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Contents

Original Article

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Experience of Covid-19 Patients - A Qualitative Case Study from Different Regions of India

Dhairya Thorat[1], S Ashok kumar[2], Sayan Bhattacharyya[3], Mahalakshmi Vijaykumar[4], Amit Banik[5], Atul Raj[6], Utpal Kumar Chattopadhyay[7]

Abstract

Introduction: Covid -19 is the infectious disease caused by the most recently discovered coronavirus. This new virus and disease were unknown before the outbreak began in Wuhan, China, in december 2019. In the latest wave of the pandemic, India has been the world's worst-hit country since April 2, forcing the States to impose new curbs to control the virus spread. As per Union Health Ministry figures, India reported 2,00,739 new Covid-19 cases in the last 24 hours, the biggest single-day spike so far, taking its overall tally to 1,40,74,564 cases. India's daily deaths due to Covid are also rising with 1,038 new deaths getting reported on Thursday, the second consecutive day the country reported over a thousand deaths. This took the overall death toll in the country to 1,73,123 till date. The country has so far reported a total of 1,45,21,654 cases and 1,75,673 deaths.

Method: Employed method was semi structured face to face and through telephonic/digital interviews with people living in different zones of India of 22 - 44 years of age. An interview guideline was developed and used by trained students in order to record the verbal consent of the patients. This article is a summarized experience of the patients afflicted to covid 19 from different regions of India focusing especially over the latest symptoms and the new therapeutic measures in order to control and treat the patients suffering from this disease. The data from the patients have been collected in accordance to different zones of India for ex. South zone includes data of patients from indian states like Tami Nadu, AndhraPradesh , Karnataka & Kerala whereas central regions include states like Madhya Pradesh, Chhattisgarh, parts of Maharashtra , Rajasthan , Bihar and Uttar Pradesh respectively. Eastern Zone included West Bengal. Oertehrn zone included data from Punjab and Jammu and Kashmir.

Results and Conclusion: Forty four eligible COVID -19 recovered people or deceased (relatives gave data and consent) (x male/y female) agreed to be interviewed and their verbal informed content was recorded. Mean interview time was of a week. Thematic analysis generated in a tabular form under various sub headings. Their life during covid 19 illness, what were the new common signs and symptoms, which geographical area they belong to and what were the precautionary measures and interventions that helped in their recovery. The experience of these people holds an importance as they were the prime patients afflicted by the infection and have a knowledge of factors that facilitated their recovery in a way as their lives were and has been affected especially during the COVID -19 second wave.of tests done during the previous day 15,66,394.

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Introduction

Coronavirus disease 2019 (COVID19) pandemic, caused by SARS-COV2, is of huge global public health and socio-economic crisis.[1] It is one of the greatest global crises since World War II, as pointed out by the United Nations.[2] One of the 1st cases of COVID-19 was reported on 17 November, 2019 in Wuhan, China.[3] On 31 December, 2019 the Chinese authorities reported the outbreak to the World Health Organization (WHO) for which an investigation was launched in January, 2020. On 30th January, the WHO declared the outbreak a Public Health Emergency of International Concern (PHEIC). It was declared a pandemic in March 2020. The coronavirus disease 2019 (COVID-19) pandemic is essentially a global health crisis, which has caused significant health-related morbidity and mortality around the world.[4]

The disease is highly contagious and leads to fatal outcomes in specific populations, especially those with comorbidities as well as the elderly. According to the World Health Organization (WHO), the current evidence suggests that the disease spreads between people by two main methods, directly (through close contact with an infected person via the mouth or nasal secretions) or indirectly (through contaminated objects or surfaces).[5] The WHO has put forward several recommendations to prevent the spread directly or indirectly. One of these recommendations is to maintain social distancing which is currently defined as keeping a distance of at least one meter from others in open public places such as parks and walking areas as well as in the confined places such as shops, restaurants, etc.[6]

The implementation of social distancing is undoubtedly challenging in densely populated or crowded areas where people live in close proximity. People living in such areas are at increased risk of contracting the infection due to the rapid transmission of the disease.

India is a thickly populated country , the living conditions in the country pose a high health risk to the residents. The country had been declared an upcoming global hotspot in the current COVID-19 pandemic due to the rapid and uncontrolled transmission of the infection both within the local community as well as the spread of the disease to the other regions of the country.[7] Of late, an alarming number of young Indians, including children are falling victim to the new strains of Novel Coronavirus while the second wave is sweeping the country. Some doctors say the reason for under-45 age group being now vulnerable is that they go to work and eat out more, but there is no definitive proof.[8] They are also more prone to the double mutant.[8] It is hence very important to explore the experiences of COVID-infected patients from the time of their diagnosis or the emergence of their symptoms through to their recovery, especially the patients from hotspots.This can not only help the healthcare organizations to adopt new care models and streamline the workflows but also help improve the quality of life of infected patients in high risk communities, during the current and future outbreak of pandemic diseases. Also strain variation and mutants are there, making symptoms variable and the virus difficult to detect.[9]

Methods

Study design & Sampling: In this study, we adopted qualitative methodology and employed semi-structured telephonic/digital interviews with the eligible participants who agreed for the interview.

Participants Settings: Forty four (44) participants living in different regions of the country were interviewed. The participants living in different zones of India, were of 22-44 years of age, and having suffered and recovered during 1st or 2nd wave of COVID-19 (either hospitalized or not during their illness), were deemed eligible for the recruitment.

Semi-structured Interviews: To facilitate the interviews, the interview guide was developed in the English language and then translated into the different local languages depending on the zones by the interviewer. The interview guide comprised open-ended questions like what were the new common signs and symptoms , which geographical area they belong to and what were the precautionary measures and interventions that helped in their recovery. The interview guide was checked by two experienced academic staff members. The interviews were expected to take 15-20 minutes each.

Three research students conducted the semi-structured interviews. The interviews were conducted with the recommended health precautionary measures in place. Informed consent was taken from each participant prior to the interview. Social media like email and Whatsapp were used sometimes. Sometimes for admitted

patients or deceased patients, their relatives were questioned.

Data Analysis: Qualitative data in the transcriptions were analyzed using the inductive method of analysis and is represented by a tabular form. The initial step of the analysis involved familiarizing with the data through reading the transcripts and recording what were the common signs and symptoms shared by patients along with what were the interventions that facilitate their recovery in different zones of the country.

Result

Zones of India			Representing features	Treatment taken	Remarks	
Central	South	Eastern			Alive	Dead
	✓		Fever, Sore throat, dry cough, tastelessness	Azithromycin, Paracetamol, Cetirizine, Vitamin supplements	yes	
	✓		Wheezing	same	yes	
	✓		Fever, Cough	same	yes	
	✓		Fever, sore throat, dry cough, rashes in the pubic area and face	Same	Yes	
	✓		Sore throat, fever, myalgia, rigor, chills, vomiting, Diarrhoea, menstrual bleeding	Augmentin, Paracetamol, Dexamethasone, Deriphyllin, Enasiparin, Zincovit, Limcee	Yes	
	✓		Severe cold, chills, head ache, fever, Dyspnea	Levocetrizine, Paracetamol, Pantoprazole, Ivermectin, Amoxycillin + clavulunate, vitamin supplements	Yes	
	✓		Fever, myalgia, cough, cold, head ache	Paracetamol, Azithromycin, Zincovit, Evion 400	Yes	
	✓		Fever, myalgia, head ache, dyspnea	Parcetamol, Taxim 400, vizylac, Zincovit, Limcee	Yes	
	✓		Myalgia, Cough, Head ache	Remdesivir, Paracetamol, Zincovit, Limcee	Yes	
	✓		Head ache, Myalgia	Azithromycin, Ranitidine, Vitamin, Limcee	Yes	
	✓		Fever, cold, myalgia, tonsil pain, difficulty in swallowing	Azithromycin, Paracetamol, Zinc and Vitamin c	Yes	
	✓		Sore throat, Back pain, Heas ache, fever	Ivermectin, Vitamin supplements	Yes	
	✓		No signs, CT Scan - Co- rads 5 (elevated)	Ivermectin, NSAIDs, ,remdesivir, vita. c + zinc	Yes	
	South		Fever, dry cough, Weakness, Shortness of breath	Ventilation, Hydroxychloroquine, Immune boosters, nutritious diet	Yes	
	South		Severe respiratory distress, chest pain, Bodyache, fever.	Ventilation, Paracetamnol, Nutritive food, Immune boosters	Yes	
	South		Joint pain, fever, diarrhea, weakness, sore throat	Home isolation, Paracetamol, Antihistaminics, Nutritious diet	Yes	
	South		Severe respiratory distress, Fever, weakness, cough, patient known Diabetic	Ventilation, Hydroxychloroquine, Immune boosters, Paracetamol		Yes (dead)
	South		Severe respiratory distress, Fever, weakness, Diarrhoea, bodyache, Headache, known Hypertensive.	I.V. Vitamin C, Hydroxychloroquine, Ventilation, Immune boosters.		Yes (dead)

Table 2: Data from Central Zone.

Zone	Presenting features	Treatment	Alive	Dead
Central Zone	Persistent fever, headache, bodyache, cold and cough, CT scan - 2-5% lung damage.	azithromycin, doxycycline, Pantoprazole, Montelukast, pulmoclear, ivermectin, paracetamol.	Yes	
	Diarrhoea, fever, cold and cough, CT- scan- pneumonia.	Antihistaminic syrup , Vitamin D3 , Ivermectin, medroc, fabfitfun, doco, doxycycline.	Yes	
↗	Difficulty in swallowing and breathing, headache &bodyache, fever.	paracetamol, cetirizine, amoxicillin, vitamin supplements.	Yes	
↗	Mild covid infection, fever.	rest, hydration, diet , azithromycin, lecopeM, gargle with warm water.	Yes	
↗	Shortness of breath, fever, cough, SaO2/O2 level below 90-92 %.	azithromycin, doxycycline, solpure C, sypphensedyl, dolo.	Yes	
↗	Fever, cold & cough body ache, weakness.	Paracetamol, Azithromycin, ivermectin, livicee, calorol sachet.	Yes	
↗	Persistent fever, headache, sore throat, myalgia.	ivermectin, azithromycin, doxycycline, zincola, livocitrizine, crocin.	Yes	

Table 3: Findings in Northern Zone.

Zone	Presenting Feature	Treatment Taken	Alive	Dead
North (Punjab)	Fever, cough, respiratory distress, known Hypertensive and Hyperlipidemic	I.V. Vitamin C, Hydroxychloroquine		yes
North (Punjab)	Cough, shortness of breath, fever, diarrhea, gastritis	Ventilation, Paracetamol, Ranitidine	Yes	
North (Punjab)	Severe respiratory distress, Fever, bodyache	Remdesivir, Ventilation, Paracetamol		Yes
North (Punjab)	Running nose, fever, sore throat, mild difficulty in breathing	Home isolation, immune boosters, Vitamin C, Nutritive diet, Antihistaminics	Yes	
North (Punjab)	Fever, Headache, Sore throat, Weakness, lack of taste and smell	Multivitamin tablets, Hydroxychloroquine, Dexamethasone.	yes	
North (Jammu and Kashmir)	Running nose, Fever, severe respiratory distress, cough	Ventilator, Paracetamol, Hydroxychloroquine, fluid therapy		Yes
North (Jammu and Kashmir)	Fever, shortness of breath, vomiting, sore throat	Paracetamol, Remdesivir, Zinc tablet	Yes	
North (Jammu and Kashmir)	Fever, diarrhea, acute dyspnoea	Paracetamol. Fluid therapy, immune boosters.	Yes	
North (Jammu and Kashmir)	Acute dyspnea, fever, headache	Hydroxychloroquine, nutritious food, Multivitamins	Yes	
North (Jammu and Kashmir)	Loss of smell and taste, Shortness of breath, cough, fever.	Home isolation, Fluid therapy, Immune boosters, Vitamin C, Paracetamol	Yes	

Hence findings were variable region to region. There were completely asymptomatic people and some with only anosmia and running nose. Rhinitis and nasal discharge were most common early findings in Eastern zone, while fever and cough were commenst initial features in Central Zone. In Southern zone patients had more commonly fever and myalgia or bodyache as intial symptoms. All the participants got tested by PCR except one who was diagnosed by CBNAAT.

Table 4: Findings in Eastern Zone.

Zone	Representing feature	Treatment taken	Alive	Dead
Eastern	Asymptomatic, tested before operative procedure. Tested positive twice and took 1 dose of vaccine in between two episodes.	Vitamins and antipyretic	yes	--
Eastern	Fever and dry cough.	Vitamins, Ivermectin, Doxycycline and antipyretic.	yes	--
Eastern	Fever , dry cough and shortness of breath.	Favipiravir, Vitamins, Ivermectin, Doxycycline and antipyretic.	yes	---
Eastern	Anosmia only	Doxycyline, Zinc tablet, Vitamin C tablet.	Yes	
Eastern		Antibiotics and Vitamins	Yes	
Eastern	Diarrhoea and vomiting		yes	
Eastern (patient originally hails from Western Zone but staying here since last 2 years)	Rhinitis, nasal congestion, slight dry cough.	Doxycycline, Ivermectin, Zinc with Vitamins, Pantoprazole, Betadine oral gargle, Nebulization.	yes	
Eastern	Loss of taste and smell	Taken but not specified	yes	
Eastern	Dry cough, fever, weakness (tested due to contact with positive case).	Vitamin C, Zinc, Ivermectin, Doxycycline , antipyretic and antiemetic when needed.	yes	

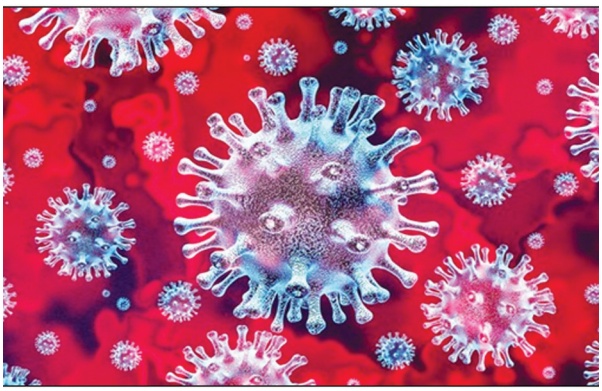

Fig: Experience of COVID-19 patients - a qualitative case study from different regions of India.

Discussion

COVID-19 disease pandemic is essentially a global crisis. However, the individuals and especially those who suffer from COVID-19 continue with their life with its basic needs. Exploring their experiences provides an insight into how their lives are affected and measures that can be taken, on individual and social levels, to ease their lives and make them valuable members of society again. This study indicates that the participants who were social media users were well-aware of the COVID-19 and the related issues. The participants highlighted that after the lifting of the lockdown, the precautionary measures were not being observed by the people in the same way as they were being observed during the lockdown period. The initial symptoms reported by our study participants were in line with the initial symptoms reported by the patients in other studies . However diarrhoea and headache are among the new most common symptoms of COVID-19.[10] Other rare manifestations like hair loss can also be seen.[11] The COVID-19 pandemic has had a direct impact on the medication supply worldwide especially in India since a large number of cases coming everyday there has been a deficiency in supply of medications, and this could have also contributed to the worsening of conditions, as highlighted study participants. The majority of the participants reported using the medicines to control their symptoms. Some of them mentioned the use of antibiotics, which seems inappropriate to use in the COVID19 infection as it is a viral infection but can be needed to prevent or treat secondary infections. This can even be disadvantageous by increasing the bacterial resistance in the long run. However, in some cases, the use of antibiotics may be beneficial since COVID-19 sometimes co-exists with bacterial infections according to data of WHO. Others reported that the home remedies helped in their recovery from COVID-19. Since these complementary medicines like Garlic and Turmeric have an anti-inflammatory effect, these might have played a role by increasing their immunity against COVID-19.[12] Many treatment options are now there like Chloroquine, monoclonal antibodies, Interferon alpha and antibiotics.[13] People need to be aware of which medicine to take and when.

Support from family and friends are also the key to the survival for individuals in these circumstances and it has been particularly highlighted in this pandemic by the participants. Regional variation in symptoms could be due to environmental factors or could be due to strain and variant variation from region to region. One should remember that there can be a lot of variation in clinical presentations of COVID-19 infection and rare features like vomiting and diarrhea can be the only finding. Also joint pain can be the presenting feature.There was some regional variation in that shortness of breath was found more in Northern region. Also, interestingly most deaths were seen in patients who were Diabetic, hypertensive or Hyperlipidemic. These seem to be the most dangerous predisposing factors for severe outcome in these patients. There are not much studies from India in this regard and more such studies are needed.

Conclusion

This study presents the experiences of COVID-19 recovered patients from different regions of india especially during the 2nd wave of the infection. Social media can be used widely to raise and sustain awareness before, during and after lockdowns, regarding COVID-19, mechanisms by which it is transmitted and the precautionary measures which should be observed to minimize the disease transmission. Appropriate precautionary measures, including isolation, must always be observed during the COVID-19 illness to prevent the transmission to others. Mental health support should be considered for vulnerable patients. The authorities must ensure adequate food and medicines supply during the 2nd wave of infection. Our findings will help in implications of better care models and streamline the workflows for improving patient's quality of life during and after their illness in high-risk countries like India , during this pandemic, and in future disease outbreaks.

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Review Article

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Challenges for Nurses Working at Critical Care Unit at Newly Established Tertiary Care Cancer Centre - Ventilator Associated Pneumonia Nursing Care

R Surendra Naik[1], Avadhesh Kumar Yadav[2], Rajendra Kumar Sahu[3], Ram Niwas Sharma[4]

Abstract

Introduction: Nosocomial pneumonia associated with mechanical ventilation (due to endotracheal tube or tracheostomy) develops within 48 hrs. or more than 48 hrs. ***Epidemiology:*** VAP occurs in 10-65% of all ventilated cases, Hospital-acquired pneumonia (HAP)is the second most common hospital infection., 90% of all nosocomial infections occurring in ventilated patients are types of pneumonia. The Indian study indicates the incidence of VAP is 57.14% and the incidence density of VAP was 31.7/1000 ventilator days, another study indicates the VAP rate was 6.242/ 1000 ventilator days. The mortality rate ranged from 16.2% to 74.17%. The highest mortality rate was reported from a study in India. ***Pathogens:*** Staphylococcus aureus (44%) are the most frequently isolated microbes. Acinetobacter baumanii (30%), Pseudomonas aeruginosa (12%), Stenotrophomonas maltophilia (7%), Klebsiella pneumoniae (6%), and Serratia marcescens (2%) were isolated from the transtracheal aspirates or bronchoalveolar lavage in patients with VAP. ***Types of pneumonia:*** Community-acquired pneumonia, Hospital-acquired pneumonia, and Ventilator-associated pneumonia Common signs and symptoms are Difficulties in breathing, Tachycardia Fever, Sweating, Shivering, Loss of appetite, Pain in the chest, Hemoptysis, Headache, Fatigue, Nausea, Vomiting. ***Complications:*** Septicemia, Lung abscess, Acute respiratory distress syndrome (ARDS), Middle ear infection, Blood infection, Meningitis, Sepsis, Pericarditis, Atelectasis, Pleural effusion, Hypotension, Tachypnea, Confusion, Septic shock, Decreases in breath sounds, and Unequal chest expansion. ***Conclusion:*** Nurses play a key role in the intensive care unit, they need to know about VAP, they have to Conduct a Physical examination of the patient and clinical pulmonary infection score (CIPS) to be recorded. they Check vital signs (Temperature, Pulse, Respiration, Blood pressure, and oxygen saturation. Assist the intensivist in the assessment of Progression of infiltrate. They are responsible for the Management of a patient with pneumonia by providing quality nursing care.

Keywords: Nosocomial pneumonia; VAP; HAP; HAI.

Introduction

Nosocomial pneumonia associated with mechanical ventilation (due to endotracheal tube or tracheostomy) develops within 48 hrs. or more than 48 hrs. of admission and which was not present at the time of admission.[1] Nosocomial pneumonia is associated with mechanical ventilation (due to endotracheal tube or tracheostomy). Nosocomial pneumonia is characterized by the presence of a new or progressive infiltrate, signs of systemic infection (fever, altered white blood cell count), changes in sputum characteristics, and detection of a causative agent.[2]

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Epidemiology

- VAP occurs in 10-65% of all ventilated cases, Hospital-acquired pneumonia (HAP) is the second most common hospital infection.
- 90% of all nosocomial infections occurring in ventilated patients are types of pneumonia.
- European study indicates the incidence of VAP is 8.0% and the incidence density: 12.3/1000 ventilator days.[2]
- The Indian study indicates the incidence of VAP is 57.14% and the incidence density of VAP was 31.7/1000 ventilator days, another study indicates the VAP rate was 6.242/ 1000 ventilator days.[3]
- A study indicates Mortality in VAP patients is 61.84%. Acinetobacter baumannii (37.63%) and Klebsiella pneumoniae (36.55%) are the commonest organisms isolated followed by Pseudomonas aeruginosa and Staphylococcus aureus.[3]
- A systematic review indicates Ventilator-associated pneumonia incidence rate. Ranged from 2.13 per thousand ventilator days to 116 per thousand ventilator days differing greatly between countries. The highest VAP prevalence rate was reported from the Medical Intensive Care Unit (MICU), India. The mortality rate ranged from 16.2% to 74.17%. The highest mortality rate was reported from a study in India.[4]
- Mortality Rate is 27% & 43% with antibiotics Resistant organisms, in VAP mortality rate is caused by Pseudomonas or Acinetobacter is a higher rate of 76%.
- Mortality is highest for infections caused by A. baumannii (83.33%) and K. pneumoniae (71.42%).[5]

Pathogens

Staphylococcus aureus (44%) are the most frequently isolated microbes. Acinetobacter baumanii (30%), Pseudomonas aeruginosa (12%), Stenotrophomonas maltophilia (7%), Klebsiella pneumoniae (6%), and Serratia marcescens (2%) were isolated from the transtracheal aspirates or bronchoalveolar lavage in patients with VAP.[5] An Indian study report indicates the most common organisms isolated from an endotracheal aspirate of patients who developed VAP are Pseudomonas aeruginosa, Methicillin-resistant Staphylococcus aureus (MRSA), Klebsiella pneumoniae, and Acinetobacter baumannii.[5] Most strains of Pseudomonas (55.56%) are resistant to commonly used beta-lactam antibiotics known to be effective against Pseudomonas. All strains of Staphylococcus aureus are MRSA and most isolates of K. pneumoniae (85.71%) are extended-spectrum beta-lactamase-producing. About 50% of isolates of Acinetobacter are resistant to carbapenems.[5]

Pathogenesis

The main pathogenic factor in the development of VAP is biofilm formation within the tracheal tube (TT) and microaspiration of secretions.[7] The normal protective upper airway reflexes and prevents effective coughing are affected by the tracheal tube. The colonization of aerobic gram-negative bacteria occurs in the oropharynx. The contaminated secretions of the oropharynx pool above the tracheal tube cuff and slowly gain access to the lower airway through a fold in the wall of the cuff. A bacterial biofilm, which is impervious to antibiotics, gradually forms on the inner surface of the tube and serves as a nidus for infection.[7] This pathogen-rich biofilm is pushed into the distal airways by ventilator cycling and in the setting of immunosuppression associated with critical illness causes pneumonia. The long-term requirement of mechanical ventilation increases the risk of developing VAP. patients in a supine position increase the risk of microaspiration and enteral feeding via a nasogastric tube increases the risk of aspiration of gastric contents.[7] It is the main responsibility to prevent VAP to reduce biofilm formation and microaspiration.

Types of Pneumonia

- Community-acquired pneumonia
- Hospital-acquired pneumonia
- Ventilator-associated pneumonia

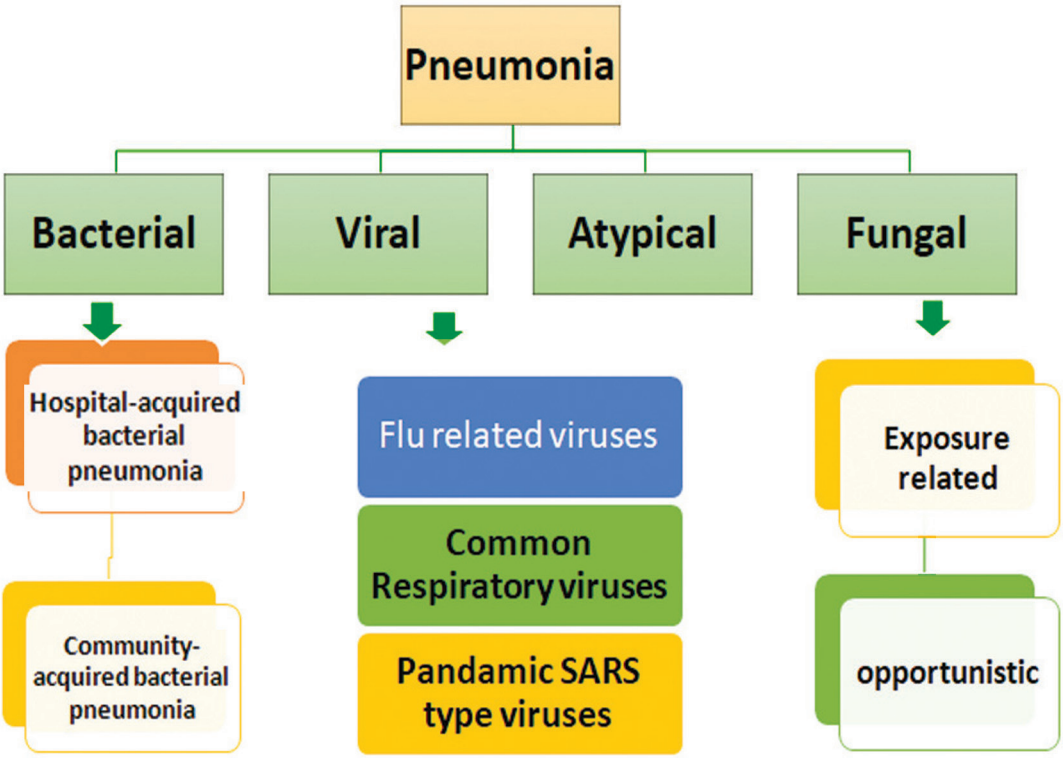
Community-Acquired Pneumonia

Early-onset of pneumonia less than 98 hrs. of intubation or ICU admission causative pathogens is streptococcus pneumoniae, Hemophilus influenza, staphylococcus aureus. Antibiotics sensitive

Hospital-Acquired Pneumonia

Late-Onset Pneumonia more than 98 hrs. of ICU admission or intubation, common causative pathogens pseudomonas aeruginosa, methylene resistant staphylococcus aureus (MRSA), Acinetobacter, Enterobacter, antibiotics resistant.

Ventilator Associate pneumonia: one type of hospital Acquired pneumonia that occurs more than 48 to 72 hrs. after endotracheal intubation.


Pneumonia
Bacterial
Viral
Atypical
Fungal
Hospital-acquired bacterial pneumonia
Community-acquired bacterial pneumonia
Flu related viruses
Common Respiratory viruses
Pandamic SARS type viruses
Exposure related
opportunistic

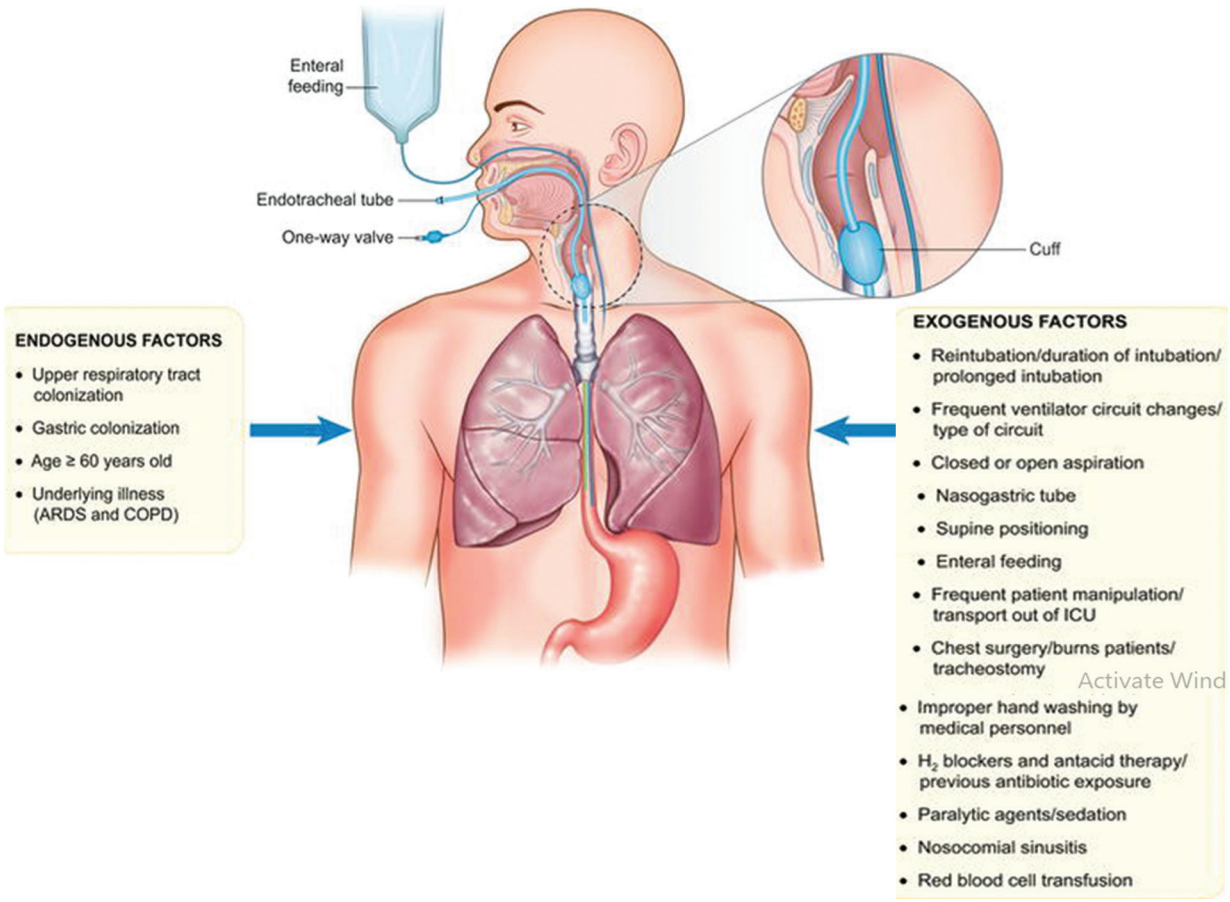

Enteral feeding
Endotracheal tube
One-way valve
Cuff
ENDOGENOUS FACTORS
Upper respiratory tract colonization
Gastric colonization
Age ≥ 60 years old
Underlying illness (ARDS and COPD)
EXOGENOUS FACTORS
Reintubation/duration of intubation/ prolonged intubation
Frequent ventilator circuit changes/ type of circuit
Closed or open aspiration
Nasogastric tube
Supine positioning
Enteral feeding
Frequent patient manipulation/ transport out of ICU
Chest surgery/burns patients/ tracheostomy
Improper hand washing by medical personnel
H2 blockers and antacid therapy/ previous antibiotic exposure
Paralytic agents/sedation
Nosocomial sinusitis
Red blood cell transfusion

Figure presenting Aspiration of organisms from the oropharynx and GI tract, Direct inoculation, Inhaled Bactria, and Hematogenous spread.

Risk Factors

Environmental factors

- Indoor air pollution is caused by cooking and heating with biomass fuels (such as wood or drug).
- Living in crowded homes.
- Prenatal smoking.

Secondary Disease

- Stroke
- Multiple sclerosis.
- Amyotrophic lateral sclerosis
- Head injury
- Senile dementia, Alzheimer's disease
- Poor immune systems
- AIDS
- History of organ transplant
- Cancer (especially leukemia and Hodgkin lymphoma)
- Chronic obstructive pulmonary disease (COPD)
- Diabetes
- Kidney disease
- Sleep apnea
- Heart failure
- Poor nutrition
- Allergies, asthma
- Liver disease
- Mechanical ventilation

Drugs

- Chemotherapy drugs
- Immune suppressant drugs steroids

Genetic disorders (sickle cell disease. cystic fibrosis)

- Cystic fibrosis
- Immobilization
- Tracheostomy

Infection

- Colonization: (colonization of dental plaque with respiratory pathogens).
- Bacterial colonization of the oropharyngeal area.
- Aspiration subglottic secretions
- Contaminated equipment's
- Contaminated hands (cross-contamination of hands)
- Supine position

Common Symptoms

- Difficulty in breathing
- Tachy cardia
- Fever
- Sweating
- Shivering
- Loss of appetite
- Pain in chest
- Hemoptysis
- Headache
- Fatigue
- Nausea
- Vomiting
- Complications:
- Septicemia
- Lung abscess
- Acute respiratory distress syndrome (ARDS)
- Middle ear infection
- Blood infection
- Meningitis
- Sepsis
- Peri carditis
- Atelectasis
- Pleural effusion
- Hypotension
- Tachypnea
- Confusion
- Septic shock
- Decreases in breath sounds
- Unequal chest expansion

Nursing Assessment and Care

- Conduct a Physical examination of the patient.
- Clinical pulmonary infection score (CIPS) to be recorded.
- Check vitals signs (Temperature, Pulse, Respiration, Blood pressure, and oxygen saturation.

- Send blood investigation (CBC, (WBC count), Blood culture, Biochemistry test)
- Do Chest X-ray.
- ABG/pulse oximetry
- Serological studies, viral or legionella titers, cold agglutinins
- Assist the intensivist in the assessment of Progression of infiltrate.
- Send aspiration fluid (sputum) for gram stain /Culture
- Microbial investigation -
- Endotracheal aspiration (blind method suctions of ET secretion)
- Bal (Broncho alveolar lavage
- Percutaneous aspiration/open biopsy of lung tissues.
- Mini Bal (blind method catheter is advanced till resistance is meet.
- Protected specimen brush (minimizes contamination during Bronchoscopy because the brush is contained in a protective sheath.
- Fiber optic Bronchoscopy or transcutaneous needle aspiration /biopsy.
- Prognosis: with treatment most, types of bacterial pneumonia will stabilize in 3-6 days.it often takes a few weeks before most symptoms are resolved .in person require hospitalization, mortality may be as high as 10%and in those requiring intensive care it may reach 30-50%.

Nursing Management of a patient with pneumonia

- Take a careful physical examination of patients to help to get an etiological diagnosis.
- Assess the elderly patient's unusual behavior, alter mental status, dehydration excessive fatigue, and concomitant heart failure.
- Observe for anxious, flushed appurtenance shallow respirations splitting of affected sides, confusion, dehydration
- Auscultate for crackles overlying affected sites and for bronchial breath sounds when consolidation is present
- Education and training in the appropriate airway management
- Strict hand hygiene for airway management
- 2nd hourly ET cuff pressure monitoring
- Apply moisal eye drops 2nd hourly
- Oral hygiene (chlorohexidine mouth wash 2nd hourly
- Positioning changing every 4th hourly
- Maintain head end elevation 35 to 45 degrees
- Promote procedures and protocols that safely avoid or reduce the time on the ventilator
- Suctioning properly (subglottic, or endotracheal).
- Maintain aseptic technique while caring for the patient.
- Sedation vacation as advised by the intensivist
- Need for antacid assessment to the patient
- Use different sizes catheters for oral and nasal suctioning.
- Assess the ventilator circuit days and change
- Chest physiotherapy loosens and mobilizes secretions.
- Administering antibiotics as per physician's order.
- Maintain VAP (ventilator-associated pneumonia) bundle as per infection control policy.
- Provide adequate oxygen support to the patient.
- Maintain adequate airway clearance
- Maintain adequate hydration
- Provide health education regarding vaccination, aseptic techniques.

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Review Article

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Microorganisms and Autoimmunity

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Abstract

Autoimmume diseases occur when the host's immune system reacts against own or self antigens. Many microorganisms can trigger and initiate autoimmunity by various mechanisms.These things are very interesting to note and study. Hence here we try to present relevant information about epidemiology and pathogenesis behind microbes causing autoimmunity.

Keywords: Autoimmune, infection, vaccination.

Introduction

Microbes play a role in induction of autoimmunity. Microbes, both pathogenic and commensal, can stimulate production of autoantibodies that bind to brain and can influence behaviour in susceptible hosts.[1] This is now a very interesting and hot topic of research. Any disruption of normal microbiome may trigger autoimmunity. Non-pathogenic microorganisms found in various parts of body are called commensal microbiota. There are three major features of host–commensal interactions. Mechanisms of central tolerance, or deletion and inactivation of self-reactive lymphocytes and their inhibition by regulatory T cells (Tregs) exist to minimize autoimmunity. Potentially autoreactive immune cells are always found in the host.[2]

Autoimmune diseases can be broadly divided into two large groups: Group I consists of diseases that need innate–adaptive immunity connection, and Group II, or those for which this connection is not important. Group II diseases occur due to the loss of control over one of the principal mechanisms controlling adaptive immunity, like negative selection or generation of Tregs.[2]

Conventional commensal microbiota is free of specific pathogens. However they can harbour microbes that are not pathogenicnormally. This category of commensal microorganisms can confer protection against autoimmunity.[2] Bonafide pathogens can either suppress or provoke autoimmunity. Coxsackie B3 viruses can induce type 1 Diabetes mellitus in the mouse model.[3]

Mechanisms by which microbes induce autoimmunity

Microbes can initiate or precipitate autoimmunity in many ways. Firstly, molecular mimicry can be important for autoimmunity. Acute Rheumatic fever is a disease caused by destruction of myocardium due to cross-reactivity or molecular mimicry with Group AStreptococcal antigens.[4] Klebsiellapneumoniae,can carry antigens mimicking MHC class I molecule HLAB27 and, hence can possibly induce Ankylosing spondylitis.[2]

Secondly, there can be induction of co-stimulation and cytokine production by APC (Antigen presenting cell) activated by infection, which also presents self-antigens, activating autoimmunity. This is called "bystander activation.[2] Thirdly, specific commensal bacteria induce production

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of cytokines affecting autoimmunity. Segmented filamentous bacteria stimulate generation of Th17 and Th1 types of T-cell responses.[2] Whereas Th17 cells are critical for defence against somepathogens, they also contribute to autoimmunity. Th17 cells induced by SFB (Segmented filamentous bacteria) can affect autoimmune reactions in remote organs, likejoints.[2]

In this chapter the author has tried to present in a concise manner all available information in this respect.

Evidence in illnesses

Neuropsychiatric illnesses

An increased prevalence of familial autoimmunity, exposure to pathogens prenatally and postnatally, and findings of anti-brain antibodies are common in schizophrenia, obsessive-compulsive disorder and autism. So differences in exposure timing and genetic vulnerability are important determinants of neuropsychiatric outcomes.[5]

Diabetes mellitus

A initially high level of amyloid-producing E. coli in the intestine, followed by their depletion, most likely due to prophage induction, can lead the initiation of autoimmunity and T1D progression. The diabetogenic role of E. coli prophagesis supported by activation of E. coli prophages with mitomycin C resulting in pronounced amyloid release from preformed microbial biofilms. Together with metagenomics data, these findings suggest that same process might occur in gut of children who develop autoimmunity and T1D.[6] Enterovirusescan also causeT1D in humans.[7] Seasonal incidence of T1Dare documented afterEnterovirus infections. However the etiological link is enigmatic.[7] A higher frequency of enterovirus infections has been found in siblings with type 1 diabetes as compared to nondiabetic controls.[7] Additionally, higher titres of enterovirus antibodies are seen in pregnant mothers whose children later develop T1D.[7]

Protein produced by common gut bacteria trigger the onset of autoimmune diseases like multiple sclerosis (MS), rheumatoid arthritis, and ulcerative colitis.

Some patients with autoimmune disorders display higher than normal levels of a "mimic protein" (ubiquitin) produced by Bacteroidesfragilis, a Gram negative anaerobe normally found in gut.[8] Ubiquitin tagging (ubiquitylation) of proteins affects nearly every eukaryotic cell function. Ubiquitin is also involved in the development and function of immune system.[9] B. fragilis is unique in being the only bacterium to encode an ubiquitin homologue. B. fragilis is produces and exports a eukaryotic ubiquitin which is closely related to mammalian ubiquitin and is structurally similar.The B. fragilis gene sequence indicates a past horizontal gene transfer from an unknown eukaryotic source. It encodes a protein with 63% identity to human ubiquitin.[9] B. fragilis ubiquitin can cross human gut lining and generate immune response. People with lupus and RA are more likely than healthy volunteers to have antibodies to BfUbb (B. fragilis ubiquitin). Interestingly, another role of Bacteroides spp. is also important. Some B. fragilis strains produce a capsular polysaccharide that stimulates dendritic cells to alter ratio of T helper cells and producesIL-10, which reduces production of proinflammatory IL-17.[9]

Autoimmunity in HUS

Haemolytic uraemic syndrome (HUS) is a severe disease with renal failure, microangiopathicanemia and thrombocytopenia. Several mechanisms leading to HUS are identified, like infections with enterohaemorrhagic Escherichiacoli, and genetic mutations of complement genes, which result in defective complement control on surface of host cells. In atypical HUS, autoantibodies that bind complement inhibitor Factor H are important.[10] Susceptibility to reactive arthritis, an acute inflammatory joint disease after intestinal bacterial infection, is associated with MHC class-I genes, notably HLA-B27. The disease follows infection with intracellular bacteria, including Chlamydia, Salmonella, Shigella, and Yersinia species. This association is established based on isolation and analysis of antibody responses. These bacteria enter body through mucosa and invade cells. Yersinia enterocolitica is taken up by M cells in Peyer's patches through interaction between bacterial surface invasin and host β1-integrins. Yersinia can use phagocytes to translocate through endothelium, reaches bloodstream and synovium.[11] Reactive arthritis and ankylosing spondylitis have a very strong association with the MHC class I allele HLA-B27. HLA-B27 is found in about 80% of cases with reactive arthritis and in over 95% of cases with primary ankylosing spondylitis. Ankylosing spondylitis can be preceded by reactive arthritis. Several studies indicate persistence of bacteria and bacterial antigens in patients with reactive arthritis. These patients have continued IgA antibody responses against the triggering microorganisms. Mononuclear phagocytes carrying antigens of arthrogenic microorganisms

(LPS, heat shock proteins) can enter peripheral circulation. They are the major source of microbial antigens reachingsynovium. In Yersinia-induced arthritis, LPS, 60-kDa heat shock protein, and urease β-subunit have been detected in joint by immunohistochemistry or immunoblotting.[11]

Guillain-Barre syndrome (GBS)

GBS or autoimmune demyelinating radiculoneuropathy is an inflammatory disease of the peripheral nerves that can follow infection with Campylobacter jejuni, Epstein-Barr virus, cytomegalovirus, and Mycoplasma pneumoniae. GBS shows lymphocytic infiltration and demyelination in peripheral nerves. The onset is sudden and limb weakness progresses to maximum disability within 1 week of onset. C. jejuni is the principal agent associated with GBS. Campylobacter, the commonest cause of bacterial diarrhea in the US, are Gram-negative bacilli that readily invade the intestinal mucosa.[11] In GBS, involvement of C. jejuni has been documented by serology,and direct isolation from GBS patients. In astudy, C. jejuni is found in 26% of GBS patients and 2% of household controls.[12] Infection with C. jejuni stimulates formation of antibodies cross-reacting with peripheral nerve antigens. Patients with GBS develop antibodies specific for LPS of C.jejuni thatcrossreactwith gangliosides from peripheral nerves. Gangliosides are membrane-anchored glycosphingolipids. The outer polysaccharide of LPS from Campylobacter bear structural similarities to gangliosides of peripheral nerves. The Campylobacter O:19 serotype shares an identical tetrasaccharide with GM1 ganglioside and a pentasaccharide with GD1a ganglioside.[11] Serotypes O:23 and O:36 share a branched tetrasaccharide with GM2 gangliosides. Patients with GBS develop antibodies against LPS of certain C. jejuni strains that crossreact with gangliosides from peripheral nerves. Gangliosides are membrane-anchored glycosphingolipids with hydrophilic extracellular oligosaccharide. Serotypes O:23 and O:36 share a branched tetrasaccharide with the GM2 ganglioside.[13]

GBS can also occur after CMV infection. CMV-related GBS has a different clinical pattern from other GBS groups. Patients are significantly younger, and initially have a severe course with a high frequency of breathlessness, and frequently develop cranial nerve involvement and severe sensory loss. This is in contrast to C. jejuni infection, which causes motor GBS.[14] Studies have reported the presence of IgM anti-GM2 antibodies in GBS patients after CMV infection.[15] CMV related GBS is also associated with increased soluble adhesion molecules and interleukin-2 receptor in blood, suggesting activation of T cells. The histological picture of the AIDP form of GBS is similar to experimental autoimmune neuritis, which is T cell–driven. Similarities between CMV and Schwann cell or myelin proteins has also been noted.[15]

Miller-Fisher syndrome(MFS) is a less severe and rarer variant of GBS. The worldwide incidence of GBS is 1 to 2 in 100,000, with the MFS variant producing a subsetof cases (1 to 2 in 1,000,000). MFS affects more men than women and has a mean age of 43.6 years at onset of symptoms. MFS presents with at least 2 of the following features: ataxia, areflexia, and ophthalmoplegia. It is commonly associated with the involvement of lower cranial and facial nerves and does not involve motor weakness of limbs.[16] MFS is thought to result from aberrant acute autoimmune response to prior infection by Campylobacter jejuni, Cytomegalovirus, EBV, or HIV. A cross-reaction between peripheral nerve antigens and microbial components is said to drive the inflammatory process of MFS.[15] Several studies report that IgG anti-GQ1b antibody, isfound in MFS. The feature of ophthalmoparesis in MFS occurs from direct action of anti-GQ1b antibodies on the neuromuscular junction between the cranial nerves and ocular muscles.

Role of microbiome in autoimmune disease

The human microbiomerefers to the entire habitat, including microorganisms, their genomes and the surrounding environmental conditions. When the equilibrium between microbial habitat and host is disturbed, dysbiosis is caused. Commensal microorganisms play a central role in maintaining homeostasis and health, not only by blocking microbial activity but also by reinforcing immune system through specialized mechanisms.[17]

Oral microbiota

The oral microbiome (OMB) is responsible for the manifestation of many intra- and extraoral diseases. A dysbiotic shift of oral host microorganisms triggers disease entities, like dental caries, periodontal diseases, periimplant inflammation and halitosis.[17] There are oral bacteria which prevent pathogenic colonization by other microbes (colonization resistance). Also, the antagonistic or synergistic interaction between commensal and pathogenic microorganisms is responsible for eliciting oral diseases. Sjogren's syndrome or SS is a systemic chronic autoimmune disease,

characterized by B-cell hyperactivity, that produces antibodies and lymphocytic infiltration of exocrine glands resulting in their destruction. Salivary and lacrimal glands are primarily attacked, leading to a significant reduction in saliva and tear production, which then leads to the most prominent symptoms of the disease, oral and ocular dryness. Firmicutes have a significantly higher frequency in patients, but Spirochaetes are significantly depleted in SS. Streptococcus and Veillonella show almost a two-fold increase in SS. Also, Veillonellaatypica and Veillonellaparvula dominate in patients, but Prevotellamelaninogenica dominates in controls. So, the microbiome is less diverse and richn in patients, where a depletion of nearly 17% in number of genera is detected.[17] A microbial protein (von Willebrand factor type A) carrying the peptide Ro60 , is present in the commensal oral bacteria Capnocy to phagaochracea. It can activate T cells with a receptor for Ro60 (SSA) through dendritic cells. SSA autoantibodies might be produced when activated Ro60-reactive T cells activate B cells into plasma cells. If next-generation sequencing methods for analyzing OMB in patients with SS reveal an increased relative abundance of C. ochracea in the mouth, the microbiome–SS connection can be explained by molecular mimicry theory.[17]

Rheumatoid Arthritis (RA) is a chronic systemic disease of the synovium characterized by inflammation, hyperplasia and formation of autoantibodies, like the rheumatoid factor and anticitrullinated protein antibodies. This leads to symmetric polyarthritis and destruction of cartilage and bone. The OMB may trigger RA. There is evidence to suggest that periodontal pathogens Aggregatibacteractinomycetemcomitans and Porphyromonasgingivalis are autoimmunity triggers for RA. A. actinomycetemcomitans produces leukotoxin A, which forms pores on neutrophil membranes, producing neutrophil hypercitrullination, which leads to the release of citrullinatedautoantigens in gum. Research has also shown that 47% of patients with RA have had previous A. actinomycetemcomitans infection as compared with 11% in controls.[17]

Microbiome in other parts of body

Recently, scientists have found that autoantibodies formed against the cell wall mannan of the yeast Saccharomycecerevisiae , were detected in several autoimmune diseases with different manifestations, like RA, SLE and Anti-phospholipid syndrome. Anti-S. cerevisiae antibodies (ASCAs) are a serological marker of Crohn's disease (CD) in about 32% cases. Also, S. cerevisiae is used as adjuvant in vaccines. This has led to a hypothetical risk of developing abnormal immune activation after an autoimmune/inflammatory syndrome induced by adjuvants (ASIA).[18] Inflammatory bowel diseases (IBD) ,is an example of how alteration of gut microbiome can induce disease. Both CD and UC are associated with a reduced complexity of the commensal microbiota and shiftto a dysbiotic state. In a similar manner to that observed during acute mucosal infections, both CD and UC are characterized by the outgrowth of proteobacteria, in particular Enterobacteriaceaeand Fusobacteriaceae.[18] Moreover, adherent-invasive E. coli, Yersinia and Clostridium difficile are more common in patients affected by Crohn's disease than healthy individuals and, in mouse models, these bacteria have been shown to be contributors to IBD.

Enterococcusgallinarum, SLE and other autoimmune diseases

The events before establishment of infectious-related autoimmunity depend on microbiome changes of an individual with time. Enterococcus gallinarum, a Gram-positive gut pathobiontcan translocate, in gut barrier breakdown, into any systemic organ like liver and induce experimental autoimmune disease in genetically susceptible mice; namely, Systemic lupus erythematosus (SLE).[19] So Enterococcus gallinarum, present in the gut of lupus-prone (NZW x BXSB) F1 mice, has emerged as a candidate pathobiont for triggering SLE.[20] The same can happen in man and should be explored.In lupus patients, autoantibodies target many antigens, like double-stranded DNA (dsDNA), phospholipids, cardiolipin, and b, 2-glycoprotein. Genome-wide association studies have identified a definite genetic risk for SLE. However disease onset can occur in response to environmental insults of a biological, chemical, or physical nature.[21] In fact, E. gallinarum has also been isolated from stool samples and liver biopsies from patients having autoimmune hepatic disease and lupus patients with hepatic involvement.[20] SLE patients with Ribosomal P autoantibodies have higher anti-E. gallinarum IgGtitersthan healthy controls. In addition to anti-Ribosomal P antibody, higher anti-E. gallinarum titersare also significantly found to be associated with presence of anti-ds DNA and anti-Sm (anti- smooth muscle) autoantibodies.[20] Also, anti-E. faecalis IgGtiters are significantly higher in patients positive for antibodies to dsDNA, Sm, chromatin, and

RNP(Ribonucleoprotein) autoantigens.Growing usage of broad-spectrum antibiotics has increased prevalence of infections caused by E. gallinarum, slowly leading to multi-drug resistance and nosocomial infections of urinary tract, abdominal and biliary tracts.[19] Liver-resident E. gallinarum induces hepatic overexpression of ERV gp70 (Endogenous Retroviral Glycoprotein 70) that causesanti-ERV immune complex formation and systemic autoimmunity. This can also drive lupus kidney disease viaTLR-7.[22] E. gallinarum can induce expansion of plasmacytoid dendritic cells (pDCs) in lamina propria of small intestine of mice. These pDCs are potent producers of type I IFNs(Interferons), linked to SLE.[21] AlthoughE. gallinarum is a relatively minor component of the gut microbiome of lupus mice, it is prominent in internal organs, like liver. Hence, hepatocytes from lupus mice were co-cultured with E. gallinarum, E. fecalis, and B. thetaiotaomicron. Among these, E. gallinarum efficiently induces the transcription of IFNα and the lupus autoantigens b, 2-GPI and Erv gp70.[21] A specific antagonist blocking AhRsignaling reduces the levels of serum anti-dsDNA autoantibodies in E.-gallinarum-monocolonized mice, supporting the role of AhR-Th17 axis in inducing autoimmune inflammation.[21] Also, this autoimmune activity may be via the TLR 7 expression. SLE is found more in women (90%) then men, and the TLR7 locus is among X-linked genes that might promote disease in females. If further studies confirm a specific anti- E. gallinarum antibody signal in patients, this could be a very useful biomarker for SLE.[21]

Link of SLE with other gut bacteria and parasitic tissue infections

Infections caused by other pathogens, or the lack of them are associated with development of SLE . Epstein–Barr virus (EBV) and CMV, for example, have been linked with SLE by many reports.[23] Other studies have identified hepatitis B virus (HBV) as protective against SLE.[23] About 2.5% of SLE patients were found positive for presence of HBV-core antibody, compared to 10.7% from normal controls, which suggests a potential benefit of HBV infection. Helicobacter pylori seronegativitywas found to be associated with an increased risk and also earlier onset of SLE in African Americans, indicating a protective role of the bacterium.[23] Antibiotics, which can remove commensal gut bacteria can trigger lupus flares in humans. These include Trimethoprim–Sulfamethoxazole,Tetracycline derivatives and aminopenicillins.[23] Butyrate produced by Clostridium spp. can promote differentiation of regulatory T cells (Tregs) in colon, spleen, and lymph nodes to suppress inflammation. Also, removal of certain gut commensals with antibiotics can lead to decreased bacterial metabolites, such as homoserine lactone, N-acetylmuramic acid, and N-acetylglucosamine which are immunosuppressive, causing SLE progression. Dietary components influence SLE by changing composition and function of gut microbiota, immunomodulation, and by exerting epigenetic changes.[23] Lipopolysaccharide (LPS) is a Gram-negative cell wall component recognized by TLR4. In SLE, soluble CD14 (sCD14), released by monocytes in response to LPS, is increased in blood.[23] The level of sCD14 can be correlated with disease activity. Enhanced TLR4 signalling by LPS stimulation can induce SLE. LPS can do so by inducing neutrophil activation and migration, which promote development of SLE.[23] Inhibition of TLR4 reduces autoantibody production and diminishes glomerular IgG deposits in kidney in lupus-prone mice.

Lipoteichoic acid (LTA), an important component of Gram-positive bacterial wall, is also important in lupus pathogenesis. LTA is a ligand for TLR2, whose expression is increased in T cells, B cells, and monocytes in blood in SLE. Another bacterial antigen and component of bacterial biofilms, amyloid fiber (curli), is reported to induce autoantibody production in mice.[23] Amyloid fibers can tightly bind to extracellular DNA in bacterial biofilms. These Amyloid-DNA composites are strong stimulators of both innate and adaptive responses, and promote IL-6 and TNFα production and type I interferon response in mice models.[23] Injection of curli-DNA composites greatly increase autoantibody level in lupus-prone mice, and stimulate autoantibody production in wild-type mice.

Lactobacilli are known to be beneficial to the host when administered in adequate amounts. Health benefits provided by consumption of Lactobacilli are: prevention of constipation, hepatic disease, infections, allergies, and as recently suggested, inhibition of autoimmune diseases such as IBD and T1D.[23] Some Lactobacillus strains canmodulate host microbiota, inhibiting the formation of NETs (Neutrophil Extracellular Trap), improving antioxidant status, and increasing expression of genes that encode for junction and adhesion proteins. Thus some strains of Lactobacillus can be used for managing SLE.

Toxoplasma gondiiinfection may be beneficial for SLE. IFNγ and IL-10 expression are reduced

in the spleen of mice in the presence of T. gondii, suggesting the suppression of T helper 1 (Th1) and Th2 responses, respectively, both shown to be pathogenic for murine lupus.[23] Studies have found that female SLE patients have more active monocytes with enhanced TLR4 responsiveness than male patients, which can explain the gender preponderance of SLE.

Role of microbes in Multiple sclerosis

Multiple sclerosis (MS) is an autoimmune demyelinating disease, caused by a complex interaction of genetic and environmental factors. MS is the commonest cause of non-traumatic neurological disability in young adults.Numerous causative factors have been postulated, including exposure to several bacteria.[24] Mycobacterium spp., Chlamydia pneumoniae, Helicobacter pylori, and other bacteria are risk factors for MS with different mechanisms of action. Bacteria express specific pathogen-associated molecular patterns (PAMPs), which are recognized by cells of the innate immunity equipped with pattern-recognition receptors (PRRs). Human MyD88 is most important adaptor protein for inflammation used by all TLRs (except TLR 3). Helminth antigens modulate immune responses in B cells and dendritic cells isolated from parasite-infected MS patients by TLR2, through signalling pathways including MyD88-dependent pathway.[24]

Nod-like receptors (NLRs) are intracellular proteins that bind peptidoglycans of bacterial cell wall.[25] Nucleotide binding oligomerization domain (NOD)1 detects gram-negative bacteria like Chlamydia or Helicobacter pylori, whereas NOD2 is involved in recognizing mycobacteria.[25] NLR family members are positive and negative regulators of inflammatory responses; mutations in NLRP1 gene are linked to MS.[24] Microglia are resident macrophages of CNS that are the first line of defence in response to pathogens. Circumventricular organs are structures permitting substances like hormones to leave brain without disrupting BBB and allow microglia to sense signs of infection via TLRs, NLRs, and scavenger receptors.[26] Mycobacterium tuberculosis, Streptococcus pneumoniae, and others can penetrate BBB or the blood–CSF barrier and enter into CNS, and release toxic cell wall components. This promotes further production of inflammatory factors by activated microglia, with neurotoxic or neuroprotective functions, depending on stage of disease.[24] The microbiota has an important impact in bidirectional interactions between enteric nervous system and the CNS. Some commensal Clostridia stronglyinduceTregs and maintain gut homeostasis, whereas others contribute to Th17 cell expansion in MS.[24] Another interesting study revealed that CD4 T cells were responsible for IL 17A activation and demyelination in mice models of EAE or Experimental autoimmune encephalomyelitis. Treating the mice with Ampicillin ameliorated these symptoms.[27] This further substantiates microbial pathogenesis theory in MS.

Lactobacillus spp. in gut may worsen MS.Research suggests that antibiotic or probiotic strategies that are developed to help prevent or treat multiple sclerosis should consider host genetics, pre-existing gut microbiome, and the timing or mode of intervention. Scientists found that Lactobacillus reuteri, commonly used in probiotics, can increase disease severity in mouse model of MS, in genetically susceptibleanimals.[28] Hence both genetic makeup and gut microbiotaare important.

Psoriasis and autoimmunity

Psoriasis is a chronic proliferative autoimmune disease with about 0.3-4.8% prevalence. Its aetiology is still undetermined, but genetic and environmental factors are important.[29] One of the considered environmental factors is infestation with Malassezia yeast. Malassezia's role in psoriasis is still not determined, but itmay be related.[29] Malassezia yeasts induce Th1 and Th2 related cytokine, chemokine, and PGE2 production in PBMCs from patients with psoriasis and atopic dermatitis.Malassezia have role in pathogenesis of atopic dermatitis and psoriasis by inducing allergic and inflammatory reactions. In a study on psoriasis skin biopsies with positive and negative Malassezia, TGF1 up regulation, Integrin chain and HSP70 expression in keratinocytes due to Malassezia was proven. So Malasseziahelps in overproduction of molecules important in cell migration and hyperproliferation.[29] Malassezia also has a role in the psoriatic Koebner phenomenon by chemotaxis of PMNLs.M. furfur up-regulates TGF-β1, integrin chain, and HSP70 expression in keratinocytes. In biopsies of M. furfur-positive psoriasis-affected patients, an increase in TGF-beta1, integrin chains, and HSP70 expression was found.[30] M.furfur can exacerbatePsoriasis.[30] Malasseziaglobosais associated with exacerbation of scalp Psoriasis.[31] Chronic plaque psoriasis or psoriasis vulgaris is caused and aggravated by Malassezia. The association was first proposed in

1873. Narang et al., in 2007 also observed them in lesions and lesionsrespondedto fluconazole.

In psoriatic patients withscalp lesions, eyebrows, ears and seborrhoeic areas of trunk involvement, Malassezia has strong association.[32]

Vitiligo andautoimmunity

Vitiligo is anautoimmune disease characterized by hypo pigmentation of skin, and affects 0.5 to 1% people worldwide. There is loss of pigment resulting from the massive destruction of skin melanocytes. Patients exhibit progressive skin depigmentation after environmental triggers. Depigmentation is due to skin-infiltrating cytotoxic T cells,in genetically predisposed individuals, acting against melanosomal proteins.[33] Hereditary factors support autoimmune aetiology. In lesional skin, there is less diversity of skin microbiota and increase in Firm cutes. In non-lesional skin there is abundance of Actinobacteria.[34] Also, levels of serum metabolites like taurochenodeoxycholate and L-NG-monomethyl-arginine in vitiligo patients differ from healthy individuals and show significant correlations with microbial markers.

Gut dysbiosis influences systemic immunity and is implicated in autoimmune conditions. Microbial diversity helps maintain immune homeostasis, but individual species may be pathogenic, like Ro60-producing commensal bacteria in lupus.[33] Ampicillin can induce reactive oxygen species (ROS) formation in bacterial and human cells, affecting gut permeability. ROS formation is important in Vitiligo, where increased cytokine production correlates with increased ROS and reduced antioxidant levels.[33] Ampicillin use causes outgrowth of proinflammatory bacteria and provides antigens taken up by gut dendritic cells to activate T cells against melanocytes. Corynebacterium, Ruminococcus, Jeotgalibaca and Psychrobacter correlate with disease duration and serum IL-1β levels in vitiligo.[35] Vitiligo subjects harbour a skin microbiota that is unique. Notably, a previously uncultured Corynebacterium species appears moreinvitiligo than control subjects.[36]

Bacteria and antiphospholipid syndrome

Antiphospholipid syndrome (APS or APLA) is an immune disorder that increases risk of developing blood clots.[37] There are lung clots, strokes, heart attacks, and in pregnant women, miscarriages or still births in APS. It is an acquired autoimmune disorder that manifests clinically as recurrent venous or arterial thrombosis and/or fetal loss. Laboratory findings include persistently elevated levels of antibodies against membrane anionic phospholipids like anti-cardiolipin antibody, anti-phosphatidylserine or associated plasma proteins, like beta-2 glycoprotein I (β2GPI) or a circulating anticoagulant.[38] There is also a relationship between Roseburiaintestinalis, a commensal gut bacterium and APLA.[37] Roseburiaintestinalis triggers disease in genetically predisposed people. In them, T and B cells react to a blood protein involved in clotting, and similar amino acid antigens of the bacterium. Rose buriaintestinalis, an anaerobic Gram-positive bacterium common in gut of APS patients, has many homologous sequences to major B and T cell epitopes and stimulates lymphocytes. Over time, this ongoing "cross-reactive" response causes tissue damage and chronic disease. Other bacteria can also be implicated. Scientists showed that mice immunized with proteins from Haemophilusinfluenzae, Neisseriagonorrhoeae or tetanus toxoid develop antibodies that recognize Cardiolipin, β2GPI and the amino acid sequences contained in the proteins.

Systemic sclerosis(SSc)

SSc is a complex and heterogeneous disease, with clinical forms ranging from limited skin involvement (limited cutaneous systemic sclerosis) to diffused skin sclerosis and severe and often progressive internal organ involvement (like diffuse cutaneous systemic sclerosis). Moreover anti-nuclear antibody (ANA), anti-topoisomerase I (antiScl-70) antibody, anti-centromere antibody (ACA) and anti-RNA polymerase III antibody (anti-RNAPIII) are found in SSc.[38] SSc patients have decreased Faecalibacterium and Clostridium, and increased Fusobacterium and γ-Proteobacteria, as compared to healthy controls. SSc patients also have increased Bifidobacterium and Lactobacillus, which are typically decreased in inflammation. Patients with moderate to severe gastrointestinal symptoms have decreased B. fragilis and increased Fusobacterium compared with those with littlesymptoms. Dysbiosis (lower abundance of F. prausnitzii and Clostridiaceae and relatively high load of Lactobacillus) is pronounced in SSc with pulmonary fibrosis, oesophageal dysfunction and malnutrition. There is also abundance of Rhodotorulaglutinis in SSc. R. glutinis can activate immune system and lead to skin sclerosis.[39]

Microbes and Inflammatory bowel disease (IBD)

InIBD, anautoimmune disease where environmental triggers are important,there are dysregulated

immune responses against gut microbiota, leading to chronic gut inflammation. The major forms of IBD are ulcerative colitis (UC), limited to colon, and Crohn's disease (CD), which affects whole GI tract.[40] In IBD, there is reduction in potentially anti-inflammatory microbes like Bacteroidetes, Lachnospiraceae , and Faecalibacteriumprausnitzii alongside increases in inflammatory microbes (Proteobacteria and Ruminococcusgnavus). More mucosa-associated bacteria results in greater contact between gut microbes and immune system and leads to anti-bacterial immunity and IBD.[40] In IBD patients, specific bacteria, like the butyrate producers Faecalibacteriumprausnitzii and Roseburiahominis are decreased.[40]

In mice models, high fibre-rich diets or direct administration of SCFA are beneficial; loss of the SCFA receptor, Gpr43 is pathogenic. Tryptophan metabolites are ligands for the aryl hydrocarbon receptor (AhR), which activates IL-22 and IL-10 and is negatively associated with colitis.[40] A tryptophan-free diet exacerbates pathology. So, microbes can be used for treating IBD. Administration of probiotics has shown success in animal models and patients.[40] However, broad scale benefits are yet to be found.

Crohn's disease affects approximately 1.4 million North American people. Due to the similarities between Crohn's disease and Johne's disease, a chronic enteritis in ruminants caused by Mycobacterium aviumparatuberculosis (MAP), MAP can cause of Crohn's disease.[41] MAP is included in the Mycobacterium avium complex (MAC) along with M. avium and M. intracelluare. Like other mycobacteria, it contains a thick and hydrophobic cell wall that resists decolourization with acid- alcohol, leading cells to be acid fast.[41] The bovine immune response to subclinical MAP infection starts with a Th1 type, or cell mediated response against the infected macrophages. The major source of MAP in the environment is by shedding of MAP in the faeces of infected ruminants. MAP along with faeces is deposited onto pastures where runoff can contaminate ground or surface water.[42]

Secondarily infected animals include rabbits and wild deer, which also shed MAP into environment via faeces. MAP cannot replicate outside host cells. However, it survives in environment for 12 weeks to 1 year. MAP is hence also present in the human food supply, in dairy and meat products.[43] The thick lipid cell wall allows it to survive pasteurization; live MAP has been found in retail milk and cheese products.[41] Crohn's disease has symptoms like abdominal pain, diarrhoea, bleeding, bowel obstruction, as well as systemic symptoms. CD has an estimated annual healthcare cost of over 1.7 billion USD. Common clinical features between Johne's and Crohn's disease are intermittent diarrhoea, weight loss, primary site like the ileocecal area, mucosal ulcerations, and granulomas. So MAP can be the etiological agent of Crohn's disease.[41] The first report of a possible link between MAP and CD was made even before original descriptions by Crohn.[44] In 1913, T.K.Dalziel noticed that clinical and gross appearances in CD were very similar to those in cattle with Johne'sdisease. However not everyone with MAP develop CD.

Most calves exposed to MAP become subclinically infected and approximately 10% develop Johne's disease. Approximately 1/3rd of the world population is infected with Mycobacterium tuberculosis, but clinical disease occurs in 5–10% infected people.[41] A genetic association with CD was identified in the Nucleotide-binding Oligomerization Domain-containing protein2, or NOD2 encoded by the CARD15 gene. This protein functions as an intracellular pattern recognition receptor for Mycobacteriaceae. NOD2 activates NFkBsignalling following binding to microbial peptidoglycans. NOD2 mutations confer susceptibility to Crohn's disease by altering the receptors' recognition of pathogens or the downstream activation of NFkB in monocytes. The SLC11A1 (Solute carrier 11A1), formerly NRAMP (natural resistance-associated macrophage protein 1), is an ion transporter across phagosomal membranes and induces microbicidal functions in macrophages.[41] It plays a role in innate immune response to mycobacterial infections. Polymorphisms at locus 823 C/T are strongly associated with CD. Autophagy is an important component in innate immunity and contributes to clearance of intracellular microbes. The genes ATG16L1 and IRGM encode proteins involved in autophagy show a strong association with CD susceptibility.

Can microbes or microbial modulation cure autoimmune diseases?

Reports about faecal matter transplants (FMTs) or probiotic pills have given some hope that there can be an easy way to prevent or treat autoimmune diseases. For MS, treatment is a targeted dietary intervention that shifts the community from pro-inflammatory bacteria to anti-inflammatory type.[45] Scientists hope that better knowledge about gut microbiome during first 3 years of life, will lead to disease-preventing interventions. Those might

include giving babies well-defined compositions of microbes, so that a child's immune system develops optimal tolerance to self without sacrificing ability to fight infection. That is the kind of therapy that can have global impact because bugs or microbes are cheap.

Modulation of microbiota can help treat autoimmune diseases. Such approaches include prebiotic diets, antimicrobial interventions, faecal microbiota transplants, and selective probiotics. One new approach is the use of selective bacterial candidates to modulate the microbial composition. Use of single microbe for treatment is advantageous as microbes grow at different speeds and if needed, a single microbe is easy to target.[46]

Fungi in autoimmune diseases

Fungi do mediate immune disorders.Fungi contribute to auto-reactivity against self-antigens due to shared epitopes between fungal and human proteins like manganese superoxide dismutase ,thioredoxin, cyclophins and acid ribosomal proteins. The mechanism is thought to be molecular mimicry maintaining severe chronic allergic diseases such as atopic dermatitis.[47]

Currently, the evidence for fungal exposure being linked to the induction of autoimmune diseases is controversial. Studies suggest that fungal proteins have a role to play in autoimmune diseases. However, further studies are needed to establish the role of fungi in the immunopathology of autoimmune diseases.[47]

The involvement of microbial triggers in IBD, including Crohn's disease (CD), is increasingly evident with metagenomic sequencing that have identified dysbiosis in CD compared with healthy subjects. The vast majority of CD microbiome research has focused on complex bacterial communities and microbiome dysbiosis in the gut with 16S metagenomic sequencing. However, emerging data suggest fungal opportunistic pathogens are also associated with IBD pathogenesis and chronicity. CD patient populations display elevated antibodies against fungal targets, even before disease diagnosis.[48]

Parasites and autoimmunity: Chagas' disease (CD)

Chagas' disease is caused by Trypanosomacruzi, with reduviid bug as vector. That Chagas' disease has an autoimmune component, was based on finding of circulating antibodies against heart tissue antigens in patients and mice chronically infected with Trypanosoma cruzi. Later, T lymphocytes reactive with heart or nerve tissue antigens were found in chagasic mice and patients, extending the concept to include cell-mediated immunity.[49] Initial studies have showed presence of serum antibodies reactive to endocardial, vascular, and interstitial (EVI) antigens in a large proportion of chagasic patients. These antibodies can be removed by absorption with T. cruzi epimastigotes (suggesting cross-reactivity of some T. cruzi antigens with EVI antigens) and are absent in sera from normal individuals or patients with nonchagasic cardiovascular diseases. A later report described the presence of antibodies against Schwann sheaths of myelinated somatic and unmyelinated autonomic peripheral nerves in sera of patients with acute CD (aCD) and also chronic Chagas' heart disease (cCHD).

The anti-EVI antibodies were also present in sera from patients with malaria and VL , cross-reacted with Trypanosomarhodesiense antigens, and could bind a carbohydrate epitope expressed by cells from various species as well as several other heterologous antigens. Scientists identified a 160-kDa T. cruzi surface protein on flagellum, which they termed Fl-160. Normal mouse sera do not recognize the Fl-160 fusion protein.[50] Mouse anti-Fl-160 antibodies cross-react with a 48-kDa protein of axonal and myenteric plexus cells. Immunofluorescence studies reveal that Fl-160 is localized on flagellum of T. cruzi trypomastigotes. The antibodies cross-react with lysates of nerve and brain tissue but not from cardiac, skeletal muscle, liver, or kidney tissue. Also the finding that 44% of tested chagasic sera display reactivity with Fl-160 indicates that the anti-Fl-160 antibodies are involved in nerve damage, seen occasionally in patients with CD.[49] Peoplehave reported anti-heart and anti-skeletal muscle reactivity and anti-skeletal muscle glycolipid antibodies in CD.[51] Immunofluorescence studies showed positive staining by chagasic sera, which also has higher anti-glycolipid antibody titres than control sera. Also, the antibody titres were higher in patients with cCHD than in those with aCD.[51]

Viruses and autoimmunity

CMV or HCMV or Human Cytomegalovirus, can be important in precipitating GBS and MS. It can also initiate mononucleosis in adults. In autoimmune diseases with high levels of inflammation and chronic immune stimulation, such as RA, a causative role of HCMV has been hypothesized. After specific HCMVpp65 antigen-mediated long-term stimulation, increased anti-HCMV IgG antibodies and intracellular IFN-γ-

producing HCMVpp65-specific CD28-CD8+ T-cells are observed in RA and juvenile arthritis (JIA). This indicates a possible enhancement of inflammatory response following endogenous HCMV reactivation.[52] HCMV can induce or perpetuate autoimmunity through different ways like: (1) antigen-specific (like molecular mimicry) and (2) non antigen-specific (or bystander activation). From an immunopathological viewpoint, HCMV can trigger or sustain autoimmunity via the following 3 mechanisms: (i) autoantibody production, (ii) enhanced inflammation, and (iii) vascular damage.[52]

In systemic sclerosis also, HCMV issignificant. In recent years, workers have studied the interplay between HCMV and immunity in SSc and inflammation. In HCMV-infected human dermal fibroblasts, researchers found increased HCMV-specific CD8+ T-cell responses associated with disease development, and also enhanced expression of fibrosis and apoptosis-associated factors that are important in SSc.[52]

Discussion

Hence now it can be summarized that many different microorganisms can initiate and precipitate many autoimmune diseases by many mechanisms. Bacteria, fungi, viruses, parasites all can be responsible for these disorders. Diseases like Diabetes mellitus, Psoriasis, Systemic Lupus Erythematosus and Multiple sclerosis can all have possible or established microbial link. These things should be researchedmore. If microbial aetiologiesand link behind these autoimmune diseases are more and more explored, new strategies can be formulated to target these microbes flaring up autoimmunity.

A complex interplay of hosts genotype, host microbiota, environment, diet and microbial aetiology can help in developing myriad autoimmune diseases. Thus new avenues for therapy of debilitating autoimmune diseases might emerge. This could well be the topic of research of the future and can bridge the gap between understanding of communicable and non-communicable diseases also. Microbiologists and immunologists can work in tandem for more research in this very interesting field.

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Subject Index

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[1] Flink H, Tegelberg Å, Thörn M, Lagerlöf F. Effect of oral iron supplementation on unstimulated salivary flow rate: A randomized, double-blind, placebo-controlled trial. J Oral Pathol Med 2006; 35: 540-7.

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Article in supplement or special issue

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Corporate (collective) author

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Reference from electronic media

[9] National Statistics Online—Trends in suicide by method in England and Wales, 1979-2001. www.statistics.gov.uk/downloads/theme_health/HSQ 20.pdf (accessed Jan 24, 2005): 7-18. Only verified references against the original documents should be cited. Authors are responsible for the accuracy and completeness of their references and for correct text citation. The number of reference should be kept limited to 20 in case of major communications and 10 for short communications.

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