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Review Article

Status of Research in the Field of Chemotherapy for Infectious Diseases in the Last 5 Years

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The Indian National Science Academy has published two Status Reports on Pharmacological Research (1984 & 2000). The International Council for Science (*ICSU*) National Committee for Pharmacology has commissioned the third status report on Pharmacological Research in India covering the last 5 years. This report covers research done in chemotherapy of infectious diseases barring tropical diseases. The areas covered in chemotherapy included drug-discovery, observational studies, pharmacokinetics-pharmacodynamics and safety studies. We largely relied on Pubmed for our search. Work conducted in India and where at least one of the authors was affiliated to the Department of Pharmacology was included. Salient features of the studies were summarized. Lacunae in the current scene of research were explored and way forward suggested.

Keywords: Infections; Research; Status; Antimicrobials

Introduction

The story of chemotherapy for infectious diseases is as interesting as the evolution of the concept of various kinds of microorganisms, invisible to the naked eye, causing diseases. Paul Ehrlich and Alexander Fleming are associated with modern history of antimicrobials (Aminov, 2010). Paul Ehrlich conceptualized the idea of *magic bullets* which would selectively kill pathogens without affecting host cells. The concept was based on his observations made on aniline and other synthetic dyes. He began his quest for magic bullets by screening compounds which could target syphilis. The sixth compound in the six hundredth series, compound 606, was salvarsan, the first antimicrobial against *Treponema pallidum*, developed through a process very similar to modern day screening procedures. This was in 1909. Close on its heels came prontosil, sulfonamidochrysoidine.

While the discovery of the above two categories of antimicrobials was through a systematic process, penicillin discovery was rather serendipitous. Interestingly, Fleming in his far reaching oversight had cautioned against the dangers of development of resistance due to improper and excessive use of antimicrobials - "*The time may come when penicillin can be bought by anyone in the shops. Then there is the danger that the ignorant man may easily underdose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant*." (Fleming, 1945) Antimicrobial resistance has been an issue of concern since then. While the issue of rising incidence of resistance to first line agents for *Mycobacterium tuberculosis* predominated much of previous decade, resistance in other bacteria presents additional serious concerns of the present times. The need for newer antimicrobials is more evident now than ever before. While chemotherapeutic agents targeting bacteria were chased with waxing and waning vigour, diseases due to viruses and fungi started occupying the seats of attention.

While idoxuridine (Bauer, 1985), the first antiviral agent used to manage herpetic keratitis, made humble beginnings, some of the newer antiviral agents represent billion dollar markets (Gohil, 2014).

Rising use of antibacterials and

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immunosuppressants brought along an increase in fungal infections. We now have an armamentarium of antifungals to choose from. However, development of resistance is posing increasingly familiar problems.

The aspects of chemotherapeutic agents for treating infections which needed to be researched went beyond discovery. The concept of pharmacokinetics-pharmacodynamics (PK-PD) and population pharmacokinetics (Pop-Pk) were recognized as extremely important not only for effective cure of infections but also for prevention of resistance (Riggs, 1997). Rational use of antimicrobials has needed constant oversight since antimicrobial use is directly correlated with the development of resistance. Safety has remained a concern since sulfinalimide elixir tragedy, wherein a new raspberry flavoured formulation of the antibiotic sulfanilamide led to the death of several children (Ballentine, 1981). Consequently, antimicrobial stewardship is now recognized as the need of the hour (Shafiq, 2016; Infectious Diseases Society of America, 2015; Doron and Davidson, 2011; Shafiq *et al*., 2017)

The Indian National Science Academy has published two Status Reports on Pharmacological Research (1984 & 2000). The International Council for Science (*ICSU*) National Committee for Pharmacology has commissioned the third status report on Pharmacological Research in India covering the last 5 years. The current report covers research done in the area of chemotherapy (excluding tropical diseases) in India.

Methodology

We basically followed methodology described previously (Shafiq and Malhotra, INSA report on research in Clinical Pharmacology, 3017, *In press*). Briefly, we used various combinations of search terms to minimize redundancy and maximize the number of studies included as per the inclusion criteria. Various domains that were searched included – discovery; epidemiological studies such as drug utilization, questionnaire-based studies, studies answering practice related questions, pharmacoeconomics, pharmacogenomics; pharmacokinetics and/or pharmacokinetics-dynamics; safety/toxicity. The main source of information was PubMed. We used a filter of time limit of five years. In PubMed, use of this filter yielded articles from the year 2012 till the current date. Search terms were varied to include "*antimicrobials*", "*antivirals*", "*antifungals*" and "*antituberculosis*" and "*pharmacology*" and "*India*". In addition, a search was made keeping in mind some articles which may have appeared by the name of the disease, for example, "*enteric fever*", "*pneumonia*", "*tuberculosis*", were used. Only 5 more articles satisfying inclusion criteria could be added to the initial search when searches were made with specific infections. Each of the search terms were combined with Pharmacology and India. Studies wherein the affiliations of at least one author to Pharmacology Department was reported were included. For excluding tropical diseases we used the WHO definition - "*Tropical diseases encompass all diseases that occur solely, or principally, in the tropics. In practice, the term is often taken to refer to infectious diseases that thrive in hot, humid conditions, such as malaria, leishmaniasis, schistosomiasis, onchocerciasis, lymphatic filariasis, Chagas disease, African trypanosomiasis, and dengue*." (Tropical Diseases, 2017). The flow of studies is summarized in Fig 1.

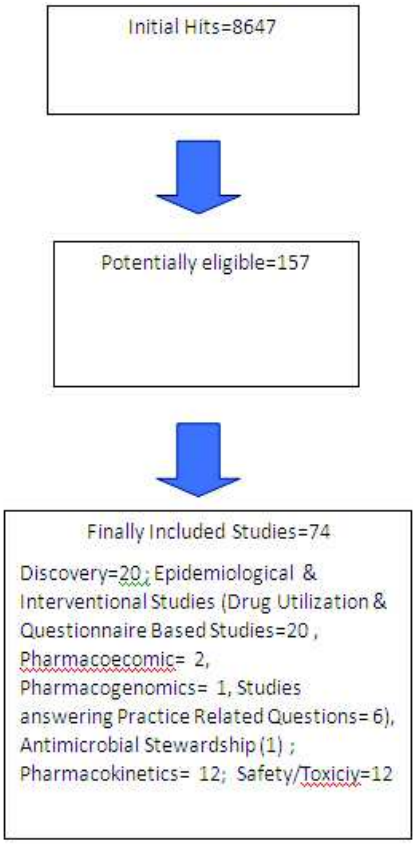

Fig. 1: Flow of studies through various stages of screening and selection

Discovery

A dwindling pipeline of antimicrobials in the wake of growing antimicrobial resistance is a major contemporary concern. Various approaches are used for screening purpose such as in-silico screening, synthesis of compounds using medicinal chemistry approach, tapping complementary and alternative medicine systems for potentially active compounds, novel formulations of existing antimicrobials and screening of antimicrobials from other naturally occurring pathogens. While the first two were explored to some extent, no research with the last approach could be identified. We also looked for novel concepts evaluated in a preclinical or clinical setting.

Evaluation of plant products for their antimicrobial use has been investigated. In a murine model of tuberculosis (Barua *et al*., 2016), the antimycobacterial activity of *Alstonia scholaris* and *Mucuna imbricata* was evaluated. Methanolic extract of the former was found to be useful alone and in combination with rifampicin. In another study, 4-aminoquinolone piperidine amides were identified with potent cidality on *Mycobacterium tuberculosis*. Decaprenylphosphoryl-β-d-ribose 2'-epimerase was identified as the primary target responsible for this activity (Naik *et al*., 2014).

Using medicinal chemistry, novel esterquats (monoesterquats and diesterquats) were synthesized from 11-bromoundecanoic acid and different alkyl amines and their efficacy against gram positive bacteria and fungi was explored (Yasa *et al*., 2016). Using similar approach, clavaminols were synthesized and some selected compounds were shown to have bactericidal as well as antifungal activity (Kumar *et al*., 2016). Antibacterials and antifungal properties of congeners of 5-nitrofuran-triazole were evaluated (Kamal *et al*., 2015). Derivatives of nitroimidazole compounds were evaluated for their efficacy against *Trichomonas vaginalis* (Mandalapu *et al*., 2016) A library of sixty 2-methyl-4/5-nitroimidazole derivatives was synthesized and they were largely found to be more potent than metronidazole. This approach is in consort with contemporary approaches adopted in drug discovery for antimicrobials.

More specific targeting for identifying some leads in antimicrobials was undertaken for histone acetyltransferase Rtt109, a potential therapeutic target in *Pneumocystis jirovecii* species (Sugumar *et al*., 2016). Bioinformatics was used to find phytochemicals which could bind with the above targets. Baicalin was found to have good binding with the target site.

Modification of immune system for combating infections was explored. Atorvastatin, combined with imipenem, was shown to decrease bacterial load in an animal model of sepsis associated with lung injury (Adil *et al*., 2015). The authors demonstrated an effect on inflammatory markers such as IL-1β and TNFα and MPO and ICAM-1 (Sood *et al*., 2015). A similar immunomodulatory approach was evaluated for diarylheptanoids from *Alnus nepalensis* which was shown to attenuate LPS-induced inflammation in macrophages and endotoxic shock in mice (Saxena *et al*., 2016). Daidzein, an isoflavone extract from soy, an inactive analog of the tyrosine kinase inhibitor genistein, showed a beneficial effect in preventing organ damage due to sepsis in a murine model (Parida *et al*., 2015).

Development of novel formulations of existing drugs to provide therapeutic advantage was explored by some researchers. Some examples were corneal targeting of nanoformulation of netilmicin for decreasing frequency of administration (Chandasana *et al*., 2014); inhaled microparticles for antitubercular drugs (Parikh et al, 2014), nanoformulation of levofloxacin for sustained action against mycobacterial tuberculosis (Kumar *et al*., 2012), a novel delivery system for intestinal targeting of ganciclovir (Mabrouk *et al*., 2016), nanoformulation of darunavir for improving biovailability (Bhalekar *et al*., 2016), and sustained release nanoformulation of amphotericin B (Chhonker *et al*., 2015).

In a clinical study for one of the complementary and alternative medicines, Qurse-e-istisqua (Q-e-I), a Unani medicine commonly prescribed to treat liver disorders, patients with HCV hepatitis were randomized to receive either standard of care alone or in combination with Q-e-I (Rehan *et al*., 2015) . The authors concluded that the medication did not affect viral replication but had anti-fibrotic effect. The study was found wanting in quality and the conclusions were not in consonance with the results.

Vi polysaccharide typhoid vaccines cannot be used in children <2 years owing to poor immunogenic

and T-cell independent properties (Mitra *et al*., 2016). The vaccine was conjugated with tetanus toxoid to improve immunogenicity in children less than 2 years of age. A cluster randomized trial was undertaken to test the immunogenicity and efficacy of the vaccine. Vi conjugate typhoid vaccine conferred 100% protection against typhoid fever.

An interesting randomized controlled trial was conducted to evaluate the efficacy of ofloxacin alone and in combination with dexamethasone in chronic suppurative otitis media (Panchsara *et al*., 2015). No difference was found between the groups and the authors concluded that dexamethasone use may be redundant. The study was recognized as a source of evidence for addressing an important practice-related question.

Epidemiological and Interventional Studies

Various categories of studies were considered under this heading. These included prescription audits & drug utilization, questionnaire-based studies, studies exploring treatment regimens, pharmacoeconomic and pharmacogenomic studies.

Prescription Audits and Drug Utilization

Several studies were identified from various parts of the country. Though some of them were pertinent to the local practices, no study was identified which could be considered as sufficiently representative of practices in the country. Over-prescription of antibiotics was identified as a problem for non-bacterial diagnosis in a prescription audit of teaching and non-teaching hospitals in a Madhya Pradesh district (Landstedt *et al*., 2017). In a retrospective analysis of in-patients with community acquired pneumonia done in Delhi, it was seen that there was an over-prescription of beta-lactams and beta-lactamase inhibitors and overall increase in patients being prescribed more than two antibiotics (Kotwani *et al*., 2015). The authors emphasized the need for dissemination of guidelines for the management of pneumonia and the need for stewardship. In another observational study, done in uncomplicated upper respiratory tract infections, the authors observed a similar unnecessary use of antimicrobials (Kotwani and Holloway, 2014) Corroboration of correlation of antimicrobial resistance with antimicrobial consumption came from a JIPMER, Puducherry study. Valid consumption and resistance data during the period Dec 2010 to Jun 2013 were obtained at 6-monthly intervals and resistance was found to correlate with antimicrobial consumption (Joseph *et al*., 2015). A rather unexplored, albeit important area, was addressed in a study evaluating efficacy and safety of anti-tuberculosis drugs in HIV patients (Kapadia *et al*., 2013). In HIV positive patients, association of anxiety and adherence to treatment was also noted in a small study (Panigrahi *et al*., 2015).

In a prospective, questionnaire based study, investigators were able to garner the perceptions and opinions of clinicians on various aspects of antimicrobial misuse (Chatterjee *et al*., 2015). The authors suggested that training of medical students and interns in rational antibiotic use, implementation of antibiotic policy, improvement in microbiology support and regular surveillance on this issue could be instrumental in tackling the problem of antimicrobial misuse. Drivers for antimicrobial use were explored in an interesting study from Vellore (Chandy *et al*., 2013a). Perceived patient benefit, unrestricted autonomy and business-cum-industry pressures were found promoting inappropriate use of antibiotics.

Surveillance of antibiotic consumption in the community has always been a challenge. Undertaking periodic assessment of consumption at community level, a surveillance system was established (Chandy *et al*., 2013b). Another area where considerable misuse of antimicrobials may be prevented was surgical prophylaxis as was noted in a retrospective analysis in a tertiary care hospital (Khan *et al*., 2013)

With increase in multi-drug resistant infections, the use of polymyxins has increased considerably, as highlighted in an audit in a neonatal unit (Jasani *et al*., 2015). Treatment issues for another emerging pathogen, *Burkholderia cepacia* complex were evaluated in a systematic review (Gautam *et al*., 2015) Antimicrobial susceptibility data analysis showed a high incidence of resistance among uropathogens (Chatterjee *et al*., 2016). Antibiograms were a source of information showing rising trend of vancomycin-resistant enterococci with nearly 24% isolates demonstrating resistance (Phukan *et al*., 2016). Importantly, three of the isolates were found to be resistant to linezolid. Analysis of virulence and resistance mechanisms of *E. coli* isolates was

undertaken to throw light on pattern of transfer of resistance (Basu *et al*., 2013). A horizontal transfer of resistance genes from pathogens to commensals occurring as a consequence of excessive antimicrobial use was highlighted.

Fixed-dose-combinations of antimicrobials have evoked special attention (Shafiq, 2016a). A retrospective study reported the effectiveness of a combination of ceftriaxone, sulbactam and EDTA (Patil and Jambulingappa, 2015). The purpose of conducting this analysis in eighteen patients was not clear and no remarkable conclusion could be deciphered. Various combinations of beta-lactams and beta-lactamase inhibitors are being used without evidence or with poor quality evidence. A prospective study showed the combination of cefotaxime/ sulbactam and cefepime/sulbactam o be equally effective in the management of urinary tract infection (Kaur *et al*., 2014). There are several issues with the study methodology, analysis and conclusions drawn. Similarly, many questions remain unanswered from a study based on *in vitro* susceptibility data comparing cefoperazone-sulbactam and cefoperazone-tazobactam (Patankar *et al*., 2012).

Pharmacoeconomic Studies

Economic burden of antimicrobial use is a topic of major concern. In an intensive care unit, the cost of treatment due to healthcare associated infections was Rs. 17,000 per patient and one-year cost 1 million rupees (Misal *et al*., 2016). One study found Whitfield ointment plus oral fluconazole to be more cost-effective than topical 1% butenafine for tinea infections although the methodology for cost-effectiveness analysis was not elucidated (Thaker *et al*., 2013).

Pharmacogenomics

Pharmacogenomics has been infrequently evaluated in this field. The effect of variations in the N-acetyltransferase-2 gene on isoniazid metabolism showed 60% population (South Indian) comprised slow acetylators and the two-hour isoniazid concentrations differed significantly among three genotypes (Hemanth *et al*., 2017).

Practice-related Issues

An important aspect of antimicrobial use was evaluated in a prospective study undertaken to compare surgical site infections in spinal surgeries following 24-hour versus 72-hour antimicrobial prophylaxis (Marimuthu *et al*., 2016). No significant difference in surgical site infections was noted. In a randomized, controlled study, the need for antimicrobials for tooth extraction was investigated (Arora *et al*., 2014). Three days of amoxicillin-clavulanic acid was not found to have any significant benefit over infection rates as compared to placebo given for the same duration. In another study answering a practice related query, a short course (3 days) of norfloxacin, co-trimoxazole and levofloxacin was shown to effectively achieve microbiological cure in patients with urinary tract infection (Vacchaani *et al*., 2015). However, the study had several methodological and analytical issues and cannot be regarded as robust evidence to make a claim for short course of treatment with these antimicrobials for urinary tract infections. In a retrospective analysis of snake bite cases, it was noted that use of antibiotics is a common practice and ampicillin was the most commonly used antibiotic (Palapallil, 2015). The study made no attempts to address the need for antibiotics in snake bite, an issue which perhaps needs a nuanced addressal. Azitrhromycin as a treatment option for enteric fever was explored in a meta-analysis (Trivedi and Shah, 2012). In comparison to older fluoroquinolones, azithromycin was marginally better in reducing the chance of clinical failure (RR 0.46; 95% CI 0.25-0.82), while in comparison to ceftriaxone, it significantly reduced the chance of relapse (RR 0.1; 95% CI 0.01-0.76). Feasibility of management of neonatal sepsis in a community setting is an important issue. The same was addressed by means of a systematic review showing that combination regimens involving gentamicin may be a feasible option but the susceptibility patterns of pathogens responsible for the same may need a relook since data were from studies conducted over a decade ago (Jaiswal *et al*., 2016).

Antimicrobial Stewardship

While a 2014 communication by ICMR (Chandy *et al*., 2014) highlighted the ICMR programme on antibiotic stewardship with an emphasis on the role of clinical pharmacologists in this exercise, only one original research from India could be identified wherein a stewardship model for resource-limited setting was evaluated. The authors demonstrated how

strategies of stewardship taking into consideration the practice-related situation in India could be used to bring down antimicrobial consumption and reduce irrational use of antibiotics (Shafiq *et al*., 2016b).

Pharmacokinetics

An important aspect of optimal use of antimicrobials is administration in a dose which maximizes the probability of attainment of adequate concentrations at the target site. Similarly, population pharmacokinetic studies are instrumental in delineating doses based on variables affecting drug disposition. Such studies were singularly missing. There were however, some studies which described pharmacokinetics or drug interactions of some antimicrobials. Plasma concentration monitoring of cefotaxime in critically ill patients in an intensive care unit showed a wide variability in pharmacokinetic parameters (Abhilash *et al*., 2016). Some comparisons undertaken to explain this variability could not help in establishing pharmacodynamic response as a consequence of pharmacokinetic variability. The same authors also reported the pharmacokinetics of imipenem in critically ill patients but the study could not lead to any important conclusion regarding pharmacokinetics-pharmaco-dynamics (Abhilash *et al*., 2015) Pharmacokinetics of colistin, although now better described than before, did not have data from our patient population. This was presented for the first time in a study done in critically ill patients with gram negative MDR infections (Karnik *et al*., 2013). A wide inter-individual variability was noted, which is in consonance with earlier studies.

A pop-PK study of ceftriaxone-sulbactam was reported as a study done in healthy volunteers and infected individuals (Sharma *et al*., 2016). However, the "infected individuals" part was only a simulation exercise. Weight was recognized as an important covariate and the conclusion was that 3g given every 24h is sufficient for bacteria with MI $\leq 8\mu g/mL$ while 3g every 12h is needed if MIC is 8-32ìg/m.

Pharmacokinetics of antitubercular drugs was more extensively evaluated. In pediatric HIV-infected and non-infected population, it was noted that the 2-hour plasma levels of isoniazid, rifampicin and ethambutol were inadequate (Mukherjee *et al*., 2016). The study made a case for revised higher doses of anti-tubercular drugs in children. While in this study no difference between HIV-infected and non-infected children was seen, in another study, lower serum concentrations of rifampicin and pyrazinamide were found, and they were associated with poor treatment outcomes in children with tuberculosis related to HIV (Ramachandran *et al*., 2016). Peak rifampicin and isoniazid concentrations were found to be inadequate in this study also. It was highlighted that rifampicin dose may not be adequate in pediatric population if administered according to RNTCP guidelines (Arya *et al*., 2015). Inadequate levels of pyrazinamide in children were noted when given as recommended (Roy *et al*., 2012). Correlation between higher rifampicin level and drug-induced hepatotoxicity was observed in a study (Satyaraddi *et al*., 2014).

Drug levels of isoniazid and pyrazinamide in diabetics with TB were lower as compared to non-diabetics, which was attributed to delayed absorption and quicker elimination of these drugs (Kumar *et al*., 2017).

Foraying into less travelled territories, the penetrability of intraocular penetration of oral moxifloxacin was compared to topical administration (Sharma *et al*., 2015). Significantly higher levels in ocular fluids were seen after topical administration making it a suitable route of administration.

Only one drug interaction study was found (Rajagopalan *et al*., 2013). Levofloxacin was found to significantly elevate lithium levels in rabbits.

Safety

Adverse drug reactions and unwanted interactions represent negative consequences of antimicrobial pharmacotherapy that need to be detected, evaluated, and understood with the ultimate aim of their prevention and minimization of patient harm. Most commonly identified antibiotic related adverse reactions especially in critical care settings include anaphylaxis, nephrotoxicity, dermatological toxicity, diarrhea, hepatotoxicity and cytopenias (Granowitz and Brown, 2008). There were several isolated case reports of ADRs with specific antimicrobials (Garg *et al*., 2015; Balaji *et al*., 2014; Das *et al*., 2014; Kameshwari *et al*., 2014). However, these were not considered further due to lack of any systematic investigation into causes or frequency of occurrence. Similarly, several studies and systematic reviews

evaluated the occurrence of ADRs among people receiving pharmacotherapy in hospitals and/or in community settings (Geer *et al*., 2016; Tandon *et al*., 2015; Hiware *et al*., 2013; Patel and Patel, 2016; Patel *et al*., 2014; Patel *et al*., 2013). Although antimicrobials were often found to be a major contributor to adverse reactions experienced by patients, these studies were not included since their primary focus was not on antimicrobial safety.

Several clinical studies compared the safety (and efficacy in some cases) of antimicrobials including combinations. A study in acne patients investigated the efficacy and safety of commonly prescribed topical preparations. Given the plethora of topical preparations available to dermatologists (keratolytics, antimicrobials, retinoids), this study compared clindamycin, benzoyl peroxide, nadifloxacin and topical tretinoin and found that benzoyl peroxide plus clindamycin was more efficacious, while benzoyl peroxide plus nadifloxacin was the safest (Kaur *et al*., 2015).

A comparison of ofloxacin alone with ofloxacin plus dexamethasone in chronic suppurative otitis media found no difference in adverse events although steroid may have facilitated fungal colonization of external auditory canal (Panchasara *et al*., 2015). Efficacy, safety and cost-effectiveness of triple drug regimens for *Helicobacter pylori* eradication showed that lansoprazole+tinidazole+clindamycin was efficacious and safe but clarithromycin+amoxicillin+omeprazole was the most cost-effective, although the authors failed to draw comparisons for efficacy/ safety among the three regimens (Ghosh *et al*., 2012).

An interesting retrospective study, conducted in HIV patients with cerebral toxoplasmosis, compared pyrimethamine/sulfadiazine (preferred regimen) with cotrimoxazole/clindamycin. In this study, the latter fared better more frequent achievement of complete response, lesser mortality and fewer adverse reactions (Goswami *et al*., 2015). As per the authors this was the first study reporting the use of cotrimoxazole/ clindamycin thereby overcoming the limitations imposed by pyrimethamine/ sulfadiazine (toxicity and consequent treatment withdrawal).

Renal safety of single high-dose amikacin was compared with gentamicin in combination with metronidazole for surgical prophylaxis. The study showed both drugs to be associated with acute kidney injury (16% with amikacin versus 24% with gentamicin) within 1 week of administration although all patients had normal serum creatinine levels at one month (Giri *et al*., 2016).

The impact of diabetes mellitus on treatment outcomes and safety of directly observed treatment, short-course (DOTS) strategy in tuberculosis patients showed that diabetics had higher sputum positivity at the end of intensive phase, poorer outcomes at the end of treatment, and more ADRs (restlessness, hypoglycemia, back pain, feet pain) compared with non-diabetics (Siddiqui *et al*., 2016). An important limitation of this analysis was failure to rule out causal association with concomitant antidiabetic medications. A study evaluating safety of antitubercular treatment in HIV patients showed majority of ADRs were mild and were causally linked as possible or probable using Naranjo scale (Kapadia *et al*., 2013).

A prospective study which analyzed the pattern of adverse drug reactions among patients who were prescribed antibiotics in the otolaryngology department of at a tertiary care hospital showed beta-lactams were the most frequently prescribed, diarrhea was the most common ADR, followed by neurotoxicity, cutaneous reactions, liver and renal ADRs, with elderly being at the greatest risk (Khan *et al*., 2013). Another survey included children admitted to pediatric ward at a tertiary care hospital in eastern India (Baidya *et al*., 2017). Nearly 80% received antimicrobials, majority being prescribed cephalosporins. The initial choice was usually empirical and median duration of treatment was 7 days. Most antimicrobials were prescribed parenterally and surprisingly only 2% children experienced any ADR. A study in HIV patients receiving antiretroviral regimens showed gender differences in ADRs with rash being more common in females while hypertriglyceridemia was seen predominantly in males (Rather *et al*., 2013). Fear of ADRs as well as actual occurrence of ADRs were important causes for non-adherence to antiretroviral therapy (Panigrahi *et al*., 2015).

A study on data collected under Pharmacovigilance Programme of India over three years at a tertiary care hospital found that nearly 15% of reported ADRs could be attributable to antimicrobials, with rash being the commonest and injectable ceftriaxone being the most commonly implicated antimicrobial, 90% of

ADRs were moderate in nature, a staggering 75% were probably and remaining possibly linked to antimicrobial drug therapy (Richa *et al*., 2015).

Discussion

The current report attempted to summarize the work done in the field of chemotherapy for infectious diseases barring tropical diseases mainly through PubMed search. The inherent nature of the topic posed limitations on search. Though an attempt was made to maximize the articles, it was not possible to cover all. Since the topic spanned bacterial, mycobacterial, viral and fungal infections, the routine principles of searching could not be adhered to. It is likely that some important articles have been missed out. Inferences could only be made based on the affiliations listed in 'author affiliations' section. If the affiliation of only the first or corresponding author was mentioned, then it could not be ascertained if any of the remaining authors was a pharmacologist. Such articles, however, were relatively few in number.

Discoveries in the field of antimicrobials had slackened worldwide in the previous decade due to several reasons of which compromised economic returns is extremely important. However, several initiatives by governments, particularly for drug discovery against resistant bacteria have been recently given a push (Leupke *et al*., 2017). Two examples are, CARB-X (Combating Antimicrobial-Resistant Bacteria Biopharmaceutical Acclerator) and ND4BB (New Drugs for Bad Bugs). These are multi-disciplinary initiatives with pharmacologists needing to play important roles. Back home, such systematic initiatives from our funding agencies remain in the pipeline. Central Drug Research Institute is a standalone institute currently equipped with steering drug discovery in a holistic manner. More such institutes are required and perhaps some dedicated to the needs of discovery of drugs for resistant organisms.

It was interesting to note that the work on discovery of agents was dominated by specialists from allied branches such as pharmacy, chemistry, and bioinformatics. An increased role of pharmacologists in this area would be instrumental in directing discovery to translation for she/he will be able to understand myriad of issues that go into enabling a potential molecule to be converted into a viable drug (Hughes and Karlen, 2014). Further, strangely, antimicrobials have been receiving attention from microbiologists. The same attention is missing from Pharmacologists when the fact remains that antimicrobials are groups of drugs which need a much nuanced approach involving different branches of pharmacology. It was encouraging to see that the approach of reformulating existing chemotherapeutic agents for improving therapy is growing and is getting refined.

As mentioned earlier, observational studies of various kinds were frequently published. What was lacking was holistic studies and a system for undertaking regular surveys for elucidating patterns of antimicrobial use. The role of pharmacologists in this area needs to increase several-fold. A group which will work in collaboration with the government machinery to develop this system is urgently needed. This need has been highlighted by the National Action Plan released by Government of India (National Action Plan 2017). While a lot of misuse of antimicrobials was recognized, interventional strategies for tackling it were rarely explored. It was interesting to note that beside the routine exercise of elaborating the defined daily doses (DDD), investigators explored pertinent issues such as – rationale, economic impact (albeit patchily), pharmacogenomics and drivers for prescription.

Antimicrobial stewardship, which recognizes the role of pharmacologists needs to be initiated in a big way (Chandy, 2015). While our group was able to model such a system in the institute (Shafiq *et al*., 2016b), pharmacologists in other institutes need to train themselves in such an exercise and initiate similar services at their respective institutes. Pragmatic trials answering questions related to duration of therapy, optimal empiric/prophylactic regimens, doses are other areas where pharmacologists must generate data to provide evidence for best treatment.

PK-PD and pop-PK studies are extremely important in designing the dosage regimen of antimicrobials. A serious dearth of articles was found in this area, which should become the forte of pharmacologists. The reasons could be basic neglect of antimicrobials by pharmacologists and lack of resources (equipment, personnel, and funds) to undertake such studies. Antitubercular drugs received

a better treatment though. However, these studies were predominantly from a few centers. Since these studies are resource-intensive, overall compromised funding for health research may be an equally important reason for the paucity of studies.

Safety of antimicrobials is an important issue but despite an active pharmacovigilance program in the country, no remarkable studies could be found. Though case reports were not included for the current analysis, none of the publications could be considered as important in highlighting any novel adverse effect. Drug-induced liver injury, e.g., for antitubercular drugs, a commonly occurring problem, was largely unaddressed.

We propose that the undergraduate and postgraduate curriculum should ensure a kind of reorientation in learning about antimicrobials. Topics like antimicrobial resistance, antimicrobial stewardship, and dose optimization based on PK-PD need to be taught. A greater emphasis also needs to be placed for core pharmacology based areas such as discovery, PK-PD, pharmacoeconomics and pharmacogenomics studies of antimicrobials. This would be best addressed by a consortium of pharmacologists/clinical pharmacologists working with clinicians on a common problem. The efforts would need funding from appropriate sources. This seems like a daunting task in view of the current status of funding for health research.

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