constituents – Bark contains β–sitosterol, α- amyrin and its acetate and lupeol.

Bacopa monnieri (L.) Penn. (Scrophulariaceae)

Vernacular names: *Sanskrit* – Brahmi; *Tamil* – Neerbrahmi.

Habit – Decumbent or creeping herbs rooting at nodes. Flowers solitary, bluish or pinkish.

Distribution – Almost all districts in Tamilnadu, India and tropics.

Uses – used in epilepsy, insanity and other nervous diseases.

Chemical constituents – Plant contains nicotine, luteolin bacogenin A1, A2, A3, betulinic acid, bacoside A, A3, B & β–sitosterol.

Piper longum Linn. (Piperaceae)

Vernacular names: *Sanskrit* – Pippali; *Tamil* – Thippili.

Habit – Aromatic climbers with stout roots; stem jointed. Leaves ovate, cordate. Spikes cylindrical, peduncled. Fruits ovoid, yellowish-orange.

Distribution – India, cultivated in many places.

Uses – Roots and fruits used in respiratory tract diseases, as a counter irritant and analgesic for muscular pains and inflammations; as snuff in coma.

Chemical constituents – Roots contains alkaloids – piperlongumine, piperlonguminine, piperine, sesamine, piperolactum A & B. fruits yiels essential oil contains piperidine alkaloids, piperononaline, piperundecalidine etc.

Piper nigrum Linn. (Piperaceae)

Vernacular names: *Sanskrit* – Maricha; *Tamil* – Milagu.

Habit – Much branched climbing shrub rooting at nodes. Leaves entire, cordate. Flowers minute in spikes. Fruit ovoid or globose, bright red when ripe.

Distribution – south – west India, largely cultivated.

Uses – fruits used in fever, anaemia, cough, diarrhoea, as stimulant, in weakness due to fever, as a stomachic, and malaria. Externally applied as rubefacient for sore throat, piles.

Chemical constituents – Stem contains sesquisabinene , piperine, hentriacontane, β–sitosterol. Fruits contains piperine, oleoresin and volatile oil.

Zingiber officinale Rosc. (Zingiberaceae)

Vernacular names: *Sanskrit* – Sunthi; *Tamil* – Inji.

Habit – Slender aromatic rhizomatous herbs with leafy stem. Leaves linear-lanceolate, distichous, subsessile. Flowers greenish-yellow with dark purple or purplish black tip, in spikes.

Distribution – Extensively cultivated in many places all over the world.

Uses – Carminative and stimulant and also given in flatulence and colic.

Chemical constituents – Rhizomes contains diarylheptanoids, essential oil, zingiberene, zingiberenol, sesqui-thujene, cumene, myrcene, limonene, gingerol, shagoal, zingerone and paradol.

Tinospora cordifolia (Wild.)Hk.f. & Th. (Menispermaceae)

Vernacular names: *Sanskrit* – Guduchi; *Tamil* – Seenthilkodi.

Habit – Large climbing shrubs; bark greyish-brown or creamy-white, warty. Leaves membranous broadly ovate, cordate at base. Flowers greenish-yellow, appearing when the plant is leafless, in axillary and terminal racemes or panicles. Drupe ovoid, shining, succulent, light red when ripe.

Distribution – India, Srilanka.

Uses – Stem is an ingredient of several ayurvedic preparations used in general debility, dyspepsia, fever and urinary diseases. Leaf decoction given in gout.

Chemical constituents –Plant containe quaternary alkaloids – magnoflorine, tembestarine and isoquinoline alkaloid – jatrorrizine, furanoid diterpene, clerodane, tinosporidine, tinosporoside etc.

Leucas aspera (Wild.) Link (Lamiaceae)

Vernacular names: *Sanskrit* – Dronapushpi; *Tamil* – Thumbai.

Habit – Erect herbs with diffuse quadrangular branches. Leaves linear-lanceolate. Flowers white, in verticils. Nutlets oblong.

Distribution – India and Malaysia.

Uses – Juice of leaves applied externally in psoriasis, chronic skin eruptions and painful swellings. Flowers given with honey in coughs and cold.

Chemical constituents – plant contains sterol, alkaloids, galactose, oleanolic acid, ursolic acid etc.

Piper betle Linn. (Piperaceae)

Vernacular names: *Sanskrit* – Tambulavalli; *Tamil* – Vettrilai.

Habit – woody climber with adventitious roots. Leaves broadly ovate, slightly cordate and often obliqual at base. Male flowers in dense spike; female spikes pendulous. Fruits black in the fleshy spike.

Distribution – Native of Malaysia, cultivated in india.

Uses – decoction of leaves used for healing wounds. Roots with black pepper used to produce sterility in woman. Leaves yield essential oil which is used in repiratory catarrh and diphtheria, also as a carminative.

Chemical constituents – Leaves contains iodine, vitamin B, essential oil contains – chavibetol, chavibetol acetate, caryophyllene, allylpyrocatechol, camphene, eugenol etc.

These plants possess properties to modulate the immune system by induction, expression, amplification or inhibition of any part or phase of the immune response. Plants like *Solanum trilobatum, Wrightia tinctoria, Tinospora cordifolia* and *Leucas aspera* has been extensively used in Siddha preparations. Crude extracts of these plants possess wide range of properties like increase in total WBC count, boosting the phagocytic index of macrophages, polyclonal B cell activation, increase secretion of Interleukin-1 and tumor necrosis factor (TNF). Immunomodulation through plants provide inexpensive, safe, viable and natural means of seeking an effective alternate treatment.

6. Study methods

6.1 Virus preparation and assay

High-titer stocks of RSV were prepared on HEp2 cell monolayers. Virus titers were determined by plaque assay on STAT1_/_ mouse fibroblasts. Equivalent number of plaques was counted on STAT1_/_ fibroblast and HEp2 monolayers, but they appeared much more rapidly on the knockout murine cells: 36 h versus 5 days, respectively (Gitiban et al, 2005).

6.2 Study animals and infection

Juvenile chinchillas (*Chinchilla lanigera*) 3 months of age and weighing 300 to 350 g, were used. Male and female BALB/c mice were also used for the study**.** Mice were infected i.n.

following methodologies that were developed to deliver an inoculum specifically to the upper airway using a very small volume (Johnson et al., 1996, Visweswaraiah et al., 2002). Briefly, each mouse was mildly anesthetized, placed in a supine position, and given 10^3 PFU of RSV in a 20-µl volume. Two microliters per naris were delivered at 0, 2, 7, 9, and 11 min. Chinchillas were also inoculated i.n. with RSV, again delivered specifically to the upper airway. The dosages (in total PFU delivered), 10^3 were administered by passive inhalation of droplets of viral suspension delivered to the nares of chinchillas that were lightly anesthetized with xylazine (2mg/kg of body weight) and were lying in a prone position. (Gitiban et al, 2005).

6.3 Treatment with polyherbal formulation

The feed and water were provided to the animals *ad libitum*. The animals were grouped into two groups of 3 animals each as polyherbal formulation treated and non treated control. However, both groups were infected with RSV. The animals were infected only after 10 days of treatment with polyherbal formulation. After 5 days of infection, the animals from both groups were euthanized and the visceral regions were examined to assess the rate of infection.

6.4 Lavages and recovery of tissues for quantitative viral culture

RSV-infected mice under treatment and control groups were sacrificed at various time points by CO_2 inhalation. For virus titration, lungs and nasal mucosa were immediately frozen in liquid nitrogen. Prior to plaque assay, tissues were weighed and homogenized in 1 ml phosphate-buffered saline (PBS). Tissue homogenates were assayed as described above (Gitiban et al, 2005).

6.5 Serum neutralization assay

RSV (500 PFU/ml) was mixed with serial dilutions of chinchilla serum and incubated at room temperature for 30 min. These mixtures (100µl) were used to inoculate confluent monolayers of mouse STAT1_/_ fibroblast cells grown in 24-well plates. After 1-h incubation at 37°C, infected cells were washed and fed with growth medium plus 0.5% methylcellulose. After 2 days, plates were stained with crystal violet and plaques counted. The neutralizing titer was defined as the serum dilution that resulted in 50% reduction in plaque number compared to controls that had no serum (Gitiban et al, 2005).

7. Histology study

Sections through the NP of mice were obtained following formalin fixation and decalcification. For immunohistochemistry, sections were blocked with a Vector Avidin/Biotin blocking kit. Sections were visualized using a biotinylated mouse anti-goat secondary antibody, streptavidin-horseradish peroxidase, the chromogen AEC and a hematoxylin counterstaining.

8. Predisposition of Chinchilla to infection of the upper airway with RSV following i.n. challenge

A dose-effect was clearly detectable in chinchillas inoculated with increasing doses of RSV. At the lower dosages assayed, no signs of illness were noted at any time of post challenge. Conversely, animals that received higher dosages of the virus without polyherbal formulation treatment showed signs of acute respiratory tract infection. The symptoms of viral infection like ruffling of fur and lethargic behavior were observed by day 3-4 after challenge in all the animals that did not receive pre-treatment with polyherbal formulation.

In addition, nasal lavage fluids recovered from the RSV-infected chinchillas (control) had an abnormal yellowish-green tint and was notably turbid. There was no such change observed in polyherbal formulation treated group of animals. This latter observation is consistent with histopathological evaluations that showed hypersecretion of mucus into the ET lumen in tissues recovered from untreated chinchillas; such change was not seen in the case of polyherbal formulation treated group. Plaque assays conducted with homogenized NP mucosa and NP lavage fluids indicated that the chinchilla was permissive to RSV infection. Both NP mucosal tissue homogenates and NP lavage fluid specimens were positive on days 4 and 8 after challenge. Preliminary evidence in support of restriction of viral replication to the uppermost airway following i.n. challenge was supported by the absence of viral plaques when tracheal mucosa and lung tissue recovered 4 days after challenge in the treatment group even after receiving highest dose of RSV. This clearly indicates that the polyherbal formulation pretreatment prevent viral multiplication within 4 day of challenge.

9. RSV infection results in goblet cell hyperplasia, hypersecretion of mucus, and the clear presence of RSV within cells lining the ET

Examination of NP and ET mucosae from control animals showed the presence of mild inflammation. Periodic acid-Schiff–Alcian Blue staining showed sparse mononuclear submucosal infiltrate with eosinophils, marked goblet cell hyperplasia with mucus hypersecretion into the lumen of the ET. However no such abnormalities were observed in the polyherbal formulation treated animals. The relative abundance of mucus in the ET lumen, the number of heavily stained goblet cells, and the intensity of staining of submucosal glands in an RSV-infected chinchilla treated vs untreated with polyherbal formulation was observed. Clear distinction in the histological findings in the treated and control group was seen.

10. Conclusion

RSV is the chief cause of most of the upper respiratory infections in human being. The focus of the present study was to evaluate the immunomodulatory effect of polyherbal formulation (SIVA syrup) against RSV infection in animal model. Immunomodulatory potential of medicinal plants have been extensively studied by several researchers. (Benny et al., 2004; Kripa et al., 2011; Sunila & Kuttan, 2004). We have established the immunoprotective/immunomodulating effect can be achieved using polyherbal formulation earlier in our studies (Ranjith et al., 2010). Polyherbal formulation increases the phagocytosis index to several times over control when tested against murine phagocytes *in vitro* (Ranjith et al., 2008). Further, the effect of polyherbal formulation on the humoral

antibody production in animal model by using SRBC as an antigen was also established (Ranjith, 2009). Candidal infections are quite common when the first line of host's defence mechanism get abrogated. Revalidation of the immune protection effect of polyherbal formulation in preventing experimental candidal infection in animal model was also confirmed (Ranjith, 2009). Findings of all the above studies clearly suggest that polyherbal formulation of medicinal plants is a very potent immunomodulator and has a significant role in the health and well being.

Several compliments have been received from various practitioners of alternative medicines in India for the role of SIVA in the management of upper respiratory tract infections especially in children, particularly of viral origin. The present study clearly established that polyherbal formulation has very specific effect of immune protection against upper respiratory tract infection caused by RSV in animal model. Comparative viral and hematological examinations of pretreated and control animals reveal that polyherbal formulation offers strong protection against RSV infection.

One of the plant compounds in the polyherbal formulation is *Indigofera asphalathoides* which is extremely bitter in taste. Most of the bitter principles viz., *Azadirachta indica, Phyllanthus niruri, Terminalia chebula* are known to have high antiviral activity. Further the therapeutic role of the bitter fraction in the bitter-gourd is also well known. The use of the bitter plant – *Indigofera aspalathoides* in the traditional drug preparations date back to Siddha era which is around 2000 BC. In the recent years, modern science has proved the role of bitter principles and bitter yielding plants have high therapeutic value including antiviral activity.

The exact mode of action of polyherbal formulation on RSV is not clearly understood. However, the protection of the polyherbal formulation treated group against the RSV infection could be attributed to its antiviral and immunomodulatory properties of the constituent medicinal plants in the formulation. A detailed clinical study is inevitable to substantiate the antiviral and immunomodulatory effect of the polyherbal formulation. Nevertheless immunomodulation would be the futuristic approach for the management of upper respiratory viral infections.

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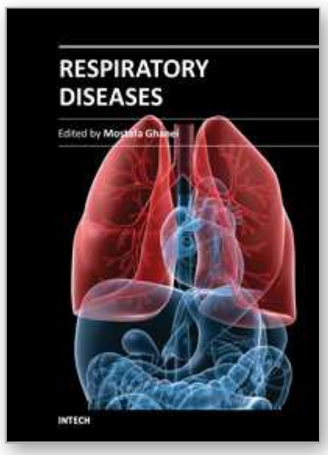

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Medicine is an ever-changing science. In this regard, Respiratory medicine is not an exception and has been evolving during recent years. As new research broadens our knowledge, advanced methods for diagnoses are better understood, providing genetic and underlying pathophysiology of diseases and new clinical experiences. Consequently, publications of new resources along with revisions of previous ones are required. The book Respiratory Diseases brings practical aspects of pulmonary diseases. It contains the result of years of experience through expert clinicians in this field from different scientific centers. The respiratory diseases are discussed according to epidemiology, pathology, diagnosis, treatment, and prognosis. It includes updated resources of the pathogenesis and some molecular aspects of the aforementioned diseases and is recommended reading for all clinicians and medical students, especially pulmonologists, to access highlighted respiratory diseases in this book.

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