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Volume 6 Number 1, January-June 2024

Role of Silver Alginate Dressings on Split Skin Graft Site to Prevent Post-operative Infection

Geetankshi Gopal Ghabru[1], Ravi Kumar Chittoria[2], Amrutha J S[3]

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Abstract

Burn injuries can be devastating, not only causing physical pain and trauma but also increasing the risk of infections, which can further complicate the healing process. Therefore, finding effective methods to prevent postoperative infections is crucial for the successful treatment of burn patients. In this study we consider the effectiveness of silver containing alginate dressings for deep partial thickness burns in a patient with accidental thermal burns. Silver alginate dressings consist of a combination of silver and sodium alginate, a natural polysaccharide derived from seaweed. The silver in it has antimicrobial properties, making it an ideal choice for preventing infection. The dressings are available in various forms, such as sheets, dressings, and ropes, allowing for versatile usage in wound care management. They are able to maintain a moist environment as well as prevents wound infection. They are found to be useful in various conditions including burn wound, skin graft donor site and other conditions like pressure injuries. Silver alginate dressings are highly effective in managing burn wounds due to their unique combination of antimicrobial and wound-healing properties. The alginate interacts with wound exudate to form a gel, maintaining a moist wound environment that promotes tissue regeneration, while the silver provides broad-spectrum antimicrobial action, preventing infections caused by bacteria, fungi, and even antibiotic-resistant pathogens like MRSA. In burn care, silver alginate dressings are particularly beneficial for partial-thickness burns (second-degree burns) and donor sites after skin grafting. They are highly absorbent, making them suitable for burns with moderate to heavy exudate, while reducing the risk of maceration in surrounding skin. The gel formation also minimizes pain during dressing changes, as it prevents adhesion to the wound bed.

Keywords: Silver; Alginates; SSG site; Donor site; Post-op infection.

Author Affiliation: [1]Junior Resident, Department of Plastic Surgery, [2]Professor and Associate Dean (Academic), Head of IT Wing and Telemedicine, Department of Plastic Surgery & Telemedicine, [3]Senior Resident, Department of Plastic Surgery, Jawaharlal Institute of Postgraduate Medical Education and Research, Pondicherry 605006, India.

Correspondence Author: Ravi Kumar Chittoria, Professor and Associate Dean (Academic), Head of IT Wing and Telemedicine, Department of Plastic Surgery & Telemedicine, Jawaharlal Institute of Postgraduate Medical Education and Research, Pondicherry 605006, India.

E-mail: drchittoria@yahoo.com

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INTRODUCTION

Burn injuries are among the most devastating and traumatic experiences individuals can endure. Once the initial trauma is over, patients are faced with the challenge of healing their wounds and preventing post-op infections. One effective solution that has emerged is the use of silver alginate dressings in the site of split-thickness skin graft (SSG) and donor site. Silver alginate dressings have been gaining attention in recent years due to their potential role in preventing postoperative infections and improving outcomes in burn patients.[1]

Silver alginate dressings consist of a combination of silver and sodium alginate, a natural polysaccharide derived from seaweed. The silver component possesses antimicrobial properties, making it an ideal choice for preventing infection. The dressings are available in various forms, such as sheets, dressings, and ropes, allowing for versatile usage in wound care management.

MATERIALS AND METHODS

This study was conducted in a Tertiary Care Centre in the Department of Plastic Surgery after getting the departmental ethical committee approval. Informed consent was obtained. The subject was a 67-year-old female who suffered an accidental burn injury and developed 35 percent deep partial-thickness burn wounds (fig. 1). She was admitted to the JIPMER Tertiary Burn Centre and was hemodynamically stabilized for the first 4 days. She underwent dermabrasion-assisted tangential excision using Manekshaw's dermabrader and split skin grafting (fig. 2). The grafted (fig. 3) and the donor site (fig. 4) were then covered with silver alginate dressing. Dressing changed on postoperative day 5 (fig. 5)

RESULTS

The wound bed preparation of large burn wound area was done using blunt dermabrasion. She further underwent dressing with silver alginate dressings. This reduced the biofilm burden and hastened the process of wound healing. She underwent multiple sessions of regenerative therapy. The wound granulated well and patient has no evidence of post infection.

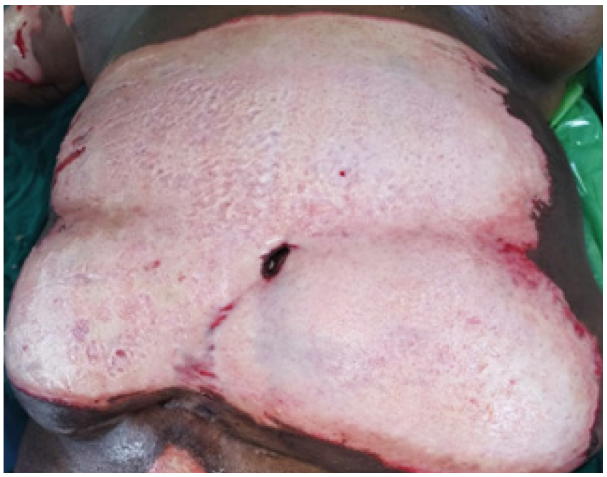

Fig. 1: Partial thickness burn wound

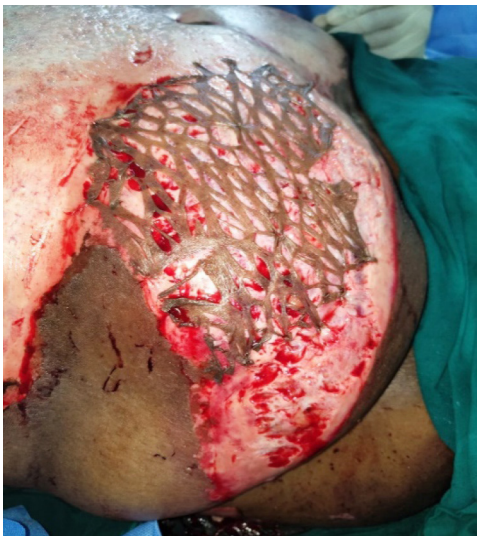

Fig. 2: skin graft site

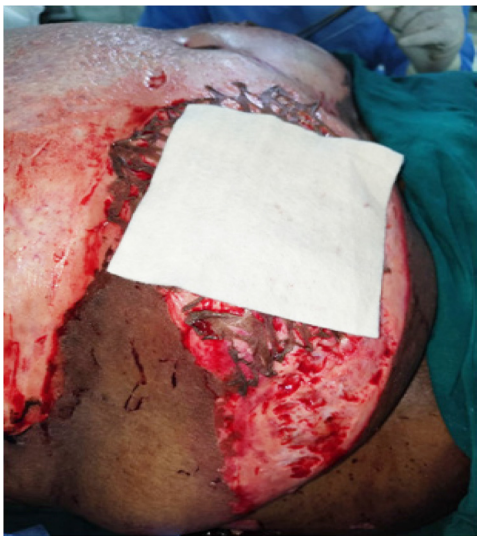

Fig. 3: Silver alginate dressing at Split Skin Graft site

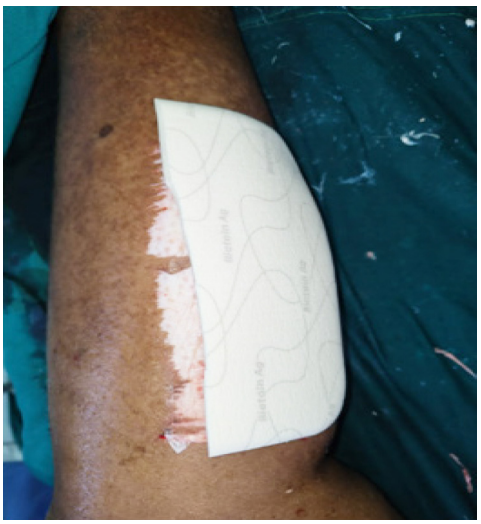

Fig. 4: Silver alginate dressing at donor Site

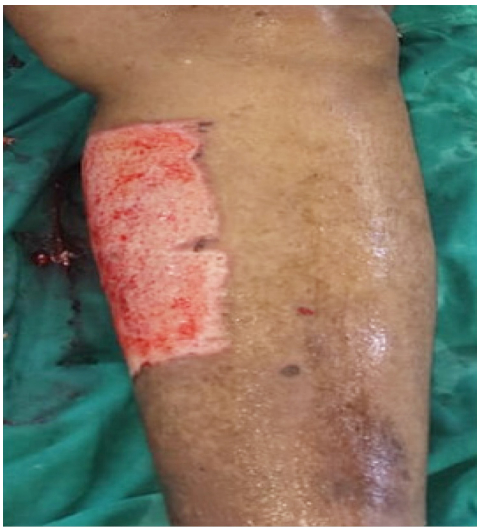

Fig. 5: Donor site after 5 days

DISCUSSION

Wound healing is a complex phenomenon that is divided conventionally into four phases- hemostasis phase, inflammatory phase, proliferative phase, and phase of maturation. Each phase overlaps with the other. Soon after the injury, the hemostasis phase begins leading to the formation of the platelet plug. Activation of platelets and the complement system leads to release of several growth factors that activate the inflammatory phase. Recruitment of leucocytes, initially neutrophil followed by lymphocytes and macrophages, is the hallmark of this phase.[2] Macrophages release several growth factors like- platelet-derived growth factor (PDGF), transforming growth factor (TGF-beta and TGF-alpha), basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF)[3] These growth factors are responsible for the proliferation, angiogenesis, deposition of collagen, and extracellular matrix (ECM) and the maturation phase. Non-healing wound is caused by an imbalance of growth factors so that these phases do not occur in a timely fashion or their progression is stopped at a different level.

Silver alginate dressings are a type of wound dressing made from natural fibers derived from brown seaweed. They have unique properties that make them highly effective in preventing infections. The addition of silver to the dressings has been found to enhance their antimicrobial properties, making them an ideal choice for wound care in burn patients.

One of the key benefits of silver alginate dressings is their ability to create a moist environment at the site of the surgical site graft (SSG)[4] or donor site.[5] This moisture aids in the healing process by promoting the growth of new tissue and preventing the wound from drying out. Dry wounds are more prone to infections[6] and can slow down the healing process. By maintaining an optimal level of moisture, silver alginate dressings create an environment that is conducive to healing.[7]

In addition to the moisture-retaining properties, silver alginate dressings also possess excellent antimicrobial activity. Silver ions released from the dressings have the ability to kill a wide range of microorganismvs, including bacteria, fungi, and even some antibiotic-resistant strains. This antimicrobial activity helps to reduce the risk of infection at the SSG or donor site.

Postoperative infections at the SSG or donor site can have serious consequences for burn patients. These infections can lead to delayed wound healing, increased scarring, and even systemic infections that can be life-threatening. By using silver alginate dressings, healthcare providers can take a proactive approach to prevent such infections and improve patient outcomes.

Another advantage of silver alginate dressings is their versatility. They can be used on both partial-thickness and full-thickness burns, making them suitable for a wide range of burn injuries. The dressings can conform to the shape of the wound, ensuring a snug fit that provides continuous protection. This adaptability makes them a practical choice for wound care in burn patients.

It is worth noting that although silver alginate dressings have shown promising results in preventing postoperative infections, they should not be seen as a standalone treatment. Proper wound care, including cleansing and regular dressing changes, is essential for optimal healing. Additionally, healthcare providers should closely monitor the wound for signs of infection, such as increased redness, swelling, or drainage.

CONCLUSION

There are multiple modalities in wound bed preparation that include debridement, Autologous Platelet Rich Plasma, Amniotic membrane grafting, Regulated Oxygen Enriched Negative Pressure Wound Therapy, regenerative grafting and biological scaffolding. Each modality contributes in some way to make the wound fit for grafting and ultimately speeds up wound healing and patient discharge timing.

Silver alginate dressings have antimicrobial properties, and help in maintain a moist environment, and its non-adherent nature make it an optimal choice for wound care management. Silver alginate dressings reduce the risk of infection, promote faster healing, and improve patient outcomes. As the field of wound care continues to evolve, silver alginate dressings stand as an essential tool in the fight against post-op infections in burn patients

Conflict of Interest: None declared.

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Role of Dried Allogenic Amniotic Membrane in Second degree Scald Burns

Naveen Kumar[1], Ravi Kumar Chittoria[2], Bharath Prakash Reddy J[3]

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Abstract

Burns are one of the most common injuries, which could be due to thermal, scald, electrical burn injuries. Scald injuries tend to be the most common type of burn injury under the age of five, accounting for over 65% of the cases. In current scenario, various scaffolds are used to improve the quality of healing process and reduce the scar formation. Collagen acts as a scaffold through which regeneration of tissues occurs and also helps in new vessel formation. Other scaffolds like amniotic membrane helps in proper epithelization and reduces scarring. It also has unique antiinflammatory, bacteriostatic property. In this study we used amniotic membrane heterograft as a biological dressing in a patient with second degree scald burn wounds.

Keywords: Amniotic membrane; regenerative; second degree scald burns.

INTRODUCTION

Wound healing is a physiological response of a living being to physical, chemical, mechanical or thermal injury. The wound healing process consists of several phases: homeostasis, inflammation, proliferation/granulation, and remodeling/maturation. Still, when the healing course deviates from the normal path, the healing does not advance past the inflammatory phase. In case of burns, there will be deficiency in normal healing. In modern medicine, usage of scaffolds either natural or synthetic has become popular and been recognized.

An ideal scaffold should consist of these key features: fitting physical, mechanical properties, physiological background to enable cell adhesion, proliferation and differentiation, a high porosity, a large surface area to volume ratio and to be flexible enough to accommodate the shape of the wound and preferably biocompatible and biodegradable.

Collagen, synthetic or natural acts as an substitute for the dermal matrix through which epithelialization occur.[1] In the process of wound healing, degradation of collagen aids in the formation of new vessels, thereby it also helps in angiogenesis.

Author Affiliation: [1]Junior Resident, Department of Orthopedic Surgery, [2]Professor and Associate Dean (Academic), Head of IT Wing and Telemedicine, Department of Plastic Surgery & Telemedicine, [3]Senior Resident, Department of Plastic Surgery, Jawaharlal Institute of Postgraduate Medical Education and Research, Pondicherry 605006, India.

Correspondence Author: Ravi Kumar Chittoria, Professor and Associate Dean (Academic), Head of IT Wing and Telemedicine, Department of Plastic Surgery & Telemedicine, Jawaharlal Institute of Postgraduate Medical Education and Research, Pondicherry 605006, India.

E-mail: drchittoria@yahoo.com

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Amniotic membrane which is a natural scaffold has its own properties which includes its anti inflammatory, bacteriostatic, anti fibrotic, anti scarring and promotion of epithelization as well.[2] Since it has low immunogenicity and has its own progenitor cells, it can be an ideal choice in terms of usage of scaffolds for healing of wounds.

Silicon acts as a barrier by reducing mechanical friction and transepidermal water loss which have been shown to be associated with the severity of a subsequent infection.[3] In vitro study shows silicone may regulate the inflammatory growth factors that cause fibrosis and promote acute wound healing. Important elements in this process include inflammatory markers such as TNF-α, TGF-β, IL-1, and IL-6 that are also implicated in acute inflammation.

MATERIALS AND METHODS

This study was conducted in Tertiary Care Centre in Department of Plastic Surgery after getting the department ethical committee approval. Informed consent was obtained. The subject was a 49-years-old male who had accidental second degree scald burn injury which involves over chest, abdomen, and right hand region. He didn't show in any hospital after that and next day came to JIPMER. Delay of 12 hrs. He was admitted in tertiary burn care unit and initial resuscitation with intravenous fluids, analgesics and prophylactic antibiotics started. On the day of admission patient underwent Regenerative scaffold + RONPWT under topical heparin irrigation. On postburn day 3, the three layered scaffold dressing was made and applied over deeper burn areas after dermabrasion assisted tangential excision. The three layers of scaffold were made bysterile amniotic membrane, dry collagen sheet and silicone sheet. The layer of amniotic membrane was in direct contact with the wound. Amniotic membrane was harvested from freshly delivered placenta. It is thoroughly washed and stored in antibiotic solution in refrigerator. The dressing was kept intact for 7 days. On the 7th postoperative day, the amniotic membrane was completely resorbed and the silicon sheet layer was also removed.

RESULTS

Intraoperative and post-operative periods were uneventful for the patient. On post operative day 7, dressing was opened and it showed significant areas of re-epithelialization and healing. All second degree superficial burn wound healed completely (Fig. 4). No complications and side effects were noted during entire procedure.

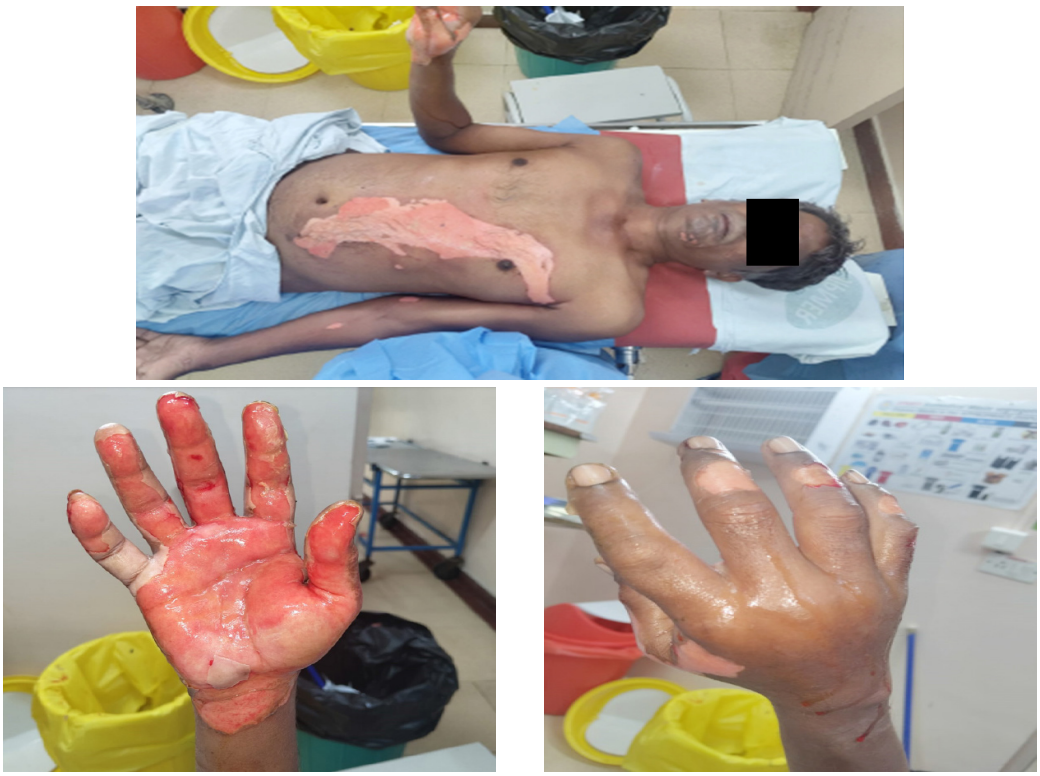
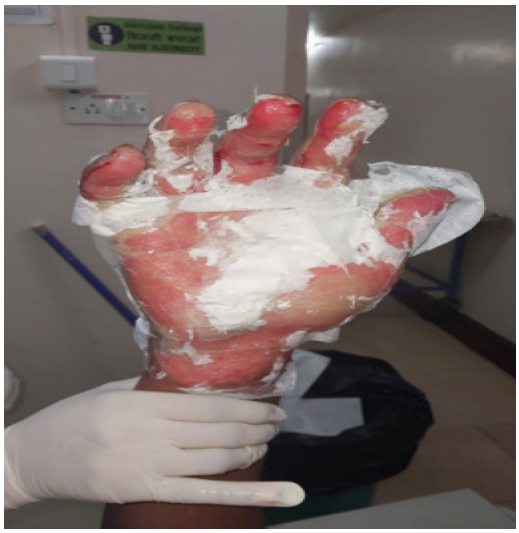


Fig. 1: On Admission



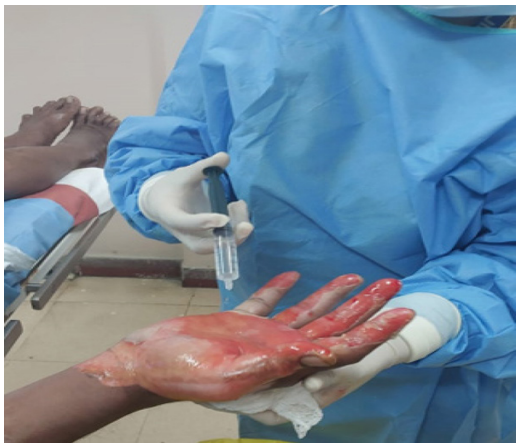
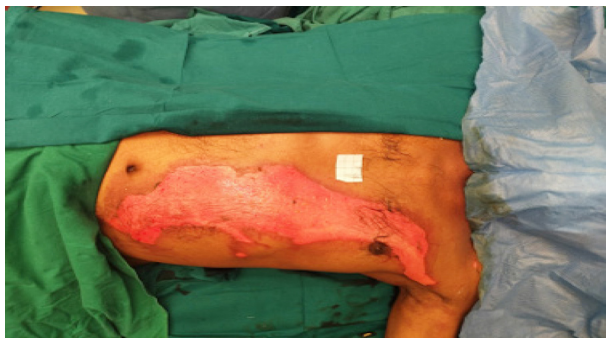


Fig. 2: Application of collagen and heparin saline irrigation



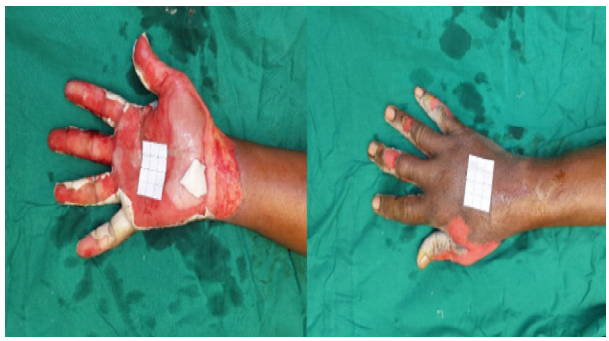


Fig. 3: Digital planimetry of raw area

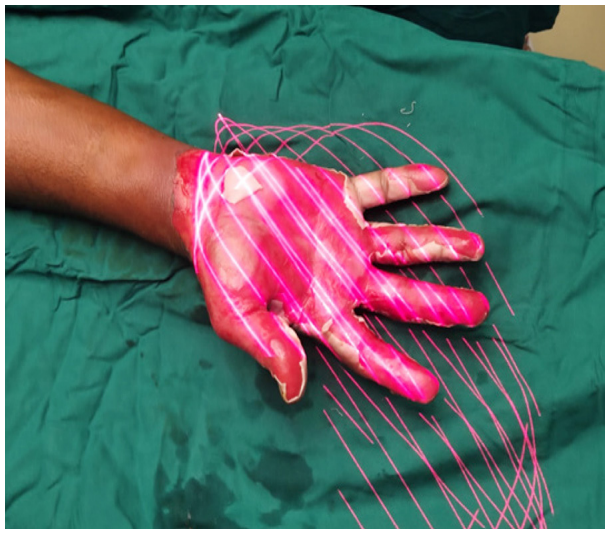


Fig. 4: Low level laser therapy of wound

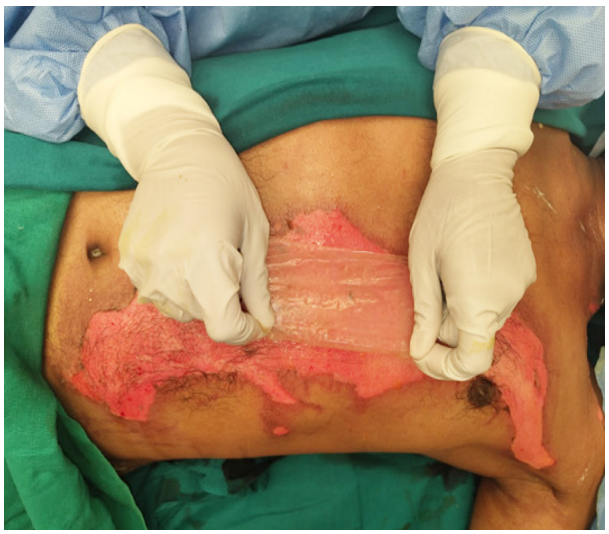
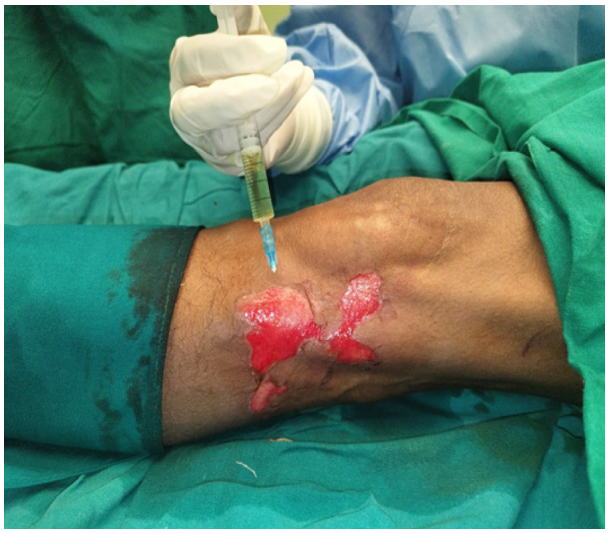


Fig. 5: Dried amniotic membrane over raw area



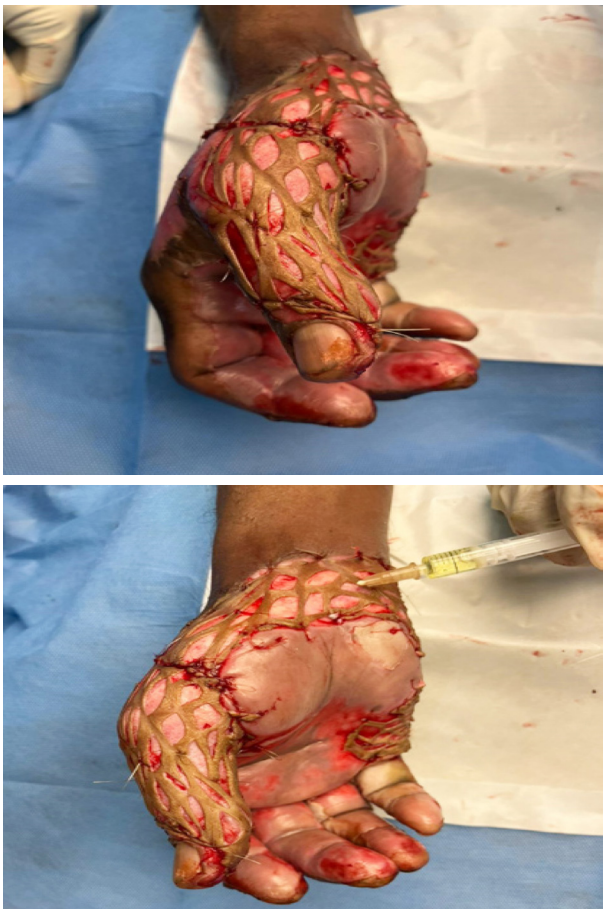


Fig. 7: Split skin grafting for hand

Fig. 8: Autologous platelet rich plasma therapy

DISCUSSION

Partial-thickness burn wounds can heal spontaneously, whereas full-thickness burn wounds require skin grafting for definitive wound closure. Historically, the gold standard for closure of excised full-thickness burn wounds is split-thickness skin autograft. Patients with very large burn wounds have limited donor sites for harvesting of autograft and may benefit from the use of skin substitutes. Engineered skin substitutes that may provide temporary wound coverage until donor sites are ready to be reharvested for autograft, or if they contain autologous cells, may provide permanent wound closure. Relatively few permanent skin substitutes are currently available, but developments in tissue engineering of human skin are expected to soon provide improved models for increased availability and enhanced healing of burn wounds.[4] Commercially available Dermal Regeneration Template is a two-layered skin regeneration system.[5] The outer layer of this system is made of thin silicone film act as the epidermis of skin. This layer helps in protecting wound from infection and controls in loss of both heat and moisture. The outer collagen glycosaminoglycan (GAG) thermal layer functions as a biodegradable template that helps in regeneration of dermal tissue neodermis by the body. The inner layer of dermal regeneration template is made of complex matrix of cross-linked fibers. The porous material of the template helps in regeneration of skin. The cross-linked fiber material of dermal regeneration template acts a scaffold for the regrowth of skin layer. Once the dermal skin layer is regenerated, the outer layer of template is removed and is replaced with a thin epidermal skin graft. This procedure leaves the wound to a flexible, growing and allows permanent regeneration of skin. It allows faster healing of wound with minimum scarring. Here we have tried to replicate the same mechanism in our indigenously made dermal regeneration scaffold. The indigenous dermal regeneration scaffold prepared from silicone sheet, dry collagen sheets and amnion is cost-effective and can be easily prepared and used on wounds. Thus, it can be used in hospital settings in developing countries where the affordability of commercial regeneration template is doubtful.

CONCLUSION

The adoption of this cost effective amniotic membrane based regenerative scaffold dressing

in second degree scald burns has been proven effective in this study. It hastens the overall healing time of second degree superficial and deep wound to within a week. Thus minimizing the total hospital stay and infection rates. However a large multicentric, double-blinded control research with statistical analysis is needed.

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Extraintestinal infections by *Escherichia coli*

Mohana Chakraborty[1], Sayan Bhattacharyya[2]

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Abstract

Extra intestinal Pathogenic *Escherichia coli* (ExPEC) is a leading cause of invasive infections. These include entities like bacteremia, respiratory tract infections, meningitis and sepsis among others. Invasive ExPEC infection complicates the clinical treatment of other conditions. It is also associated with increased mortality, duration of hospital stay, and worse clinical outcomes. Older adults having comorbidities are at highest risk of acquiring these infections. ExPEC is of particular interest in the Asia-Pacific region, due to aging populations and increasing antimicrobial resistance.

Keywords: ExPEC; Bacteremia; UTI.

INTRODUCTION

Escherichia coli are a Gram negative aerobic-to facultatively anaerobic bactwrium which is known to cause diarrhoea and dysentery commonly. It sometimes constitutes the normal resident or commensal flora of the gut in humans and other warm-blooded animals. The genus *Escherichia* was described first by the German microbiologist Theodore Escherich. Though commonly associated with gut infections; it may also be implicated in extra intestinal infections. In fact, it is a major contributor of Urinary tract infections in man. These strains are hence also termed extraintestinal pathogenic *Escherichia coli*. Extraintestinal pathogenic *Escherichia coli* (ExPEC) is the commonest Gram negative bacterial pathogen seen in humans. In fact, ExPEC causes the vast majority of urinary tract infections (UTIs), and also bacteremia in adults. It is also the second most common bacterial etiological agent of neonatal meningitis.[1]

The full list of extraintestinal infections where *Escherichia coli* is incriminated is as follows:

a. **Urinary tract infection:** *E. coli*causes a major chunk of both community-acquired and catheter associated UTI. In fact, it alone can lead to 50-70% cases of UTI in adults. Such isolates of *E. coli* are termed UPEC or Uropathogenic *E. coli*. Midstream urine specimen is generally needed for diagnosis of UTI by microscopy and culture. Several

Author Affiliation: [1]Consultant Microbiologist and Infection Control Officer, Department of Microbiology, Institute of Neurosciences, Kolkata 700017, West Bengal, [2]Associate Professor, Department of Microbiology, All India Institute of Hygiene & Public Health, Kolkata 700106, West Bengal, India.

Correspondence Author: Sayan Bhattacharyya, Associate Professor, Department of Microbiology, All India Institute of Hygiene & Public Health, Kolkata 700106, West Bengal, India.

E-mail: drsayanb@aiihph.gov.in

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virulence factors are also attributed behind causation of UTI by *E. coli*, like fimbriae, adhesins, capsule, mannose-sensitive hemaggulitinin and hemolysin. Some other virulence factors also reported commonly, are polysaccharide capsules, outer-membrane vesicles, flagella, curli, non-fimbrialadhesins, outer-membrane proteins (or OMPs) and iron-acquisition receptors. There is an overall preponderance of phylogenetic group B2 of *E. coli* among strains that cause UTI.[2] UTI is found more commonly in adult females as compared to adult males, due to factors like shorter length of perineum in females. Rising prevalence of strains that are resistant to first-line oral antimicrobial agents like trimethoprim-sulfamethoxazole, ampicillin, and fluoroquinolones are found globally among the uropathogenic *E. coli* isolates.[1]

b. ***Bacteremia:*** *E. coli* is also a leading cause of bacteremiain both adults and neonates. The most common source of suchbacteremia in adults is the urinary tract. About 2% and 6% of male patients who undergo transrectal prostate biopsy may later develop infectious complications, includin gbacteremia.[1] The overall annual incidence of *E. coli* bacteremia in adults hovers between 30 and 50 cases per 100000 populations. However, this figure increases markedly with age.

c. **Neonatal meningitis:** *E. coli* is one of the most important etiological agents causing meningitis is neonates (neonates are newborn babies less than 28 days of age), along with other bacteria like *Klebsiella pneumoniae*. It usually follows bacteremia due to *E. coli*. Neonatal meningitis is frequently caused by *Escherichia coli* and also others like group B streptococci.[3] NMEC (Neonatal meningitis associated *E. coli*) strains appear to mimicfecal commensal strains in terms of phylotype and serotype, butstill contain the RS218 plasmid. The latter harbours many sequences similar to those seen in UPEC. These isolates also frequently have the K1 capsule, which is a marker for neuroinvasiveness.[4]

d. **Liver abscess:** *Escherichia coli* have also been held responsible for the causation of pyogenic and pyaemic liver abscess. It reaches liver via portal vein and then causes multifocal abscesses there. Other bacteria may also cause liver abscess, like *Klebsiella pneumoniae* and *Enterococcus* spp. *E. coli* liver abscess reportedly has a relatively higher mortality rate. It is associated with preexisting factors like underlying malignancies, multiple abscesses and pronounced hypoproteinemia.[5] Biliary tract disease is now recognized as the commonest source of pyogenic liver abscess (PLA). Obstruction of bile flow aids in bacterial proliferation. Biliary stone disease, obstructive malignancies affecting the biliary tree, stricture, and also congenital diseases can be common triggering factors behind pyogenic liver abscess.[6]

e. **Epididymorchitis:** Gram negative bacterial flora of gut, like *Escherichia coli* are responsible for a large share of cases of epididymorchitis.[7]

f. **Superficial abscesses like ischiorectal and perianal abscesses:** *Escherichiacoli* is the predominant pathogen isolated from perianal abscesses in patients without DM (Diabetes mellitus). *Klebsiellapneumoniae*, however, has been the predominant microorganism in is chiorectal and all other abscesses in DM patients.[8] Other aerobic and anaerobic microorganisms are also responsible for these abscesses, like *Bacteroides fragilis, Peptostreptococcus,Prevotella*spp., *Fusobacterium, Porphyromonas, Clostridium* spp., *Staphylococcus aureus* and *Streptococcus* spp.[9]

g. **Community acquired pneumonia:** *Escherichia coli* community acquired pneumonia (CAP) is an under recognized entity which is associated with higher mortality when compared to other well studied causes of pneumonia. *E. coli* pneumonia is also frequently associated with bacteremia. Despite the absence of abdominal or urinary symptoms, the infection may originate from an occult gastrointestinal (GI) source, since *E. coli* is a common commensal resident of the GI tract. Conditions related to extra intestinal pathogenic *E. coli* (ExPEC) are garnering attention. There has also been an obvious trend towards the rise of pneumonia secondary to gram-negative

bacteria.

h. Other conditions like emphysematous pyomyositis, spontaneous meningitis, septic arthritis, and non vertebral hematogenous osteomyelitis may also be caused by *Escherichia coli*.[2] Osteomyelitis caused by *E. coli* generally affects the vertebrae or the ribs, and the source of spread is the gut and the urinary tract.[10]

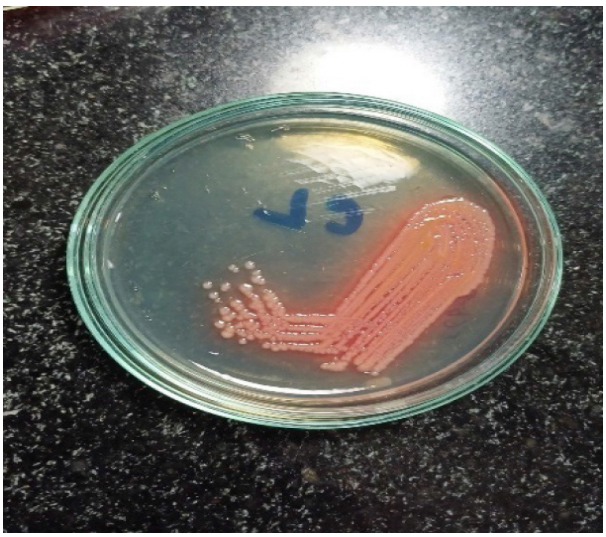

Fig. 1: *E.coli urinary isolate on CLED AGAR (with Andrade indicator)*

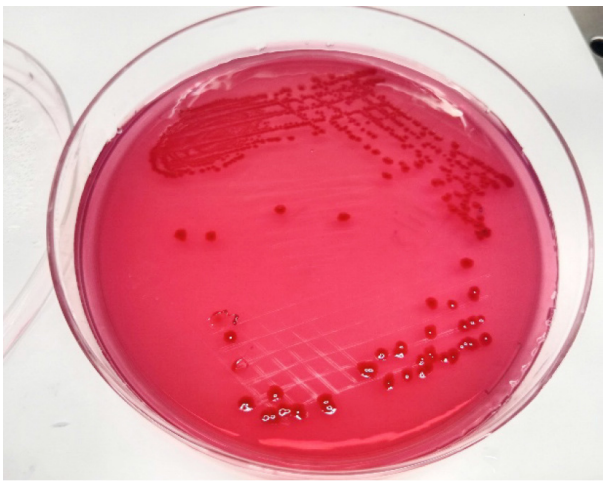

Fig. 2: *Respiratory isolate of E. coli onMacConkey Agar*

DISCUSSION

Ways to diagnose and treat these infections early on, by ExPEC should be accorded top priority. Vaccines should be researched upon, particularly against UPEC (uropathogenic *Escherichiacoli*). Extraintestinal Pathogenic *Escherichia coli* (ExPEC) is a leading cause of invasive disease, like bacteremia and sepsis. Invasive ExPEC disease (IED) has the potential of complicating the clinical treatment of other conditions as well, and is associated with increased mortality, hospitalization, and bad clinical outcomes. Older adults and individuals with comorbid conditions are at greater risk of IED. ExPEC is of particular concern in the Asia-Pacific region due to reasons like aging population and rising antimicrobial resistance.

The technique of in vivo bioconjugation is an important advance with implications that may be as far reaching as that of the original development of conjugation technology. Bioconjugation refers to the biosynthesis of polysaccharide and carrier protein within *E. coli* strains, and then there in vivo coupling by means of the oligosaccharyltransferase PglB enzyme from the N-linked protein glycosylation system. This was originally identified in *Campylobacter jejuni* and subsequently transferred to *E. coli*.[12] In the bioconjugation procedure, PglB helps transfer diverse O polysaccharides to a protein carrier (like EPA) present in the periplasm, from which the resulting bioconjugate is then harvested by a generic purification process.[13] Thus, this bio conjugation process allows for in vivo conjugation of multiple specific O polysaccharides to specific sites of any protein carrier. It also obviates the requirement for chemical detoxification of LPS. Polysaccharide-protein conjugate molecules devised by this process have a well-defined and homogenous structure. They do not suffer from loss of epitopes, which cantake place during chemical conjugation processes.

ExPEC is a global pathogen causing a spectrum of diseases affecting all ages. The increasing incidence and associated costs of disease caused by ExPEC and the major problems associated with the emergence and spread of MDR ExPEC strains implies that an effective vaccine against ExPEC infection is of urgent need. The O antigen is a feasible vaccine target which has been shown to be immunogenic in man, with induction of opsonophagocytic antibodies shown. It has been found to conferprotection against lethal challenge in preclinical models. For the first time, the technique of bioconjugation has set up the possibility of the development of a multivalent O antigen–based bioconjugated ExPEC vaccine. It is hence desirable that an effective ExPEC vaccine may be routinely implemented in adults over 50 years of age, along with existing influenza and pneumococcal vaccine coverage in this age group.

CONCLUSION

Although intestinal colonization and infection by *E. coli* is common, various extraintestinal infections are also not very uncommonly encountered and should not be neglected by any means.

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Allergic Bronchopulmonary Aspergillosis

Anubhab Moulik[1], Sayan Bhattacharyya[2]

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Abstract

Allergic bronchopulmonary aspergillosis is a tightening respiratory disease due to allergic reaction to *Aspergillus fumigatus*. The disease is of immense public health importance. Imaging of chest by CT thorax and chest X-ray shows tram-track appearance and other characteristic findings. Treatment consists of corticosteroids and other agents. These aspects have been discussed briefly in this article.

Keywords: Restrictive; ABPA; lung.

INTRODUCTION

Allergic Bronchopulmonary Aspergillosis (ABPA) is a complex hypersensitivity reaction to the fungus *Aspergillus fumigatus*. The entity primarily affects individuals having asthma or cystic fibrosis. This review highlights the pathogenesis, diagnosis, and management of ABPA, with a focus on recent advancements and challenges. Allergic bronchopulmonary aspergillosis is a form of lung disease that occurs in some people who are allergic to *Aspergillus* spp. With ABPA, this allergic reaction causes the immune system to overreact to *Aspergillus* spp which culminates in lung inflammation. ABPA causes bronchospasm (or tightening of airway muscles) and mucus build-up, leading to symptoms like coughing, breathing difficulty and airway obstruction.

Aspergillus species are molds which are ubiquitousin the environment, especially in the organic matter. There are over 100 known *Aspergillus* species worldwide, but most of the illnessesare caused by *Aspergillus fumigatus*, *Aspergillus niger*, *Aspergillus flavus*, and *Aspergillus clavatus*. An infection by *Aspergillus* species usually causes a broad spectrum of illnesses in humans. However, this depends also on the immune status of the host. Symptoms range from hypersensitivity reactions to direct angioinvasion.[1]

Aspergillus fumigatus is the most common ubiquitous airborne fungus that serves asthe principal causative microorganism for ABPA.

Epidemiology

Allergic bronchopulmonary aspergillosisis a restrictive chest disease that commonly presents in man intheir third to fifth decades of life. It is also

Author Affiliation: [1]3rd year PGT (Post graduate trainee), Respiratory Medicine, Nil Ratan Sircar Medical College & Hospital, Kolkata 700014, [2]Associate Professor, Department of Microbiology, All India Institute of Hygiene & Public Health, Kolkata 700106, West Bengal, India.

Correspondence Author: Sayan Bhattacharyya, Associate Professor, Department of Microbiology, All India Institute of Hygiene & Public Health, Kolkata 700106, West Bengal, India.

E-mail: sayantheboss@yahoo.co.in

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commonly encountered in children. This entity is also found in severe asthmatics and patients with cystic fibrosis. ABPA is seenmostly in adolescent and adult patients having asthma or cystic fibrosis. It has been estimated that about 2.5% (0.7–3.5%) of adult patients with asthma suffer from ABPA, too. In a recent meta-analysis, the pooled prevalence of A. *fumigatus* sensitisation in asthmatic adults was estimated to be about 25% in tertiary care. Of the *Aspergillus*-sensitised individuals, nearly 37% finally developed ABPA.[9] ABPA may not always require a predisposing condition; the culprit environment or such predisposing conditions has been expanded to include bronchiectasis and COPD.[10]

Aspergillus fumigatus is the commonest causative fungus incriminated in ABPA. However, other *Aspergillus* specieslike *A. flavus, A.niger,* and *A. oryzae*, can also cause ABPA, albeit less frequently. *Schizophyllum commune*, a filamentous basidiomycetousmold commonly found on the rotten wood of trees, can lead to similar pathology and a condition coined as allergic bronchopulmonary mycosis (also called ABPM).[2]

Clinical features

Symptoms of ABPA mimic those of exacerbating asthma or pulmonary cystic fibrosis, with cough producing dirty-green or brown plugs. Haemoptysis is rare. Pyrexia, headache, and loss of appetite are also commonly observed systemic findings in severe cases. Signs of airway obstruction, manifesting as wheezing and prolonged expiration, are not differentiable from exacerbation of bronchial asthma, which is a close differential diagnosis.[3] Actually, ABPA may be considered as an asthma endotype and is a treatable trait in bronchiectasis not with standing the aetiology.[11,12]

Pathogenesis

ABPA is characterized by an exaggerated immune response to *Aspergillus fumigatus*. The pathogenesis involves both type I (IgE-mediated) and type III (IgG-mediated) hypersensitivity reactions. Eosinophilic mucusplugs in the bronchi and elevated levels of total and specific IgE are key features. Recent findings suggest that extracellular trap cell death of eosinophils plays a significant role in disease mechanisms. The cells (Helper T cells) play an essential role in the hypersensitivity reaction caused by the *A. fumigatus* antigen. It presents as IgE production, eosinophilia, mast cell degranulation and bronchiectasis.[4] The interleukins primarily involved in the disease process are IL-4,5 and 13. There are also certain genetic factors which predispose to ABPA, like HLA DR2,5, mutations in CFTR, polymorphism in SP-A2 and mannose binding lectin (MBL) which also increase the overall probability of developing ABPA.

Diagnosis

The diagnosis of ABPA is indeed challenging due to its overlapping symptoms with other respiratory conditions. The International Society for Human and Animal Mycology (ISHAM) has proposed some diagnostic criteria that include patients with the following predisposing conditions:

a) Positive immediate skin reaction to *Aspergillus* antigen. In the skin test, a positive Type I Hypersensitivity reaction is typical of ABPA. It represents the presence of *A. fumigatus-specific* IgE antibodies.

b) Elevated total serum IgE levels. Elevated total serum IgE (usually over 500 IU/mL) is indicative of ABPA. The cut-off value has been reduced from 1000 IU/ml as the latter is less sensitive.[13,14]

c) Presence of precipitating antibodies (precipitins) to *Aspergillus* antigen.

d) Gel diffusion tests: They can be done to detect antibodies to Aspergillus spp.

e) Culture: *Aspergillus* spp. can be cultured from the sputum in up to two-thirds of patients having ABPA, but hyphae may not be clearly evident by direct microscopy.[5] Since Aspergillus fumigatus is a ubiquitous fungus and can also be present naturally in humans, its isolation does not necessarily guarantee causality.

Histopathology

Histopathologically, in ABPA one can document chronic bronchial inflammation, eosinophilia (that may lead to the development of an area of lung parenchymal scarring), airway remodelling, and bronchiectasis. Bronchi may show impacted mucus plug containing fungal hyphae, Charcot-Leyden crystals, fibrin and Curschmann spirals. The dichotomous branching of hyphae occurs at 45 degree angles, indicative of *Aspergillus* spp.

Recent guidelines recommend screening for A. fumigatus sensitization using fungus-specific IgE in newly diagnosed asthmatic adults and difficult-to-treat asthmatic children as the skin test fared poorly in comparison to the antibody assay.[13,14] The IgE immunoassay cut-off is 0.35 kUA/L(Kilounits

of allergen-specific IgE per liter) using FEIA (fluorescent enzyme immunoassay).[15]

a) Chest X-ray: Imaging studies, such as high-resolution CT scans, can reveal central bronchiectasis and mucus plugging, which are indicative of ABPA. Chest X-ray has 50% sensitivity for the diagnosis of ABPA. It can show parenchymal infiltrate and bronchiectatic changes, mostly in the upper lobes. However, all lobes may exhibit involvement.

HRCT (High resolution CT scan) Chest is the investigation of choice for detectingbronchiectatic changes and other abnormalities that are undetectable on a chest X-ray, like centrilobular nodules and tree-in-bud lesions.

Patients of ABPA with no obvious abnormalities evident on HRCT chest are termed as serologic ABPA (or ABPA-S).

Patients with central bronchiectasis on HRCT are, on the other hand, termed as ABPA Central Bronchiectasis (ABPA-CB). Typical radiological abnormalities seen in ABPA are "Finger in glove" opacity which is suggestive of impaction of mucus in the dilated bronchi and"tramline shadows" suggestive of parallel linear shadows which extend from the hilum in bronchial distribution and represent longitudinal impression of the inflamed, edematous bronchi. Some other findings are"toothpaste shadows" highlighting mucoid impaction of the airways, and "ring shadows" which indicate dilated bronchi with inflamed bronchial walls. The higher sensitivity, identification of the type and distribution of bronchiectasis, and recognition of mucus plus are evidentin CT scan in a better way than a digital X-ray. High attenuation mucus (HAM), or mucus which is visually denser than the paraspinal muscles on non-contrast CT thorax is said to be pathognomonic for ABPA.[16] The sensitivity and specificity of HAM are 35% and 100% respectively.[17]

Appended below shows diagnostic algorithm in ABPA

Below shows Chest X-ray with typical findings of ABPA

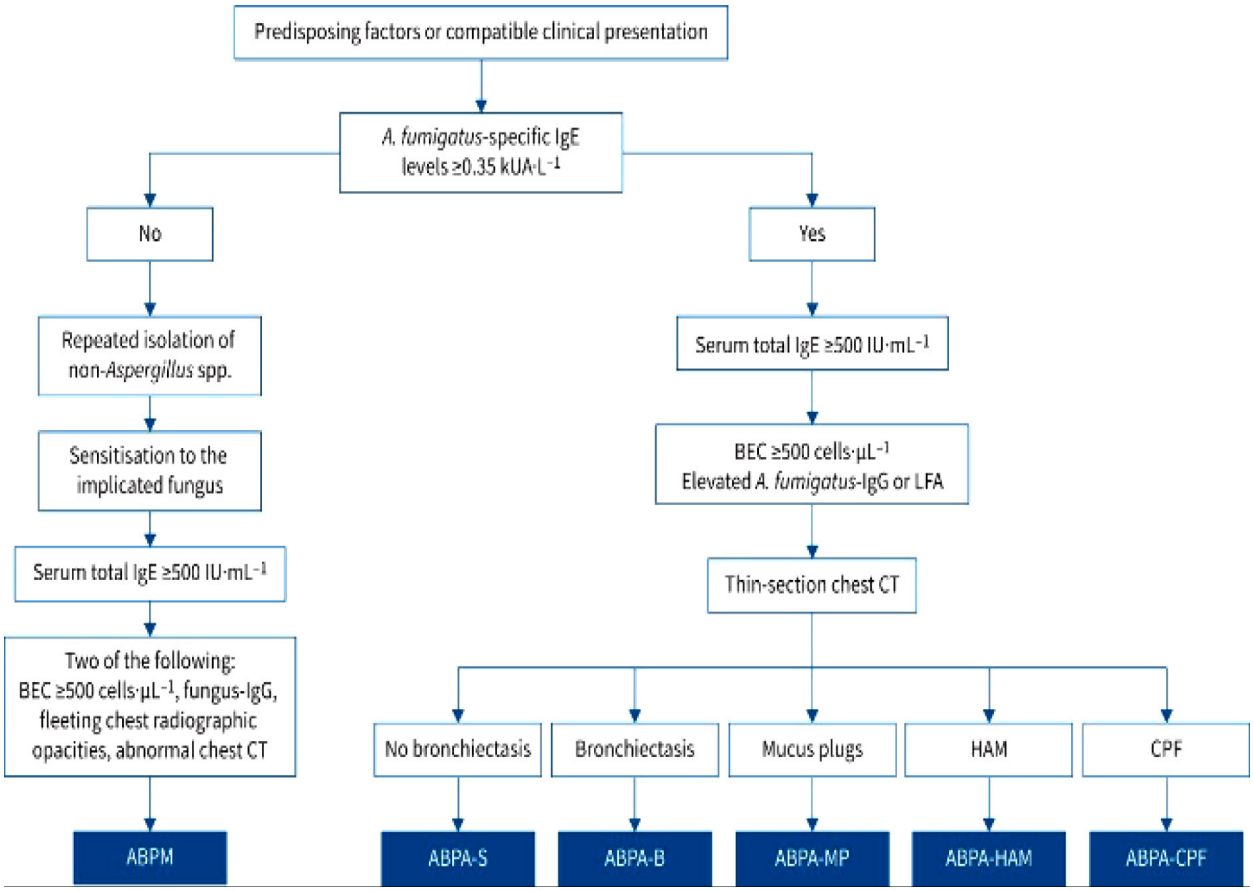

Fig. 1: Diagnostic algorithm in ABPA

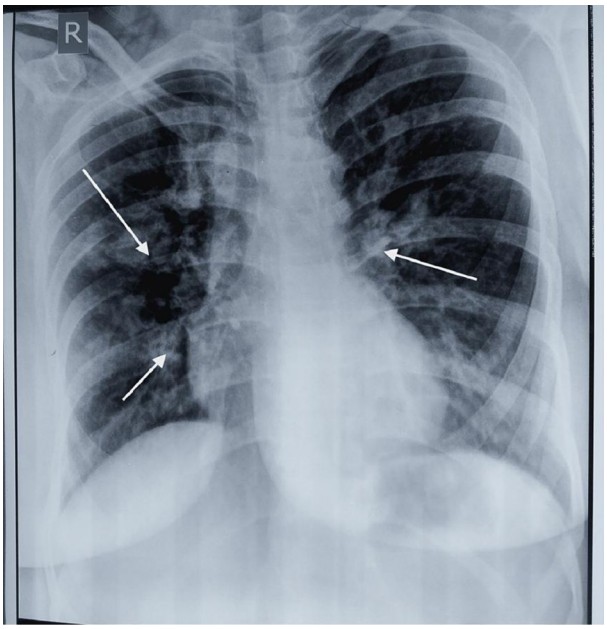

Fig. 2: Chest X-ray of ABPA *[source: ResearchGate]*

Below shows CT scan findings of ABPA

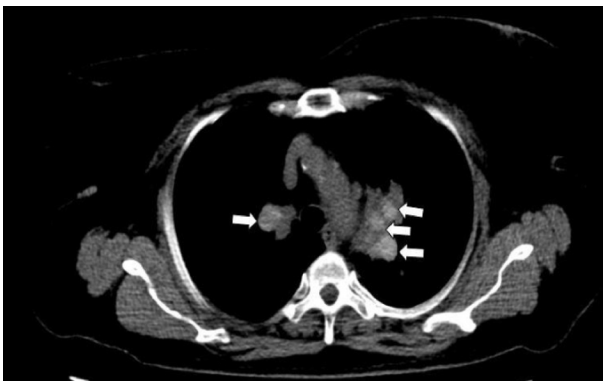

Fig. 3: CT scan findings of ABPA *[Source: www.eurorad.com]*

Appended below summarizes comparative X-ray and CT findings and typical histopathology

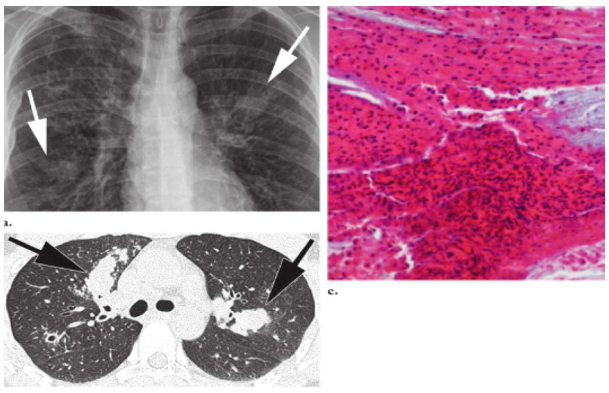

Fig. 4: Comparative X-ray and CT findings and typical histopathology

Management and treatment

The management of ABPA involves a combination of pharmacological and non-pharmacological approaches. The primary goals are to control inflammation, reduce fungal load, and prevent disease progression. Treatment options include:

Corticosteroids: Oral prednisolone is the mainstay of treatment for acute ABPA and exacerbations. The ERS 2024 recommendation is to use a dose of prednisolone 0.5 mg/kg/day for 2-4 weeks with gradual tapering and completed over 4 months. In patients with co-existent asthma, the asthma treatment needs to be optimised as these disease entities operate on a vicious interplay between themselves.

Antifungal agents: Itraconazole is commonly used to reduce fungal burden. Oral itraconazole as alternative monotherapy may be used for 4 months; however, the evidence in its favour is less in comparison to steroid. Although Voriconazole has similar efficacy as steroids, it has poor patient tolerability, thus losing credit as first line therapy.[19] The combination of steroids and azoles may even lead to exogeneous Cushing's syndrome. The clinician must be aware of that. The combination of methylprednisolone and Itraconazole is particularly notorious in this regard. Since many of these patients are also poorly controlled asthmatics, the possibility of them being on high dose inhaled budesonide or fluticasone is also high which may also lead to exogenous Cushing's syndrome, an often missed entity(20).

Antifungal drugs can help reduce the exacerbations of allergic bronchopulmonary aspergillosis (ABPA). Other than Itraconazole and Voriconazole, Posaconazole may also be used.

Biologics: As per ERS (European Respiratory Society) 2024 recommendations, there is no role of biologics at present for treating ABPA.

Treatment of ABPA aims to control inflammation and prevent further injury to one's lung. ABPA is usually treated with a combination of oral corticosteroids and antifungal medications. Corticosteroids are used to treat inflammation and mitigate the allergic reactions. Examples of corticosteroids include prednisone, prednisolone or methylprednisolone. Inhaled corticosteroids alone, like those used for asthma treatment, are not effective in treating ABPA. Usually, treatment with an oral corticosteroid is needed for months. A patient should discuss with his or her health care provider about the possible adverse effects with oral

corticosteroids and how well they can be tolerated.[6] The treatment for ABPA exacerbations (defined as sustained worsening for 2 weeks or more of clinical symptoms or the appearance of new infiltrates on chest imaging, along with an increase in total IgE by greater than or equal to 50% from the new baseline, achieved during clinical stability) follows the same guidelines as newly diagnosed ABPA. Pulsed doses of methylprednisolone have been used for treating exacerbations of ABPA which are refractory to oral glucocorticoids.[21] The overall approach to monitoring response to treatment is using a visual analogue scale of more than or equal to 50%, along with at least a 20% reduction in serum total IgE levels. Response is usually assessed after 8-12 weeks of therapy.

Challenges and Future Directions

Despite advancements in diagnostics and therapeutics, several challenges and hurdlespersist in the management of ABPA. These include the need for early and accurate diagnosis, the risk of possible adverse effects arising from long-term corticosteroid use, and the limited availability of biologics in some areas. Future research should thus focus on development of more precise diagnostic tools and also exploring novel therapeutic targets simultaneously.

DISCUSSION

From the first case description in 1952, significant advances have been made in understanding the pathogenesis and the diagnosis and treatment of ABPA. In the last twenty years, most research on ABPA has been published from India.[7] It is believed that across the world, there are about 5 million cases of ABPA. India alone accounts for nearly 1.4 million ABPA cases. The prevalence of ABPA among asthmatic patients in special clinics may be as much as 13%. Thus, a high degree of suspicion for ABPA should be present while treating a patient with bronchial asthma, particularly in specialized clinics. Early diagnosis and appropriate treatment can delayor even prevent the onset of bronchiectasis. This implies that all patients of bronchial asthma should be screened for ABPA, particularly in the chest clinics.[8] In India, the prevalence of ABPA is greater than in other countries. Early identification is a prerequisite to prevent irreversible lung damage in ABPA. There is hence an urgent and pressing need for generating increased awareness of ABPA, its diagnosis, as well as management algorithms amongst all healthcare givers.

CONCLUSION

ABPA is a complex condition requiring a multidisciplinary approach for effective management. Advances in understanding its pathogenesis and the development of new diagnostic criteria and treatment options have improved patient outcomes. However, ongoing research and clinical vigilance are essential to address the remaining challenges and enhance the quality of care for individuals with ABPA.

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A Comprehensive Overview of Epidemiological Patterns of Tuberculosis with a Special Reference of Kashmir valley

Ab Nasir sheikh[1], Tahseen Bilal Rather[2], Aasif Ahmad Lone[3], Abid-U-Satar[4], Rumais Ahmad Khan[5], Syed Mudassar[6]

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Abstract

Tuberculosis (TB) continues to be a major global health challenge, causing high rates of mortality and straining public health systems. Although there has been a gradual decline in incidence over the past few decades, in 2022 globally, there were as many as 10.6 million new cases reported by the WHO, affecting 5.8 million men, 3.5 million women, and 1.3 million children. According to the World Health Organization, TB is the second leading cause of death from an infectious agent, resulting in 1.3 million deaths in 2022. This disease disproportionately affects low and middle-income countries, with India experiencing particularly high prevalence and transmission rates. One of the major challenges in TB control is the presence of multidrug-resistant strains of M. tuberculosis in most countries, including India. In the specific context of the Kashmir valley in India, there has been a critical situation with emerging cases of multidrug-resistant tuberculosis. The COVID-19 pandemic has also posed new challenges for TB detection and control efforts worldwide, including in the Kashmir Valley. The disruptions caused by the pandemic have significantly impacted TB testing and diagnosis, potentially leading to underreporting of cases and delayed treatment. This review aims to provide an overview of global TB epidemiology, including its origins, historical context, scientific milestones and to highlight the main challenges that need to be addressed post-COVID in order to eliminate the disease as a global public health problem.

Keywords: Multidrug-resistant TB; RNTCP (revised national TB control program); latent tuberculosis infection (LTBI) Prevalence of tuberculosis, MTB; TB globally; TB in India and TB in Kashmir valley.

Author Affiliation: [1,2]Phd Scholar, [3,4]Msc Clinical Biochemistry, [6]Clinical Biochemistry, Department of Clinical Biochemistry, Sher-I-Kashmir Institute of Medical Sciences, Srinagar 190011, Jammu & Kashmir, India, [5]Msc Clinical Biochemistry, Department of Medical Laboratory Sciences, Lovely Professional University, Jalandhar 144411, Punjab, India.

Correspondence Author: Syed Mudassar, Clinical Biochemistry, Department of Clinical Biochemistry, Sher-I-Kashmir Institute of Medical Sciences Srinagar 190011, Jammu & Kashmir, India.

E-mail: syed.mudassar@skims.ac.in

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INTRODUCTION

Tuberculosis (TB) is an infectious disease caused by the strains of bacteria *Mycobacterium tuberculosis* which typically affects the lungs and if left untreated, can be fatal. However, the majority of infected people don't exhibit any disease symptoms. Tuberculosis is one of the most ancient diseases of mankind, having co-evolved with humans for thousands or even millions of years.[1] One of the oldest molecular evidences of tuberculosis has been documented in fossilized remains of an extinct bison (*Pleistocene bison*) teeth which has been radiocarbon dated to 17,870+230 years old[2] and in the remains of 9000-year-old humans recovered from a neolithic site in the Eastern Mediterranean.[3] It is believed that people have known about tuberculosis since old times, this is evident by the fact that the lungs of Egyptian mummies dating back 3000 years have been found to contain traces of tuberculosis lesions. The disease was also described in the writings of the Greek physician Hippocrates (450–370 BC), known as "the father of medicine". This disease was known as *phthisis* in Classical Greek times which means wasting away. The same reasoning led to its common label of "consumption" until recently. In the 17th century, it was termed as silvious of Leyden, after the name of the Dutchman Franciscus silvious of Leyden who first used the term ***"tubercle"*** to describe the knobby lesions found in the lungs of people who died because of this disease. However, Dr Richard Morton first established the link between the pulmonary form of tuberculosis and "tubercles," claiming that, this was because of the variety of symptoms in which this form of the disease manifested. TB was not recognized as a single disease until the 1820s, when it was named "tuberculosis" by J. L. Schönlein.[4] The bacillus that causes tuberculosis, *"Mycobacterium tuberculosis"* was discovered by Robert Koch in 1882, for which he won the Nobel Prize in physiology or medicine in 1905.[4]

The first of many drugs now used for the treatment of TB was discovered by scientists in the 1940s. As a result, tuberculosis began to fade away form the planet. But Following 1984, the total number of cases of tuberculosis reported in Asian countries began to rise which officially marked the return of tuberculosis.[5] In spite of more recent methods for TB diagnosis and treatment, millions of people continue to suffer and die from this disease. TB is one of the world's top three infectious killer diseases, with HIV/AIDS killing 3 million people per year, TB killing 2 million, and malaria killing 1 million.[6] Even though tubercle bacilli were identified nearly 130 years ago[6], a definitive understanding of the pathogenesis of this disease is still lacking.[7,8] The bacterium has the ability of attacking any area of the body, but it typically targets the lungs. Tuberculosis is mainly passed from an infected person to a normal person through the air. In case of some people, particularly those with a weakened immune system, the bacteria become active and cause tuberculosis (TB). Tuberculosis in the lungs or throat are contagious which means that the bacteria can be passed on to others[9,10] When a person infected with tuberculosis coughs or sneezes, the bacteria get released into the air in the form of droplets and the People in the vicinity may inhale these bacteria and become infected. When a normal person inhales those bacteria, the bacteria can settle in his lungs and grow[5] From there, they head towards various organs, including the kidney, spine, and brain by means of the blood. However, the other parts of the body, such as the kidney or spine, are usually not infected with tuberculosis. TB infection in healthy individuals is frequently asymptomatic due to the immune system's ability to wall off the causative bacteria. This bacterium thrives and multiplies in macrophages, eluding the patient's natural defence system present within the blood. TB infection can progress through two stages: asymptomatic latent tuberculosis infection (LTBI) and tuberculosis disease. If left untreated, this disease has a mortality rate of more than 50%. It has always been endemic, and it is likely that the other mycobacteria commonly reported from other countries were unable to emerge due to this complexity.

The development of the recent SARS-CoV-2 pandemic, there is a growing understanding of the importance of investing the early identification and treatment of transmissible respiratory diseases.[11] The lessons from the COVID-19 pandemic, demonstrated the efficacy of case detection, case isolation and contract tracing of TB cases, which provided a much-needed motivation to reorient healthcare services in high-TB burden areas and setting them towards prevention. Examining regional tuberculosis epidemiology is the best way to assess the efficacy of existing prevention and management strategies. Before the COVID-19 pandemic, tuberculosis (TB) affected one-third of the world's population.[12] The COVID-19 outbreak has jeopardized TB diagnosis, its treatment as well as prevention, compromising recent advances in TB detection and reduction. In comparison to 2019, there is a significant drop in the number of new cases of TB reported globally in 2020. According to

some studies the disruptions in TB prevention and treatment programmes may result in an additional 6.3 million new TB cases and 1.4 million additional deaths by 2025[13] India was the leading contributor to the global TB notification shortfall, followed by China, Indonesia, and the Philippines.[14] The COVID-19 pandemic has also imperilled India's public health system and highlighted its flaws. COVID-19 impacted many high-performing health programs, including the tuberculosis program.[12,15] When compared to average levels, The incidence rate of TB cases in India decreased during the lockdown period.[16,17]

World Health Organization's has started some strategies in order to End the TB, However, achieving the global targets of 'End TB 2035' requires a dramatic decrease in TB deaths and incidence cases, as well as the elimination of the economic and social burden of TB[18] Since the incidence of TB is not decreasing in line within the milestones of global End TB Strategy targets.[19] As a result, the World Health Organization's End TB Strategy establishes ambitious targets to which concerned countries must strive for the end of the global TB epidemic.[19] While it is clear that the burden of TB in Kashmir valley is disproportionately high, there is little published data characterising the local TB epidemic. It is critical to estimate the prevalence of pulmonary tuberculosis in order to guide intervention policies and program management strategies. As a result, we conducted a systematic review of published literature to get a more precise understanding of the current TB burden in order to provide a comprehensive and up-to-date assessment of the prevalence of pulmonary tuberculosis with a special reference of Kashmir valley.

Global scenario

Tuberculosis (TB), long recognised as a major cause of morbidity and mortality across the globe, has been a neglected disease in both developed and developing countries for several decades. It is one of the top ten causes of death worldwide and one of the leading causes of death from infectious diseases. Globally, controlling tuberculosis is a significant challenge and it leads to death of millions of people every year, causing a significant morbidity and mortality worldwide. Among the 15 countries with the highest estimated TB incidence rates, 13 are in Africa, while half of all new cases are from six Asian countries, viz., India, China, Indonesia, Pakistan Bangladesh and Philippines. In a report by WHO, TB is described as a global pandemic that remains a persistent developmental challenge, placing an enormous strain on authorities, especially in developing countries.[14] The recently released the World Tuberculosis Report 2022 noting the impact of Covid-19 pandemic on the diagnosis, treatment and burden of disease for Tuberculosis (TB) globally.[14] It is reported that in Every second, someone in the world is newly infected with TB bacilli and 1 in every 10 of these newly infected people will become sick or infectious later in life.[14] The report stated that approximately 10.6 million people got diagnosed with TB in 2021 which shows an increase of 4.5% from 2020 data which estimated 10.1 million cases of this disease globally while 1.6 million patients die of the disease, reversing the decline incidence of TB from many years.[20,21] Out Of the total TB deaths, 187,000 patients were also positive for HIV (Human Immunodeficiency virus). Nearly 82% of global TB deaths among HIV-negative people occurred in the African and South-East Asia regions. Similarly, the TB incidence rate (new cases per 100000 populations per year) is estimated to have increased by 3.6% between 2020 and 2021, following declines of about 2% per year for the past 2 decades.

Indian scenario

The extent of TB Problem is generally described in terms of incidence, prevalence and mortality. India accounts for one fifth of the global TB burden i.e., 1.98 million out of 9.4 million new cases annually. In India, more than 40% population is infected with *Mycobacterium tuberculosis*. Approximately 75 new smear positive TB cases occur per lakh population per year. It is also estimated that about 2, 76,000 people die due to TB annually. According to some studies in every three minutes two patients die because of tuberculosis in India.[22] In India, the TB burden remains staggering with a higher proportion of TB patients, because of its poor socioeconomic and environmental conditions. Every year approximately 1.8 million people contract the disease of which approximately 8,00,000 are infectious and until recently, 3,70,000 people died from it annually which counts for a mortality rate of 1000 patients every day.[23] The disease also has a significant impediment to social and economic development. It is estimated that 100 million workdays are lost due to this illness.[23] According to the RNTCP report, in India nearly three times more male than female TB cases are observed, although the extra-pulmonary disease has been reported more commonly in women.[24]

According to the most recent WHO TB report,

with 28% cases, India was among the eight countries accounting for more than two-third (68.3%) of the total TB cases. The other countries were Indonesia (9.2% cases), China (7.4% cases), Philippines (7% cases), Pakistan (5.8%), Nigeria (4.4%), Bangladesh (3.6%) and Democratic Republic of the Congo (2.9%)[14] The report also stated that India accounted for 36% of the global TB related deaths among HIV negative people. India was among the three countries (along with Indonesia and the Philippines) that accounted for most of the reduction in TB cases for the year 2020 (67% of the global) and made partial recoveries in 2021.[14] India's TB incidence for the year 2021 is 210 per 100,000 populations – compared to the baseline year of 2015 (which was 256 per 100,000 populations). There has been an 18% decline (7 percentage points); better than the global average of 11%, placing India at the 36th position in terms of incidence rates.[14]

Kashmir Scenario

In India tuberculosis is one of those disease having highest mortality rate, it has been observed that Tuberculosis (TB) almost kills close to half a million Indians every year.[14] The union Territory Jammu and Kashmir of India, situated in the extreme north of India, has two distinct geographical regions: Jammu and Kashmir. Kashmir Valley lies to the north of Jammu region at the altitude of 1800-4000 m above sea level. It is famous for its temperate climate with a severe winter and a moderate summer. The Kashmir valley is a demographically mountainous region where the winter season lasts four to five months, forcing people to stay indoors and rely on wood, coal and gas for heating and cooking. Many studies have identified indoor air pollution as a significant risk factor for tuberculosis disease.[25,26] The current literature suggested a number of factors associated with tuberculosis infection, including age, gender, level of education, marital status, place of residence, wealth, overcrowding, poor housing, and household environment factors.[27,28] *Mayurnath et al.* conducted the first Tuberculosis prevalence study in Kashmir in 1978.[29] Since then, there has been no relevant data on TB prevalence in Kashmir. In Kashmir, the National Tuberculosis Control Programme (NTCP) was launched in 1964 while as the RNTCP was implemented in the valley in 2004 to stop further TB disease progression in the Kashmir valley, which showed very good results and assisted in disease decline and the removal of social stigma among patients regarding the disease and treatment. According to the RNTCP data from Kashmir, over the last 10 years the ratio among male: female was nearly 1:1 (range 0.96:1 to 1.06:1).[30] A significant finding from Kashmir valley was that the prevalence of TB was higher in North Kashmir (Kupwara, Baramulla) and less in South Kashmir (Anantnag, Pulwama)[30] Although there is no statistically significant difference, the same regional difference was reported by *Mayurnath et al.* in 1978.[29] It was also observed that Females were more prone to this disease than males, and the age of female Tuberculosis patients was comparatively less than that of males.[30]

According to the latest data of INDIA TB REPORT 2023 from Ministry of Health and Family Welfare and from the data of state tuberculosis department of Kashmir, there has been a significant decrease in TB cases in the Kashmir division since 2021 which can be attributed to the strengthening of TB-control activities through RNTCP and implementation of Rifampicin-based DOTS regime. According to this report the UT of Lakshadweep and the district Budgam of Jammu and Kashmir were declared as the first UT and the first district in the country to achieve more than 80% reduction of TB incidence.[32]

In 2022, Kashmir recorded over 3376 Tuberculosis (TB) cases, with Srinagar topping the list with an estimate of 1465 cases. In 2021, The Covid-19 pandemic causes less screening for TB and during this year the Kashmir division reported less TB cases i.e., 3442 TB cases compared to 2840 TB cases in 2020.33 The state tuberculosis department reported 1465 positive TB cases in Srinagar, followed by district Anantnag with 665 Positive TB cases, District Baramulla with 599 positive TB cases, Kupwara district with 361 cases, Pulwama district with 172 positive TB cases and District Budgam with only 114 positive TB cases (Fig. 1).[33] According to the State Tuberculosis department, Tuberculosis cases have gone down in 2022 and likely every district will be TB free by 2025.

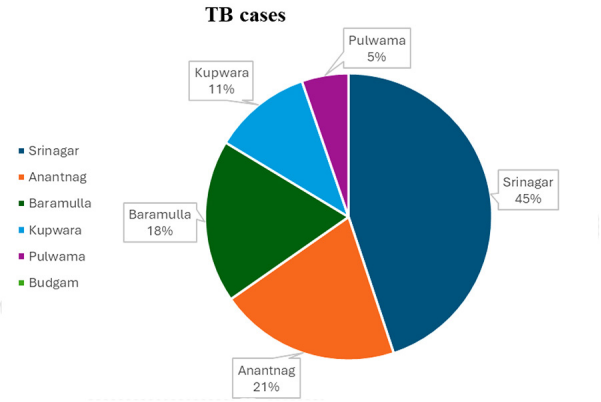

Fig. 1: Graphical representation of TB cases according to State tuberculosis department (Kashmir)

CONCLUSION

In comparison to the rest of the Indian subcontinent, the Kashmir valley has a low TB burden. In India, tuberculosis remains one of the most common diseases in terms of mortality and morbidity. This is as a result of early infection stages not being reported, misdiagnosis, and an increase in drug-resistant TB cases. India has set an ambitious goal of TB elimination by 2025. The outbreak of the Covid-19 pandemic also slows progress towards the goal. Despite this, the Government of India is making significant efforts to combat the disease through revised plans and implementation across the country. However, there is still a long way to go to significantly reduce the high incidence and prevalence of tuberculosis in India.

The aim of the review is to gain an understanding of the burden of TB in India including Kashmir in order to identify ways by which TB control can be improved. For India to successfully combat this disease, a precise understanding of the current TB burden is required. Moreover, the effective combat can only be achieved with the help of a multifaceted approach focused on enhancing diagnostic capability, ensuring quality care, and preventing the transmission. Studying the epidemiology and service usage at a micro level within these centres could be beneficial in developing the specific strategies for actively finding and addressing the cases. Having a precise assessment of the tuberculosis (TB) burden on a national scale is crucial for informing policy decisions and can greatly aid in enhancing efforts to control the disease.

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Standard journal article

[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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Unpublished article

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Personal author(s)

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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/HSQ20.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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