Medical Newsletter

as a service to the medical profession

Vol. 25
No. 02
ISSN 2309-0588
July 2015

Research Focus

Bacteriological Spectrum of Different Infections and Their Antibiogram at NICVD, Dhaka

Antibiogram of Urinary Escherichia coli Isolated in Sir Salimullah Medical College & Mitford Hospital, Dhaka

Allergic Rhinitis and Urticaria

Newer Insights of COPD Management

Statin Completing 25 years

SOFOSBUVTR A Milestone in HCV Treatment

Health News Update

Medical Research UPDATE

World Heart Day 2015
The strong relationship between Beximco Pharma and Health Care Professional has always been guided by a mission to benefit patients and to enhance the practice of medicine. As a result Beximco has successfully established its brand value within the medical community. The company shall now focus to reinforce this relationship by providing value added academic services through Medical Affairs activity.
July 1, 2015

Dear Doctor,

What a fantastic half year we have had in 2015. Our last issue had marked our epic entry into the 25th year of publication and with this present issue we are extremely honored to rejoice with you a most prestigious accomplishment that is the US FDA approval of Beximco Pharmaceuticals Ltd. Also, it is the holy month of Ramadan and a time to practice self-restraint, charity and strive for positive change. A first step to such progress is to believe that together, we can. With this confidence, we are introducing our new and enhanced Medical Newsletter. We would also like to emphasize that your constant support is a prime reason for our continuous achievements. Thank You.

Wishing you all a very blessed and peaceful Ramadan and Eid Mubarak.

With regards

S. Akhtar
Dr. Selina Akhtar
General Manager & Head of the Department
Medical Department
Beximco Pharmaceuticals Ltd.
Several clinical studies show that the majority bacteria are resistant to commonly used antibiotics in different hospitals in Bangladesh. This clearly indicates that antibiotic resistance is alarming to the community of this country.
Abstract

Background: One of the major causes of death in the current era is the infectious diseases. Aerobic bacteria are one of the most commonly isolated organisms from hospitalized patients.

Objectives: The aim of the present study was to observe the infections caused by aerobic bacteria and their antibiotics susceptibility pattern.

Methods: This retrospective study was carried out in the National Institute of Cardiovascular Diseases (NICVD) from January 2012 to December 2012 for a period of one year. Patients who were admitted in medical wards and medical ICU suffering from different infections were undertaken for this study. Proper thorough clinical examination, routine and specific investigations were done in each case. Microbiological samplings were tried on day 1, after completion of antibiotic therapy or in between as required. Aerobic bacterial culture and sensitivity tests were done according to clinical laboratory standard institute (CLSI) standard.

Result: A total of 660 samples were studied of which male (70.0%) were predominant than female (30.0%). The highest number of patients was in the age group of 30-60 years (54.0%) followed by 15-30 years (21.5%) and less than 15 years (13.0%). The mean age with standard deviation was 38.61±19.236 years. The most common isolated bacteria was E. coli (40.1%) followed by Pseudomonas species (30.4%), coagulase negative Staphylococcus (19.0%) and coagulase positive Staphylococcus (5.9%); however, β-hemolytic Streptococcus (4.2%) was detected. Urine culture has yielded Pseudomonas species (13.3%), E. coli (71.1%) and CNS (15.0%). From pus Pseudomonas species (37.3%) was isolated mostly which was 62 cases followed by E. coli (31.3%), CNS (19.3%) and CPS (7.2%). Pseudomonas species was resistant to penicillin, amoxicillin and vancomycin and ~50% resistant to cotrimoxazole, cefuroxime, ceftriaxone, piperacillin, azithromycin, cephalaxin, netilmicin and pefloxacin.

Conclusion: In the conclusion, majority bacteria are resistant to commonly used antibiotics.

Introduction

Aerobic bacteria isolated from different clinical specimens have developed resistance against the major classes of antibiotics. An antibiogram is the result of a laboratory testing for the sensitivity of an isolated bacterial strain to different antibiotics. It is by definition an *in vitro*-sensitivity. Many of these resistance mechanisms are widespread among common pathogens and cause considerable concern in several clinical situations in which treatment options have become very limited. The antibiotic sensitivity pattern of organisms is changing very rapidly over a short period. It is particularly true for developing countries like Bangladesh where antibiotics are used irrationally. Clinicians should be aware of the rising resistance of bacteria to commonly prescribed antibiotics as well as the profile of antibiotic resistance. Therefore, for rational and appropriate use of antibiotics periodic evaluation of sensitivity pattern is essential.
Results and Discussion

A retrospective study was conducted in the Department of Microbiology at National Institute of Cardiovascular Disease (NICVD) which is the referral tertiary care hospital for cardiovascular diseases in Bangladesh to find out the aerobic bacterial agents causing different infections as well as their antibiotic sensitivity pattern. A total of 660 cases were studied of which male were predominant and the highest number of patients was in the age group of 30-60 years. Most common specimen was urine, other samples include pus, wound swab, blood and throat swab.

Culture of urine has yielded Pseudomonas species, E. coli and Coagulase negative Staphylococcus (CNS). From pus Pseudomonas species was isolated mostly followed by E. coli, CNS and Coagulase positive Staphylococcus (CPS). One E. coli and two Pseudomonas species were isolated from blood. In wound swab the most common isolated bacteria was Pseudomonas species, E. coli and CNS. Among which Pseudomonas species was mostly resistant to penicillin, amoxicillin and vancomycin and ~50% resistant to cotrimoxazole, cefuroxime, ceftriaxone, piperacillin, azithromycin, cephalexin, netilmicin and pefloxacin. It was found that Pseudomonas species was still more than 90% sensitive only to imipenem. Coagulase negative Staphylococcus (CNS) was sensitive in imipenem, novobiocin and netilmicin. Coagulase positive Staphylococcus (CPS) was sensitive to only imipenem and cephalexin. Staphylococcus saprophyticus was sensitive in imipenem, novobiocin and netilmicin. Staphylococcus aureus was sensitive to only imipenem and cephalexin.

The resistance observed in Pseudomonas species could also be attributed to irrational use of antibiotics for conditions that may not clinically indicate their use, over-the counter sell of antibiotics in pharmacies without prescription by authorized practitioners, some new drug formulations which may be of poor quality and dumping of banned products into the market where the public may get access to them. The resistance shown to amoxicillin and ampicillin may be due to the antibiotics having been in use for much longer time and their oral route of administration that affects their rate of absorption into blood stream. Some of them were used as prophylaxis therefore increasing their use in patients. Over-use of antibiotics contributes to organisms developing resistance. In another study in Bangladesh it was reported that there is a trend of antibiotic resistant among the Pseudomonas species, E. coli and Staphylococcus aureus isolated from different samples and has shown that the resistant pattern gradually increases among the isolated bacteria from different clinical specimens. In view of the resistance observed, infections caused by Methicillin resistant Staphylococcus aureus (MRSA) can be expensive in terms of costs of treatment, morbidity and prolonged hospitalization.

Conclusion

Several clinical studies show that the majority bacteria are resistant to commonly used antibiotics in different hospitals in Bangladesh. This clearly indicates that antibiotic resistance is alarming to the community of this country. Since a high proportion of samples have positive cultures, infection control is recommended as a strategy to minimize spread of resistant organisms. Future studies should be extended to include cultures under anaerobic conditions to establish presence of other organisms that require such environment for growth. It is recommended that judicial antibiotic use should be carried out.
Introduction

Urinary tract infections (UTIs) are one of the most common infectious diseases encountered in the medical practices. The syndrome ranges from asymptomatic bacteriuria to perinephric abscess with sepsis. In Bangladesh 20-35% females experience at least one episode of UTI in their lives and the prevalence is 1-4% among school children. Also, the prevalence of bacteriuria among pregnant women has reported from 5-15.5%. Urinary tract infections including catheter related bacteriuria constitute the most common nosocomial bacterial infection with an average rate of 13.1 cases per 1000 hospital discharges. More than 90% of all uncomplicated UTIs are caused by E. coli infection. The recurrence rate after a first E. coli infection is 44% over 12 months. So, proper & adequate antibiotic treatment is necessary to treat and prevent recurrence of UTI. The present study has documented the distribution of urinary pathogens and the antimicrobial sensitivity pattern of E. coli isolated in Sir Salimullah Medical College & Mitford Hospital, Dhaka.

Results and Discussion

This clinical study conducted in the department of Microbiology, Sir Salimullah Medical college, Dhaka from October 2002 to September 2003 reports the antibiogram of isolated E. coli. Total 749 urine samples were collected from patients who were either admitted in-patient in the hospital or visited the out-patient department of the hospital during that period. The study reveals that maximum resistance of E. coli was found against amoxicillin (97.36%) followed by cotrimoxazole (81.88%), tetracycline (81.57%), nalidixic acid (79.82%) and cephalaxin (76.61%) while moderate resistance was shown against ciprofloxacin (59.35%) and nitrofurantoin (55.26%). Cefuroxime, gentamicin and ceftazidime were found to be sensitive against 67.54%, 66.08% and 55.84% E. coli isolates respectively. High sensitivity was observed to ceftriaxone (86.84%), imipenem was found to be 95.02% sensitive. It was observed that the sensitivity of ciprofloxacin and gentamicin was reduced from 91% to 40.64% and 90% to 66.08% respectively. This marked reduction in ciprofloxacin sensitivity may be due to the fact that the antibiotic is being overprescribed, handed out to patients who have no bacterial infections. In this study resistance was found to be increasing towards third generation cephalosporin also which should alert us that at time no antibiotics in our hands to treat the infections. The newer drug, imipenem was found to be the most effective drug which was found 95.02% sensitive against E. coli.

Conclusion

The rapid emergence of antibiotic resistant strains alert us that we should be cautious with indiscriminate use of antibiotics. Antibiotics should be prescribed with proper dose and duration after culture and sensitivity reports are available when possible.

References
Couples that Sweat Together Stay Together
Loneliness and Social Isolation Linked to Early Mortality

A meta-analysis has found that loneliness and social isolation may be associated with premature death among populations aged less than 65 years. The researchers analyzed data from 70 studies conducted between 1980 and 2014, featuring a total of over 3 million participants. The data included information regarding loneliness, social isolation and living alone. After controlling for variables such as age, gender, socioeconomic status and pre-existing health conditions, the researchers found that social isolation was interconnected to an increased risk of premature mortality. Conversely, the presence of social relationships was found to have a positive influence on health. This may be revealed that the current status of research on the risks of loneliness and social isolation is similar to that of research on obesity.

Source: www.medicalnewstoday.com

Spouse 'More Likely to Increase Exercise Levels if Other Spouse does the Same'

Past studies have suggested that married individuals are more likely to eat a healthy diet if their spouse does. Now, a new study claims the same can be said for exercise. That means counseling married couples on health and exercises together is likely to produce better results than counseling them separately. Led by researchers from the Johns Hopkins Bloomberg School of Public Health in Baltimore, MD, the study reveals that if one spouse increases their physical activity, the other spouse is much more likely follow in their footsteps. Cobb and colleagues analyzed the medical records of 3,261 spouse pairs who were a part of the Atherosclerosis Risk in Communities Study (ARIC). From 1987-89, the spouse pairs had two medical visits that were conducted approximately 6 years apart. At each visit, the physical activity levels of each spouse were recorded, and the team compared these with the recommendations set in the Physical Activity Guidelines for Americans. At the first visit, the team found that 33% of wives and 40% of husbands met physical activity recommendations. On the second visit, however, a husband was 70% more likely to meet physical activity guidelines if his wife met the guidelines on the first visit, compared with husbands whose wives were less active. In addition, a wife was 40% more likely to meet physical activity recommendations on the second visit if her husband met recommendations on the first visit. So that, one spouse could have a really positive impact on the other when it comes to staying fit and healthy for the long time.

Source: www.medicalnewstoday.com
Allergic Rhinitis and Urticaria
**Allergic Rhinitis**

Allergic rhinitis is the most common type of rhinitis, which affects 10 to 20% of the population, and evidence suggests that the prevalence of the disorder is increasing. Severe allergic rhinitis has been associated with significant impairments in quality of life, sleep and work performance. In the past, allergic rhinitis was considered to be a disorder localized to the nose and nasal passages, but current evidence indicates that it may represent a component of systemic airway disease involving the entire respiratory tract.

**Pathophysiology:** In allergic rhinitis, numerous inflammatory cells, including mast cells, CD4-positive T cells, B cells, macrophages, and eosinophils, infiltrate the nasal lining upon exposure to an inciting allergen (most commonly airborne dust mite fecal particles, cockroach residues, animal dander, molds, and pollens). The T cells infiltrating the nasal mucosa are predominantly T helper (Th)2 in nature and release cytokines (e.g., interleukin [IL]-3, IL-4, IL-5, and IL-13) that promote immunoglobulin E (IgE) production by plasma cells. This IgE production, in turn, triggers the release of mediators, such as histamine and leukotrienes, that are responsible for arteriolar dilation, increased vascular permeability, itching, rhinorrhea, mucous secretion, and smooth muscle contraction. The mediators and cytokines released during the early phase of an immune response to an inciting allergen, trigger a further cellular inflammatory response over the next 4 to 8 hours (late phase inflammatory response) which results in recurrent symptoms (usually nasal congestion).

**Diagnosis and Investigations:** Allergic rhinitis is usually a long-standing condition that often goes undetected in the primary-care setting. Screening for rhinitis is recommended, particularly in asthmatic patients since studies have shown that rhinitis is present in up to 95% of patients with asthma. A thorough history and physical examination are the cornerstones of establishing the diagnosis of allergic rhinitis.

**History:** During the history, patients often describe the following classic symptoms of allergic rhinitis: nasal congestion, nasal itch, rhinorrhea and sneezing. Allergic conjunctivitis is also frequently associated with allergic rhinitis and symptoms generally include redness, tearing and itching of the eyes. An evaluation of the patient’s home and work/school environments is recommended to determine potential triggers of allergic rhinitis. The environmental history should focus on common and potentially relevant allergens including pollens, furred animals, textile flooring/ uphostery, tobacco smoke, humidity levels at home, as well as other potential noxious substances that the patient may be exposed to at work or at home. The use of certain medications (e.g., β-blockers, acetylsalicylic acid [ASA], non-steroidal anti-inflammatory drugs [NSAIDs], angiotensin-converting enzyme [ACE] inhibitors, and hormone therapy) as well as the recreational use of cocaine can lead to symptoms of rhinitis. Therefore, patients should be asked about current or recent medication and drug use. The history should also include a family history of atopic disease, the impact of symptoms on quality of life and the presence of co-morbidities such as asthma, mouth breathing, snoring, sleep apnea, sinus involvement, otitis media or nasal polyps. Patients may attribute persistent nasal symptoms to a “constant cold” and, therefore, it is also important to document the frequency and duration of “colds”. Previous response to intra-nasal corticosteroids may also be suggestive of an allergic etiology.

**Physical examination:** The physical examination of patients with suspected allergic rhinitis should include an assessment of outward signs, the nose, ears, sinuses, posterior oropharynx, chest and skin.

**Diagnostic Tests:** Laboratory tests used in the diagnosis of allergic rhinitis include the following:
Allergy and Immunology

- **Allergy skin tests (immediate hypersensitivity testing):** An *in vivo* method of determining immediate (IgE-mediated) hypersensitivity to specific allergens.

- **Radioallergosorbent test (RAST):** Indirectly measures the quantity of IgE serving as an antibody to a particular antigen.

- **Total serum IgE:** Neither sensitive nor specific for allergic rhinitis, but the results can be helpful in some cases when combined with other factors.

- **Total blood eosinophil count:** Neither sensitive nor specific for the diagnosis, but, as with total serum IgE, can sometimes be helpful when combined with other factors.

- **Radiography:** Can be helpful for evaluating possible structural abnormalities or to help detect complications or comorbid conditions, such as sinusitis or adenoid hypertrophy.

- **Computed tomography scanning:** Can be very helpful for evaluating acute or chronic sinusitis.

- **Magnetic resonance imaging:** Can be helpful for evaluating sinusitis.

**Management**

The management of allergic rhinitis consists of the following three major treatment strategies:

- **Environmental control measures and allergen avoidance:** These include keeping exposure to allergens such as pollen, dust mites, and mold to a minimum.

- **Pharmacologic management:** Patients are often successfully treated with oral antihistamines, decongestants, or both; regular use of an intranasal steroid spray may be more appropriate for patients with chronic symptoms. Several clinical studies demonstrate that in the treatment of allergic rhinitis, simultaneous blockade of platelet activating factor (PAF) & histamine receptors could exhibit higher clinical efficacy than blockade of any one of these receptors. Some anti-histaminics have been shown to exhibit marginal PAF antagonistic properties which can not be attributed to specific interaction with PAF receptors. Oral corticosteroids may be useful in select cases.

- **Immunotherapy:** This treatment may be considered more strongly with severe disease, poor response to other management options, and the presence of comorbid conditions or complications. Immunotherapy is often combined with pharmacotherapy and environmental control.

## Urticaria

Urticaria is an allergic rash that affects up to 25% of the population at some point in their lifetime. The rash usually consists of transient, erythematous, pruritic, and circumscribed wheals, or hives. There are two main categories of urticaria depending on the course of the rash.

**Acute:** Although each urticarial lesion may last minutes to hours, acute urticaria is an episode of hives that lasts less than 6 weeks. It occurs more frequently in children than adults, and is more prevalent in adult females than males.

**Chronic:** Chronic urticaria is hives that persist or recur, usually multiple days in a week, for longer than 6 weeks' duration. Affecting up to 1% of the population, chronic urticaria is more common in adults than children. It often begins in the third to fifth decade of life and is most prevalent among women. Although both acute and chronic urticaria usually resolve on their own, chronic urticaria may persist for years.
Pathophysiology: Although urticaria can occur as a result of direct mast cell activation and degranulation, most urticaria result from immune-mediated hypersensitivity reactions. Mast cell degranulation incites the rapid release of mediators and cytokines, including histamine, substance P, PAF, tumor necrosis factor-\(\alpha\), interleukin-1, prostaglandin D2, and leukotrienes C4 and D4. Each of these contributes to the vasodilation, increased vascular permeability, and acute inflammation that leads to urticaria. The most common immunologic pathway in acute urticaria is IgE mediated.

In chronic urticaria IgG antibodies to both IgE and/or the Fc region of Immunoglobulin E (FcER1) \(\alpha\)-subunit have been described to be pathogenic in patients. Through this autoimmune mechanism, histamine release theoretically can be triggered. In patients with autoantibody-associated urticaria, there is significant prevalence of other autoimmune conditions, including autoimmune thyroid disorders, celiac disease, systemic lupus erythematosus, rheumatoid arthritis, and type 1 diabetes. Both immune complex-mediated and cytotoxic hypersensitivity are thought to be involved with urticaria owing to infectious processes. Additionally, cytotoxic reactions have been reported after blood product transfusions. Most physical urticaria result from the direct mast cell degranulation initiated by the specific physical stimulus, such as with heat, water, or vibration.

Cholinergic urticaria has been associated with hypohidrosis, the urticaria could result from leakage of the sweat into the dermis. Other theories include a muscarinic-mediated mechanism and a neurogenic reflex. The suggested mechanism for the pathogenesis of NSAID induced urticaria stems from the inhibition of cyclooxygenase-1, which shunts the metabolism of arachidonic acid toward the 5- lipooxygenase pathway. This ultimately leads to increased production and release of cysteinyl leukotrienes, thus contributing to urticaria formation. Molecular genetic mechanisms are also being sought in patients with NSAID induced urticaria.

Triggers:

Acute urticaria: About 30 to 50% of acute urticaria cases are idiopathic. The IgE mediated hypersensitivity reactions to foods, medications, latex, and insect stings, can trigger urticaria and anaphylaxis. Environmental aeroallergens include grass or pet dander, bites from mosquitoes, fleas, and bedbugs. Among the infectious agents, upper respiratory tract viruses, \textit{Mycoplasma pneumoniae}, and parasitic infections have been commonly reported in children. In adults, infectious hepatitis and mononucleosis have been implicated in acute urticaria.

Chronic urticaria: Thirty percent to 60% of patients with chronic urticaria have positive autoantibodies directed at IgE, the FcER1 \(\alpha\)-subunit, or positive autologous serum skin tests. Microbes that have been commonly associated with chronic urticaria include \textit{Helicobacter pylori}, Group A Streptococci, hepatitis B and C, \textit{Epstein–Barr virus}, and parasitic infection. Cold and heat urticaria presents minutes after contact or exposure to cold or hot objects, liquids, or air; aquagenic urticaria results from direct skin contact with water. Cholinergic urticaria precipitated by an increase in core body temperature and most often associated with exercise, are smaller (usually 1–3 mm in diameter), punctate, and usually found in primarily on the chest and back. Others include delayed pressure urticaria, vibratory urticaria and solar urticaria. Chronic urticaria has also been associated with a variety of systemic disorders, including malignancy (e.g., B-cell lymphoma, Hodgkin lymphoma), connective tissue disorders, Schnitzler syndrome, mastocytosis, hyper-eosinophilic syndrome, and Muckle–Wells syndrome.

Diagnosis: In acute urticaria laboratory studies generally are not indicated. In chronic or recurrent urticaria basic laboratory studies should include complete blood count (CBC), erythrocyte sedimentation rate (ESR), thyroid-stimulating hormone (TSH), and antinuclear antibody. If urticarial vasculitis is suspected, a punch biopsy of the lesion should be done.

Management: The mainstay is avoidance of further exposure to the antigen. Acute urticaria may progress to life-threatening angioedema or anaphylactic shock in a very short period of time, though it usually presents as rapid-onset shock with no urticaria or angioedema.

If associated angioedema is present, IM epinephrine should be given and if associated bronchospasm is present, nebulized albuterol should be instructed. Other measures...
include continuous ECG, blood pressure and pulse oximetry monitoring; administering intravenous crystalloids if the patient is hypotensive; and administering oxygen and diphenhydramine or hydroxyzine, if available.

Pharmacologic treatment options include: antihistamines, primarily those that block H1 receptors, H2 antihistamines, (such as cimetidine, famotidine, and ranitidine), used in combination with H1 antihistamines, doxepin, glucocorticoids, methotrexate, colchicine, dapsone, indomethacin, and hydroxychloroquine (for vasculitic urticaria). Patients with chronic or recurrent urticaria should be referred to a dermatologist for further evaluation and management.

**Rupatadine**

Rupatadine (RU) is a potent second-generation antihistamine that has been shown to possess a number of anti-inflammatory properties. It is a powerful antihistamine that, in addition, has been shown to be a potent inhibitor of PAF-receptors. Pharmacokinetic studies have shown that it is rapidly absorbed with a tmax of 45–60 minutes, and this has been confirmed in clinical studies. A plot of rupatadine plasma concentration versus flare inhibition highlights a hysteresis loop-like response, with the highest plasma concentration observed after 5 hours, but sustained inhibition of the flare reaction being prolonged and still clinically significant after 72 hours. This indicates that rupatadine penetrates and resides within the tissues, and explains its long duration of action, facilitating once-daily administration.

**Background:** A wide range of non-sedating second-generation antihistamines are currently available including drugs such as cetirizine, desloratidine, ebastine, fexofenadine, levocetirizine, loratadine, mizolastine, and rupatadine. The one property that they have in common is that they all act at the H1-receptor. But histamine is clearly not the only mediator involved in the inflammatory process and there is an emerging view that drugs which can inhibit a broader range of inflammatory agents may prove to be more effective in providing symptomatic relief in allergic disorders. Interestingly, some antihistamines have displayed marginal PAF-antagonistic properties; activity that cannot be attributed to specific interaction with PAF receptors. Rupatadine appears to be novel in this regard since it specifically inhibits PAF receptor. Furthermore, rupatadine has demonstrated anti-inflammatory effects through inhibition of mast cell degranulation (mediated by various immunologic and nonimmunologic stimuli), and inhibition of eosinophil and neutrophil chemotaxis, cytokine (IL-5, IL-6, IL-8, GM-CSF, and TNF-α) production, and neutrophil adhesion molecule (CD 11b and CD 18) expression.

**Clinical Evidence:** In Latin America, a large Phase IV randomized, double-blind, placebo-controlled, 12-week clinical trial was undertaken to compare the efficacy and tolerability of rupatadine 10 mg once daily with cetirizine 10 mg once daily in more than 500 patients with confirmed persistent allergic rhinitis (PER) according to Allergic Rhinitis and its Impact of Asthma (ARIA) criteria. The main results from the trial shows that in case of total symptom score (TSS), for 6 symptoms both rupatadine and cetirizine significantly reduced TSS at 4 and 8 weeks compared with baseline values, but only rupatadine produced a statistically
significant improvement at 12 weeks \(P = 0.008\). Clinical trials in patients with seasonal allergic rhinitis, perennial rhinitis, persistent rhinitis, and chronic urticaria have shown that rupatadine is at least as effective as drugs such as loratadine, cetirizine, desloratadine, and ebastine. In these trials it was very well tolerated and, importantly, it demonstrated no untoward cardiovascular, cognitive, or psychomotor effects. Recently, a 1-year study involving rupatadine 10 mg once daily in patients with PER has been published. This was an open-label Phase IV safety trial involving 324 patients followed for 6 months and 120 patients who continued treatment for 12 months. Compliance with treatment was very high in this trial; 89.6% at 6 months and 83.3% at 12 months. These data indicate a high level of satisfaction, and presumably perceived benefit, by patients taking rupatadine. Overall, the tolerability of Rupatadine was very good and the most frequent adverse effects were dry mouth, headache, and somnolence and, interestingly, all 3 adverse effects were decreased at 1-year compared with the incidence at 6 months: 0.83 versus 2.2%, 0.83 versus 6.5%, and 5.8 versus 7.7%, respectively. Another important finding in this trial was the lack of abnormal ECG findings over the 12-month study period, suggesting a lack of cardiotoxicity. It has no interactions with azithromycin, fluoxetine and lorazepam, though co-administration with erythromycin, ketoconazole or grapefruit should be avoided. These findings have clearly demonstrated the positive benefit that rupatadine has on patient well-being.

**Faster Onset of Action:** From the patient’s perspective, rapid relief of nasal symptoms and the return to their usual lifestyle would be an important attribute for any drug used to treat allergic rhinitis. In this regard, rupatadine has been reported to have a fast onset of action in patients with seasonal rhinitis, perennial rhinitis, PER, and chronic urticaria. The efficacy and safety of once-daily rupatadine in the management of allergic rhinitis in adolescents and adults (aged 12–65 years) has been investigated in a broad range of controlled trials. Results from the dose-ranging trials found the 10 mg once-daily dosage to be optimal in terms of balancing clinical efficacy and safety/tolerability. In an experimental model using the Vienna Challenge Chamber, rupatadine 10 mg once daily significantly reduced total nasal symptom scores compared with placebo within 15 minutes of allergen exposure. This rapid response compared favorably with results achieved with other antihistamines such as loratadine and levocetrizine that had previously been tested in Fig : 2.4.

**Safety Profile:** Clinical study confirmed the good long-term safety profile of RU. The study demonstrated that RU, at even 10 times the therapeutic dose, does not have any pro-arrhythmic side effects. The ECG data for RU at both 10 and 100 mg did not reveal any effect. There was no gender effect, pharmacodynamic relation of RU and its main metabolites, or imbalance in the outliers, which also confirms the lack of any effect of RU specifically on QTc duration. As regards CNS side effects, RU behaves similarly to second generation anti-histamines, and is non-sedative. Rupatadine does not affect driving performance. It has a good safety profile devoid of arrhythmogenic effects, and it has been safely administered for over one year.

**Conclusion:** Rupatadine a once-daily non-sedative, selective, long acting H1 antihistamine with antagonistic PAF effects through its interaction with specific receptors. It has faster onset and long duration of action, is as effective as other antihistamines, has good tolerability and long term safety profile. These properties make RU a suitable first-line antihistamine for the treatment of AR.

**References**
1. Allergy Asthma & Clinical Immunology, 2011;7(Suppl):S3
3. Primary Care Respiratory Journal, 2009;18(2): 57-68
4. Immunology of Allergy Clinics of North America, 2015;35: 199-219
6. Allergy, 2008;63(suppl.87):5-28
Newer Insights of COPD Management
The current epidemic of chronic obstructive pulmonary disease (COPD) has produced a worldwide health care burden. The primary physiological abnormality in COPD is an accelerated decline in the forced expiratory volume in one second (FEV₁) from the normal rate in adults over 30 years of age of approximately 30 ml per year to nearly 60 ml per year. Prevalence, morbidity, and mortality vary across countries, but in all regions, COPD is a significant public health problem in both men and women. According to World Health Organization estimation, 65 million people have moderate to severe COPD. In the United Kingdom COPD affects 6% of men and 4% of women aged over 45. This is now the fourth leading cause of death in the United States and it is the only common cause of death that is increasing in incidence. On the other hand, the burden of COPD in Asia is correspondingly greater than that in developed Western countries linked to the epidemic of tobacco exposure and indoor and outdoor air pollution. In India, prevalence rates of COPD vary from 2 to 22% in men. As smoking is highly prevalent specially in male in Bangladesh, the COPD as the cause of death should be taken cautiously with high priority.

**Pathophysiology**

Once COPD has been diagnosed, effective management should be based on an individualized assessment of current symptoms and future risks. An effective COPD management plan includes the assessing and monitoring of the disease, reducing risk factors, and management in stable and exacerbation situations.

**Non-Pharmacologic Treatment:** Abstinence from smoking results in a sustained 50% reduction in the rate of lung-function decline in patients with COPD, and smoking cessation is the only intervention known to be so effective in modifying the disease. Physical activity is reduced in patients with chronic obstructive pulmonary disease from Global Initiative for Chronic Obstructive Lung Disease stage II. Clinical characteristics of patients with COPD only incompletely reflect their physical activity. Influenza vaccination reduces serious illness and death in COPD patients by approximately 50%. Most mortalities from influenza result from secondary bacterial pneumonia, which leads to respiratory failure. Immunization should be performed once in autumn of each year or twice autumn/winter. Conversely, since 1997 the Advisory Committee on Immunisation Practices has recommended the vaccination in COPD patients, particularly those over 64 [Evidence B (Randomized controlled trials. Limited body of data)].

**Pharmacologic Treatment:** The Pharmacotherapy for stable COPD according to Global Initiative for chronic Obstructive Lung Disease (GOLD) guideline has given in Table : 3.1 and the Gold therapy at each stage of COPD (Stage I: Mild; Stage II: Moderate; Stage III: Severe; Stage IV: Very Severe) are given in Fig : 3.2.

**Inflammatory Mechanisms in COPD**

Cigarette smoke and other environmental noxious agents activates macrophages and epithelial cells to release chemotactic factors that recruit neutrophils and CD8 cells from the circulation. These cells release factors that activate fibroblasts, resulting in abnormal repair processes and bronchiolar fibrosis. An imbalance between proteases released from neutrophils and macrophages and antiproteases leads to alveolar wall destruction (emphysema). Proteases also cause the release of mucus. An increased oxidant burden, resulting from smoke inhalation or release of oxidants from inflammatory leucocytes, causes epithelial and other cells to release chemotactic factors, inactivate antiproteases, and directly injure alveolar walls and cause mucous secretion.
Indacaterol Maleate: Best Ever Option in Treating COPD

Modern therapies recommend various treatment options for treating COPD. But Long-acting β-adrenoceptor agonists (LABA) remains the mainstay of treating COPD. Use of dual therapy with a Long Acting Muscarinic Activator (LAMA) and LABA may be considered if an inhaled corticosteroid (as part of combination therapy with a LABA) is declined or not tolerated.

Indacaterol is the first true “Ultra-LABA” which is used for optimized COPD treatment outcome approved by US FDA. Because of the clinically insignificant differences in efficacy between indacaterol 75 mcg and the higher doses studied, and because of the increased frequency of serious adverse effects compared with placebo, the FDA approved only the 75-mcg dose for marketing in the U.S. In clinical trials, patients treated with indacaterol used less daily rescue salbutamol during the trial compared to patients treated with placebo. This reduces the risk of COPD exacerbations over 6 months of treatment.

Mechanism of Action: Indacaterol when inhaled acts locally in the lung as a bronchodilator. This is a nearly full agonist at the human β₂ adrenergic receptor with nanomolar potency. In isolated human bronchus, indacaterol has a rapid onset and long duration of action. The pharmacological effect of this is at least in part attributable to stimulation of intracellular adenylyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3, 5-adenosine monophosphate (cyclic monophosphate). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle.

In vitro studies have shown that indacaterol has more than 24-fold greater potency at β₂ receptors compared to β₃ receptors.

Indication and Clinical Use: Indacaterol maleate is a long acting β₂ agonist indicated for long-term, once-daily, maintenance bronchodilator treatment of airflow obstruction in patients with COPD including chronic bronchitis and emphysema. This is to be noted that this is not indicated for the relief of acute deterioration of COPD and asthma.

Dosage and Administration: This capsules must not be swallowed as the intended effects on the lungs will not be obtained. The contents of this capsules are only for oral
inhalation and should only be used with the inhaler device. This should be administered once daily every day at the same time of the day by the orally inhaled route only. If a dose is missed, the next dose should be taken as soon as it is remembered. This should not be used more than one time every 24 hours.

No dosage adjustment is required for geriatric patients, patients with mild and moderate hepatic impairment, or renally impaired patients. This is not indicated for use in pediatric population.

**Contraindications**: All LABAs are contraindicated in patients with asthma without use of a long-term control medication. This is contraindicated in patients with a history of hypersensitivity to indacaterol or to any of the ingredients.

**Side Effects**: The most commonly reported adverse effects are cough, nasopharyngitis, headache, nausea, oropharyngeal pain. Some other also reported side effects include hypersensitivity reactions, paradoxical bronchospasm, tachycardia, pruritus and dizziness.

**Use in Special Populations**:
- Pregnancy and Lactation- Pregnancy Category C. As there are no adequate and well-controlled studies in pregnant women, this should be used during pregnancy only if the expected benefit justifies the potential risk to the fetus.
- Pediatrics (less than 18 years of age)- This should not be used in patients under 18 years of age because the safety and effectiveness of this capsule under the age of 18 years have not been established.

---

### Table: 3.1 Pharmacologic Therapy for Stable COPD* According to COPD GOLD (Global Initiative for Chronic Obstructive Lung Disease) 2015 Guideline

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>Recommended First Choice</th>
<th>Alternative Choice</th>
<th>Other Possible Treatments**</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Low Risk, Less Symptoms)</td>
<td>SA anticholinergic prn</td>
<td>LA anticholinergic</td>
<td>Theophylline</td>
</tr>
<tr>
<td></td>
<td>or SA β₂-agonist prn</td>
<td>or LA β₂-agonist</td>
<td></td>
</tr>
<tr>
<td>(Low Risk, More Symptoms)</td>
<td>LA anticholinergic or</td>
<td>LA anticholinergic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LA β₂-agonist</td>
<td>or LA β₂-agonist</td>
<td></td>
</tr>
<tr>
<td>(High Risk, Less Symptoms)</td>
<td>ICS+ LA β₂-agonist or</td>
<td>LA anticholinergic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LA anticholinergic</td>
<td>and LA β₂-agonist</td>
<td></td>
</tr>
<tr>
<td>(High Risk, More Symptoms)</td>
<td>ICS+ LA β₂-agonist and/or</td>
<td>ICS+ LA β₂-agonist</td>
<td>Carboxyline</td>
</tr>
<tr>
<td></td>
<td>LA anticholinergic</td>
<td>or LA anticholinergic</td>
<td></td>
</tr>
</tbody>
</table>

*Medications in each box are mentioned in alphabetical order and therefore not necessarily in order of preference.

**Medications in this column can be used alone or in combination with other options in the First and Alternative Choice columns.

**Glossary**: SA: short-acting; LA: long-acting; ICS: inhaled corticosteroid; PDE-4: phosphodiesterase-4; prn: when necessary.
Warning and Precautions: Long acting $\beta_2$ agonists increase the risk of asthma related death. Data from a large placebo controlled US study that compared the safety of another LABA (salmeterol) or placebo added to patient’s usual asthma therapy showed an increase in asthma related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of LABA, including indacaterol maleate. Finally, this may be stated that indacaterol maleate capsule is only indicated for COPD. The safety and effectiveness in patients with asthma have not been established.

Indacaterol showed a statistically significant improvement in lung function in people with moderate to very severe COPD. This is recommended that the choice of drug treatment should take into account the person’s symptomatic response and preference, and the drug’s potential to reduce exacerbations, side effects and costs.

References
1. The Journal of Clinical Investigation, 2012;122(2):2749-2755
3. The New England Journal of Medicine, 2000;343:269-280
7. British Medical Journal, 2006;332:1202-1204
The New Panorama in Treating Stable COPD:

Inhaled bronchodilators are the mainstay of the current management of chronic obstructive pulmonary disease (COPD). Only for subjects that can be classified as group A patients according to the last GOLD classification of severity (with few symptoms and a low risk of exacerbations), a short-acting bronchodilator is recommended as first choice. For all other COPD patients long-acting formulations are preferred over short-acting formulations. Two classes of long-acting inhaled bronchodilators are available—long-acting β₂-agonists (LABAs) and long-acting muscarinic antagonists (LAMAs). Long-acting β₂-agonists directly induce bronchodilation by relaxing airway smooth muscle through stimulation of β₂-adrenoceptors, whereas LAMAs prevent acetylcholine-induced bronchoconstriction by acting as competitive antagonists on muscarinic receptors.

Because of the central role of long-acting bronchodilators in the treatment of COPD, in recent years there has been a renewed interest in the field and now once-daily (OD) bronchodilators are in development in an attempt to simplify the management of COPD patients. In effect, an important step in simplifying COPD management and improving adherence with prescribed therapy is to reduce the dose frequency. Therefore, the incorporation of OD dosing is an important strategy to improve compliance, and is a regime preferred by most patients. Indacaterol is the first ultra-LABA approved that has a 24-hour bronchodilator effect, allowing for OD administration.

Indacaterol (Onriva)

Key points:
- Once-daily dosing provides symptomatic relief in COPD
- Indacaterol (Onriva Bexiaca) once daily provides rapid-onset bronchodilation in COPD lasting over 24 hours
- Indacaterol has safety and symptom relief properties similar to that of twice-daily long-acting β₂-agonist bronchodilators.
- Indacaterol provides similar symptomatic improvement and greater improvement in lung function compared with Salmeterol and Formoterol in COPD.
- Indacaterol is no worse than Tiotropium in safety and efficacy.
- Indacaterol has been demonstrated to be non-inferior in safety and efficacy (forced expiratory volume in 1 second [FEV₁] and symptom reduction) to once-daily Tiotropium.
- Avoid indacaterol in people with asthma.
- As with other inhaled long-acting β₂-agonists, Indacaterol may result in paradoxical bronchospasm; do not use to treat acute episodes of bronchospasm, acutely deteriorating COPD, or asthma.
- Use with caution in people with cardiovascular disease.
- Use with caution in people with cardiovascular disorders and in people who are unusually responsive to β₂-agonists.

**Characteristics of indacaterol**

<table>
<thead>
<tr>
<th>Type of Drug</th>
<th>Full β₂-Agonist</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset of action</td>
<td>3±0.2 min</td>
</tr>
<tr>
<td>Duration of action</td>
<td>&gt;24 h</td>
</tr>
<tr>
<td>Half-life</td>
<td>48 h</td>
</tr>
<tr>
<td>Maximum plasma concentration</td>
<td>30-60 min</td>
</tr>
<tr>
<td>Most Probable dose</td>
<td>150-300 μg/24 h</td>
</tr>
<tr>
<td>Tachyphylaxis</td>
<td>Not seen</td>
</tr>
</tbody>
</table>

**Safety of indacaterol**

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
<td>12.4-28.4%</td>
</tr>
<tr>
<td>Increase in HR</td>
<td>&lt;15 bpm (median 3 bpm)</td>
</tr>
<tr>
<td>QT prolongation</td>
<td>&gt;60 ms</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>Same as placebo</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>Same as placebo</td>
</tr>
</tbody>
</table>

Adverse effects are comparable with placebo in the majority of studies. Abbreviations: bpm, beats per minute; HR, heart rate.

Before prescribing, please review the product information available at www.BeximcoPharma.com

SOFOSBUVIR
A Milestone in HCV Treatment
Chronic hepatitis C virus (HCV) infection is a cause of chronic hepatitis, cirrhosis and hepatocellular carcinoma. This is estimated that up to 170-200 million people (i.e. 3% of the world population) are chronically infected with hepatitis C virus. For the past two decades, interferon-based therapy has been the cornerstone of HCV treatment, but success has been limited by poor tolerability and suboptimal sustained virological response (SVR) rates, even when combined with ribavirin. However, treatment of chronic hepatitis C has undergone a significant change. In 2013, the US Food and Drug Administration (US FDA) has approved the first-in-kind nucleotide analog inhibitor sofosbuvir for the treatment of adults with chronic hepatitis C virus infection, a widely anticipated move that is expected to dramatically improved outcomes for many patients. In 2014, the European Union similarly has approved sofosbuvir as a new oral treatment for chronic hepatitis C (CHC) in adults. So, this has the clinical potential in the treatment of HCV and then the interferon-free, once-daily treatment of HCV is now becoming a reality.

**Indication**

Sofosbuvir is indicated for the treatment of chronic hepatitis C (CHC) infection as a component of a combination antiviral treatment regimen. Sofosbuvir efficacy has been established in subjects with HCV genotype 1, 2, 3 or 4 infection, including those with hepatocellular carcinoma meeting Milan criteria (awaiting liver transplantation) and those with HCV/HIV-1 co-infection.

**Pharmacology**

**Mechanism of Action**: Nucleotide prodrug that undergoes metabolism to the active uridine analog triphosphate, an inhibitor of HCV NS5B RNA-dependent polymerase; its inhibition in turn suppresses viral replication.

**Pharmacokinetics**:

- **Absorption**:  
  - Peak plasma time: 0.5-2 hr (sofosbuvir); 2-4 hr (metabolite GS-331007).
  - Area under curve (AUC) when co-administered with ribavirin (with or without peg-interferon): 828 ng•hr/mL (sofosbuvir); 6790 ng•hr/mL (metabolite GS-331007).

- **Distribution**:  
  - Plasma bound: 61-65% (sofosbuvir); minimal for metabolite GS-331007.

- **Metabolism**:  
  - Liver

- **Substrate**: P-gp transporter and breast cancer resistance protein (substrate for sofosbuvir but not metabolite GS-331007).

- **Elimination**:  
  - Excretion: Urine (78% metabolite GS-331007; 3.5% sofosbuvir).
  - Half-life: 0.4 hr (sofosbuvir); 27 hr (metabolite GS-331007).

**Dosage and Administration**

The recommended dose of sofosbuvir is one 400 mg tablet, taken orally, once daily with or without food in the morning. Sofosbuvir should be used in combination with ribavirin or in combination with pegylated interferon and ribavirin for the treatment of CHC in adults. The recommended regimen and treatment duration for sofosbuvir combination therapy is provided in table.

**Contraindication**

When sofosbuvir is used in combination with ribavirin or peginterferon α / ribavirin, the contraindications applicable to those agents are applicable to combination therapies. Sofosbuvir combination treatment with ribavirin or peginterferon α / ribavirin is contraindicated in women who are pregnant or may become pregnant and men whose female partners are pregnant.

**Adverse Reactions**

The most common adverse events (≥20%) for sofosbuvir, peginterferon a and ribavirin combination therapy were fatigue, headache, nausea, insomnia and anemia.
Table: 4.1 The Recommended Regimens and Treatment Duration for Sofosbuvir Combination Therapy in HCV Mono-infected and HCV/HIV-1 Co-infected Patients

<table>
<thead>
<tr>
<th>Patients with genotype 1 or 4 CHC</th>
<th>Treatment</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sofosbuvir + Peginterferon α + Ribavirin</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Patients with genotype 2 CHC</td>
<td>Sofosbuvir + Ribavirin</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Patients with genotype 3 CHC</td>
<td>Sofosbuvir + Ribavirin</td>
<td>24 weeks</td>
</tr>
</tbody>
</table>

Dose of ribavirin is weight-based (<75 kg = 1000 mg and ≥75 kg = 1200 mg). The daily dose of ribavirin is administered orally in two divided doses with food. Patients renal impairment (CrCl<50 mL/min) require ribavirin dose reduction.

Less common adverse reactions reported in clinical trials (<1%): Hematologic effects- Pancytopenia, particularly in subjects receiving concomitant pegylated interferon; Psychiatric disorders- Severe depression (particularly in subjects with pre-existing history of psychiatric illness), including suicidal ideation and suicide.

Geriatric Use: Sofosbuvir was administered to 90 subjects aged 65 and over. The response rates observed for subjects over 65 years of age were similar to that of younger subjects across treatment groups. No dose adjustment of sofosbuvir is warranted in geriatric patients.

Warning and Precautions

Bradycardia with Amiodarone Co-administration: Serious symptomatic bradycardia may occur in patients taking amiodarone and sofosbuvir in combination with another direct acting antiviral (DAA), particularly in patients also receiving β blockers, or those with underlying cardiac comorbidities and/or advanced liver disease. Co-administration of amiodarone with sofosbuvir in combination with another DAA is not recommended. In patients without alternative, viable treatment options, cardiac monitoring is recommended.

Use in Pregnancy: Pregnancy Category B: Sofosbuvir has been assigned as pregnancy category B by the FDA. But there is no well-controlled studies with sofosbuvir in pregnant women. Ribavirin may cause birth defects and/or death of the exposed fetus, and animal studies have shown that interferons have abortifacient effect. Extreme care must be taken to avoid pregnancy in female patients and female partners of male patients while taking sofosbuvir with any of this combination.

Nursing Mothers: It is not known whether sofosbuvir and its metabolites are present in human breast milk.

Pediatric Use: Safety and Effectiveness of sofosbuvir in children less than 18 years of age have not been established.

Drug Interaction

Drugs that are potent intestinal P-gp inducers (e.g., rifampin, St John’s wort) may alter the concentration of sofosbuvir.

Overdose

The highest dose of sofosbuvir is a single dose of sofosbuvir 1200 mg. No specific antidote is available for overdose treatment. Treatment of overdose with sofosbuvir consists of general supportive measures including monitoring of vital signs as well as observation of the clinical status of the patient.

Conclusion

This may be accomplished that the approval of sofosbuvir represents the first key step towards the new era in the management of CHC patients, since it is the first approved DAA with potent activity and high genetic barrier against all HCV genotypes. In addition, its safety profile is excellent, even when it is given in patients with very advanced liver disease and high risk of complications. Therefore, it is likely that sofosbuvir is now the backbone of this treatment approach.

References

1. Therapeutic Advances in Gastroenterology, 2014;7(3):131-140
4. www.nature.com
Healthy Heart Choices for Everyone, Everywhere

World Heart Day takes place on 29 September every year and is a chance for people across the globe to take part in the world’s biggest intervention against cardiovascular disease (CVD). This World Heart Day, the focus is on creating heart-healthy environments. By ensuring that people are able to make heart-healthy choices wherever they live, work and play, World Heart Day encourages us all to reduce our cardiovascular risk, and promotes a heart-healthy planet for those around us. Cardiovascular disease is currently responsible for 17.3 million deaths per year, and by 2030 this figure is expected to rise to 23 million. But most CVD can be prevented by addressing risk factors, such as tobacco use, unhealthy diet and physical inactivity. This year World Heart Day is dedicated to exposing how much our environments can impact and increase CVD risk factors. Too often, society “blames” the individual’s lifestyle choices for his or her CVD. But the environments in which we live, work and play can have a huge effect on our ability to make the right choices for our heart-health. Everyone has the right to make heart-healthy choices wherever they live, work and play.

What Families Can Do for a Heart Healthy Lifestyle of Children

- Eat 5 fruits and vegetables per day
- Eat breakfast daily
- Regularly eat family meals together and prepare foods at home as a family
- Limit screen time to less than 2 hours a day, including computer time and video games
- Get 1 hour of physical activity a day
- Eat a high fiber diet
- Eat a diet rich in calcium and switch to low-fat dairy products
- Limit consumption of sugar-sweetened beverages
- Limit fast food, take out, and eating out
- Breastfeed exclusively until 6 months and maintain breastfeeding after introduction of solid food until 12 months of age

Source: American Academy of Pediatrics
A steady stream of clinical trial data proceeded to establish the safety and efficacy of cholesterol reduction using statins.
Cardiovascular disease is the leading cause of death and disability in the world and contributes substantially to health care budgets. After more than 25 years in clinical use, statins have transformed the field of lipid management and cardiovascular risk reduction. Due to their proven efficacy and safety, they have become first-line therapy for individuals who are unable to manage their dyslipidemia through lifestyle changes alone.

The Norwegian physician Carl Müller was one of the first to observe the association between lipids and coronary disease in the 1930s.

Initiated in 1948, the Framingham Heart Study identified elevated total cholesterol, LDL-cholesterol, high blood pressure and cigarette smoking as major risk factors, while HDL-cholesterol was seen to be protective against heart disease. In addition to the major risk factors identified in the Framingham and Seven Countries studies, data indicate that measures of non-HDL-cholesterol and apoB, which is present in all of the pro-atherogenic lipid fractions, are also highly associated with cardiovascular risk.

In the 1950s, John Gofman characterized the lipoproteins based on their rate of flotation in the ultracentrifuge, and generated preliminary evidence suggesting that higher levels of VLDL and especially LDL were associated with increased risk for coronary heart disease (CHD), while higher levels of HDL appeared to have a protective effect.

The introduction of statins has also played an important role in the decline in cardiovascular mortality rates observed in the USA since 1970.

A major advance in the confirmation of the lipid hypothesis occurred in 1973, with the discovery of the LDL receptor by Michael Brown and Joseph Goldstein. These investigators described the role of the LDL receptor in maintaining cholesterol homeostasis.

Another breakthrough was the isolation of a competitive inhibitor of 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMG-CoA reductase) from the fungus Penicillium citrinum. This substance, called compactin or mevastatin, was the first statin to be administered to humans, although its development was soon terminated for unknown reasons. The first statin to be approved in the US was lovastatin in 1987.

By preventing the development of atherosclerotic cardiovascular disease and by reducing the risk of a future event in those with a clinical diagnosis, statins have had an enormous public health impact. Between 1988 and 2010, average LDL-cholesterol levels fell from 129 to 116 mg/dl in the USA, and HDL-cholesterol increased from 50.7 to 52.5 mg/dl. The release of new recommendations for cholesterol management from the American College of Cardiology (ACC) and the American Heart Association (AHA) generated considerable controversy among lipid experts and indicates that there are widely divergent views on the optimum strategy for treatment with statins.

**Statin in Dyslipidemia**

A steady stream of clinical trial data proceeded to establish the safety and efficacy of cholesterol reduction using statins. The first major study to demonstrate that lowering cholesterol could increase the probability of survival was the Scandinavian Simvastatin Survival Study, a secondary prevention study of 4444 patients with existing CHD and a mean cholesterol level of 272 mg/dl. Treatment with simvastatin reduced LDL-cholesterol by 38%, and it decreased coronary events by 34% and total mortality by 30%.
The first primary prevention study with statins was the West of Scotland Coronary Prevention Study (WOSCOPS) with pravastatin, which showed a reduction in coronary events but no significant effect on all-cause mortality. The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) in primary prevention was the first to show cardiovascular benefit when treating individuals at lower risk. Over a 5-year period, treatment with lovastatin reduced the risk for a first acute major coronary event by 37% in individuals with cholesterol levels considered average. Other statin trials confirmed and extended these findings in diverse patient populations, including women and the elderly. Studies with intensive statin therapy also support the view that, with regards to LDL-cholesterol, ‘lower is better’. Based on data from over 170,000 subjects treated with statins in primary and secondary prevention, the Cholesterol Treatment Trialists found a 22% relative reduction in risk for major vascular events and a 10% decrease in all-cause mortality for every 39 mg/dl (1mmol/l) reduction in LDL-cholesterol, with no attenuation of this relationship even at low LDL-cholesterol levels. Additionally, it showed that the risk for each type of major vascular event is reduced with statin treatment, except for a non-significant excess of hemorrhagic stroke.

Currently, there are seven commercially available statins. Lovastatin, pravastatin and simvastatin are fungal derivatives, while atorvastatin, fluvastatin, rosuvastatin and pitavastatin are synthetic compounds. Their primary effect is to reduce LDL-cholesterol by 20–63%, although they can also modestly increase HDL-cholesterol by 5–15% and reduce triglycerides by 10–37%. In addition, they are associated with a high degree of safety and are not associated with an increased incidence of cancer. At the end of 2013, the ACC and the AHA issued new guidelines that emphasize the importance of statin therapy in reducing risk for atherosclerotic cardiovascular disease, which includes CHD, stroke and peripheral arterial disease. The ACC/AHA guidelines incorporate a risk prediction algorithm that includes all of the variables of the ATP III version (age, total cholesterol, HDL-cholesterol, systolic blood pressure, treatment for hypertension and cigarette smoking), in addition to race. The new risk assessment formula is an improvement on the ATP III, which drew on data from the largely male and Caucasian cohort tracked in the Framingham Heart Study.

The ACC/AHA guidelines also depart from the previous version in eliminating specific lipid targets. The authoring committee maintained that randomized clinical trials have not established that ‘lower is better’ since most were fixed-dose trials comparing two statin regimens, rather than titration trials targeting a specific LDL-cholesterol or non-HDL-cholesterol goal. As a result, the guidelines...
recommend that patients be treated either with a high-intensity statin, which can be expected to lower LDL-cholesterol by at least 50%, or a moderate-intensity statin, which typically reduces LDL-cholesterol by 30–50%. Factors such as age, tolerance of side effects and concomitant medications guide the choice between high- or moderate-intensity treatment. In 2014, the National Institute for Health and Care Excellence (NICE) in the UK issued evidence-based guidelines that similarly recommend treatment according to statin intensity, rather than specific lipid targets.

**Statin in Primary Prevention**

A meta-analysis including 70388 participants without established cardiovascular disease but with cardiovascular risk factors who were randomized to statin therapy or control shows that statin therapy was associated with a significant risk reduction in all causes mortality of 12%, in major coronary events of 30%, and in major cerebrovascular events of 19%. Moreover, statin use was not associated with an increased risk of cancer. These results are in line with those previously published on the effects of statins in secondary prevention. Here data were also included from the *Justification for the Use of Statin in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER)* trial. One of the trials *Prospective Study of Pravastatin in the Elderly at Risk* (PROSPER); did report an increased risk of cancer with use of statins among men and women older than 70. Concerns might remain about the higher risk of cancer in elderly patients (70-82 years) as in PROSPER, and further follow-up studies in such patients are required. This meta-analysis also confirms that the risk of cancer is not increased in middle aged patients. Tolerance to statins is also important to tackle in primary prevention. Side effects such as an increase in creatine kinase levels and myopathy have been reported relatively frequently, but rhabdomyolysis and hepatotoxicity are rare. No significant treatment heterogeneity was found between the sexes, in elderly and young people, and between people with and without diabetes.

**Statin and Risk of New Onset Diabetes**

No drug provides health benefits without some degree of risk, and risk–benefit assessments require ongoing review as new data become available. This is certainly the case for the use of statins and the risk of new-onset diabetes. In the JUPITER Trial, involving 17,802 participants without diabetes but with LDL cholesterol levels below 3.4 mmol per liter (130 mg per deciliter) and high sensitivity C-reactive protein levels of 2.0 mg per liter or higher, the hazard ratio for newly diagnosed diabetes was increased 25% in the rosuvastatin group than in the placebo group. Despite the increase in the risk of new-onset diabetes, the participants previously considered to have low cardiovascular risk had clinically important health improvements over a median follow-up period of only 1.9 years, with a hazard rate 44% lower than that of the placebo group for the combined primary end point of myocardial infarction, stroke, arterial revascularization, hospitalization for unstable angina, or death from cardiovascular causes. In addition, rates for the key secondary outcomes were lower in the treated participants- 54% lower for myocardial infarction, 48% for stroke, 46% for revascularization, and 20% for death from any cause.

A meta-analysis of six statin trials that included 57,593 participants revealed a 13% increase in the relative risk of new-onset diabetes. Similarly, another meta-analysis of 13 randomized statin trials with 91,140 participants showed an odds ratio of 1.09 for a new diagnosis of diabetes, so that (on average) treatment of 255 patients with statins for 4 years resulted in one additional case of diabetes. Given that
Statins are used by approximately 24 million Americans, the population-attributable risk is not small, but it must be considered in the context of the simultaneous prevention of 5.4 vascular events among those 255 patients. Statins appear to have a class effect, unrelated to the individual statin, its potency, or its lipophilic or hydrophilic properties. Their effect also appears to be dose-dependent: the odds ratio for new-onset diabetes is 12% higher with intensive-dose therapy than with moderate-dose therapy, although there’s also a 16% greater reduction in the risk of cardiovascular events. Thus, statins may simply be unmasking the disease in people who were likely to develop diabetes soon. Cellular studies have suggested that statins may interfere with β-cell insulin secretion either by decreasing Ca²⁺-dependent insulin secretion or by interfering with isoprenylation of guanosine triphosphate (GTP)–binding proteins. Statin inhibition of isoprenoid biosynthesis may lead to lower expression of insulin signaling proteins in adipocytes and to reduced glucose transporter expression or translocation.

In light of the evidence, the Food and Drug Administration (FDA) recently added information to statin labels regarding an effect of these agents on diabetes, noting that increases in glycosylated hemoglobin (HbA1c) and fasting serum glucose levels have been reported with statin use, but adding that the FDA continues to believe that the cardiovascular benefits of statins outweigh these small increased risks. Given the widespread use of statins, overestimating their clinical benefit or underestimating their risk is of potentially major importance to public health. The clinical trials that defined the diabetes risk have been relatively short-term, yet statin therapy is often continued for years; thus, it’s possible that the risk of diabetes will increase with the duration of follow-up. Although diabetes is a serious health concern, the management of dyslipidemia with statins substantially reduces cardiovascular risk and improves survival; thus, current data do not support the discontinuation of statins when diabetes is diagnosed, and it remains prudent to target lipid levels according to established guidelines. Of course, it also remains important to recommend increased exercise, healthy food choices, and portion control and to help manage weight in patients with pre-diabetes levels of glycemia or metabolic syndrome.

**Conclusion**

Statins effectively reduce the risks of death from cardiovascular disease, fatal myocardial infarction, stroke and many other diseases; and it also reduces the need for revascularization. Over a period of 4 years of statin use, a reduction of 1 mmol per liter (39 mg/dl) in the level of LDL cholesterol translates into a 9% reduction in the risk of death from any cause among patients with diabetes and a 13% reduction among those without diabetes. Benefits are realized within the first year of use but increase over time. Few drugs have had such a dramatic effect on health outcomes.

**References**

1. **British Medical Journal**, 2009;338:b2376
Breast Feeding Reduces Risk of Breast Cancer Recurrence

Women treated for breast cancer who previously breast fed their babies have a 30% lower risk of recurrence than those who did not, a US study has shown. Breast feeding for six months or more was associated with even greater protection from tumor recurrence. The study analyzed information on 1636 women with breast cancer from two prospective breast cancer cohorts. The women each completed a questionnaire that included their history of breast feeding, and their tumor subtype was determined using the PAM50 gene expression assay. Results showed that women who had ever breast fed had a 30% lower risk of recurrence than women who had not (hazard ratio 0.70 [95% confidence interval 0.53 to 0.93]), and an even lower risk was found in those who had breast fed for six months or longer (0.63 [0.46 to 0.87]; \( P_{\text{trend}} = 0.01 \)). Similar associations were seen in breast cancer deaths. Gene expression analysis showed that women with basal-like tumors (high grade, triple negative tumors) were less likely to have previously breast fed than those with luminal A tumors (odds ratio 0.56 [95% confidence interval 0.39 to 0.80]). Luminal A tumors include estrogen receptor positive tumors and are the most commonly diagnosed breast cancers. They are less likely to metastasize, are treatable with hormonal therapy such as tamoxifen, and generally have better outcomes. Breast feeding was associated with reduced recurrence (hazard ratio 0.52 [0.31 to 0.89]) and death (0.52 [0.29 to 0.93]) from breast cancer in women with luminal A tumors but not other subtypes.

Source: British Medical Journal, 2015;350:h2325

Maternal Obesity Increases Type 1 Diabetes Risk in Offspring

A nationwide cohort study of more than 1.2 million children in Sweden shows overweight and obesity among women increases the risk of type 1 diabetes in their offspring even when neither parent has diabetes. The prevalence of type 1 diabetes is increasing in most countries. The researchers followed a cohort of 12,63,358 children born in Sweden between 1992 and 2004. They tracked individual linked records for each child from the date of their birth until a diagnosis of type 1 diabetes, emigration, death, or the end of the follow-up period in 2009. Information for each child was compared with data on their mother’s body mass index (BMI) during the first trimester of the pregnancy that resulted in each child’s birth. Type 1 diabetes was diagnosed in 5771 of the children during the study period. Among children of parents who didn’t have diabetes, having a mother who was obese during pregnancy (BMI ≥ 30) was associated with an increase in risk of developing type 1 diabetes of a third, when compared with children of mothers whose BMI was in the normal range (incident rate ratio 1.31 [95% confidence interval 1.20 to 3.40]; \( P \) for trend 0.0005). Further analysis showed that this increased risk was found only in children of parents without diabetes. The risk of a child developing type 1 diabetes was greatly increased if the mother (incidence rate ratio 3.17 [2.80 to 3.58]) or father (incidence rate ratio 5.27 [4.74 to 5.86]) had type 1 or type 2 diabetes, but this risk did not increase further with maternal obesity in pregnancy.

This nationwide cohort study demonstrates that paternal and maternal diabetes and first trimester maternal obesity are associated with increased risks of type 1 diabetes in the offspring, said the researchers. They concluded that prevention of overweight and obesity in women of reproductive age may contribute to a decreased incidence of type 1 diabetes.

Source: British Medical Journal, 2015;350:h2252
We are now
US FDA approved

The US Food and Drug Administration (US FDA) conducted the inspection of Beximco Pharma’s oral solid dosage facility at Tongi, during January 19-22, 2015. Establishment Inspection Report (EIR) from the US FDA was issued on 16 June 2015 stating that audit was formally concluded. There was no 483 observation issued by the US regulatory authority. A 483 form is issued when FDA has observations of non-compliance or deviation from Good Manufacturing Practices (GMP). This means that your patients are on the safer side when you trust a Beximco Pharma medicine for them.