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A Study on Prescribing and Antibiotic Resistance in Haryana

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ABSTRACT

Aim: The main aim of this paper is to increase the knowledge regarding antibiotic prescribing patterns and prevalence of resistance in an Indian setting, so as to identify targets for interventions aimed to improve clinical practice for common infections.

Methods: This paper includes five cross-sectional studies. Paper I and paper II describes the patterns of antibiotic prescribing for outpatients with suspected infectious etiology and among admitted patients, respectively. The defined daily doses (DDDs)were calculated per 1000 patients per diagnosis considered in paper I. Focus of infection specific DDDs were calculated per 100 patient days in paper II. In paper III, prescriptions for children with diarrhea were analyzed for adherence to treatment guidelines and factors associated with adherence were explored. In paper IV healthy Children were screened for nasal carriage of S. aureus to identify factors associated with nasal carriage and to describe the resistance patterns. Paper V describes the antibiotic susceptibility pattern of pathogens isolated from patients with suspected infections. Antibiotic susceptibility testing was performed by Kirby-Bauer disc diffusion method. All the studies were done using structured, pilot tested questionnaires.

Results: Overall antibiotic prescribing was 66.3%, 3732 out of 5623 outpatients (PaperI) and 92%, 5531 out of 6026 admitted patients (Paper II). Quinolones were the most frequently prescribed antibiotic group among outpatients and third generation cephalosporin's among the admitted patients (Paper I and II). For diarrhea in childrenonly 6 out of 843 prescriptions hired completely to treatment guidelines. Oralrehydration solution (ORS) was prescribed for 58%, ORS with zinc for 22% and antibiotics for 71% of the cases (Paper III). The prevalence of nasal carriage of S. aureus was 98 out of 1562 i.e. 6.3% (95% confidence interval [CI] 5.1-7.5). Of these,16.3% were methicillin-resistant S. aureus (MRSA). Overcrowding was associated with nasal carriage of S. aureus (Paper IV). Among pathogens (n=716) isolated form admitted patients (n=2568), Gram-negative pathogens predominated (62%). Extended spectrum β-lactamase (ESBL) production in E. coli isolates (n=149) was 69% (95% CI61.6–76.6) and in K. pneumoniae isolates (n=107), 41% (95% CI 31.6–50.5). MRS A constituted 30% of all S. aureus isolates (n=221).

INTRODUCTION

Antibiotics are considered an important element in the armamentarium of modern medicine. When antibiotics are used to treat diseases caused by bacteria, most of the bacteria are killed but a few surviving bacteria can respond by becoming resistant to the antibiotic used. This response is a natural adaptation for survival by the bacteria. Thus, the effective lifespan of antibiotics is limited. Many patients throughout the world suffer harmdue to antibiotic resistance because bacterial infections are not susceptible any more to antibiotics used to treat them (WHO 2012a).When Fleming discovered penicillin he had observed that some bacteria are inherently resistant and some sensitive (Fleming 1929). He forewarned the effects of "indiscriminate use" in his Nobel lecture where he noted that initially sensitive bacteria could become resistant, especially if exposed to low doses of antibiotics ('Sir Alexander Fleming – Nobel Lecture') but the scientific community continued to ignore this advice.

By the 1980s, it was believed that man had already learnt all there is to know about antibiotic resistant bacteria, which translated to a reduction in funding for research in this area. The field of antibiotic use and bacterial resistance was considered "old fashioned", thus drastically reducing the number of scientists working in the field. The last two decades however, have seen a resurgence of interest in the field of antibiotic use and resistance and can be described as the

'dawning' of awareness of the antimicrobial resistance problem especially in resourcerichcountries. The insurance companies in the United States in particular recognized this problem due to the increasing costs associated with treating resistant organisms (Alvan etal. 2011, Barbosa and Levy 2000, Boucher et al. 2009, Cars et al. 2008).

Today the topic of antibiotic resistance is in the forefront, because of the increasing realization that we lack even the basic knowledge about the mechanisms of resistance. Extensive work has been done and is going on in the field but still many questions, particularly related to horizontal gene transfer among environmental and pathogenic bacteria, remain unanswered (Alvan etal. 2011, Barbosa and Levy 2000, Boucher et al. 2009, Cars et al. 2008, French 2010,Grundmann et al. 2011, Johnsen et al. 2009). There is insufficient information about the conditions and factors that lead to the mobilization, selection and movement of resistant bacteria or resistant genes into and between animal and human populations (Alvan et al.2011). It is important to answer these questions because horizontal gene transfer maintains the acquired gene pool of resistance in a community.

REVIEW OF LITERATURE

Miyazawa et al., (2012) mentioned that Cyclodextrin (CD) is a cyclic oligosaccharide tranquil of nine l, 4-linked D-glucose units. They examined that aqueous solubility of CD was greater than that of CD but under that of -CD or γ,-CD and by them no surface movement of CD was examined. CD did not display any hemolytic activity at 4.0 × 10 -2 M CD, which was shut to its drenched resolution. The acid-catalyzed hydrolysis augmented in the subsequent order: alpha-CD < beta-CD < γ-CD . According to them CD did not illustrate any important solubilization consequence on most of the somewhat soluble or insoluble drugs in water. Nevertheless, in the case of a great guest molecule such as spironolactone (SP) and digitoxin, which have a steroidal framework, they accounted that the improvement of solubility of the guest molecule by CD was superior to that by-CD. The solubility of SP augmented about 30-fold in the existence of CD (4.5 × 10 -2 M).

Jachowicz and Nurnberg (2013) equipped solid dispersions of dissimilar ratios of Gelitacollagel as the shipper and lactose by the spray drying technique. Dissolution revision has shown that by arrange solid dispersions the closure rate and the solubility of Oxazepam amplified markedly, sovereign of the ratio of drug, carrier and lactose. The features of the solid dispersions were distinguished by X-ray diffraction and polarizing microscopic learning. An amorphous form of all equipped solid dispersions was designating in X-ray revision. Drug of solid dispersions of Oxazepam: Gelita Collagel, physical combinations and the drug alone were equipped. The best consequences from the dissolution outlines were attained for drug surrounding solid dispersions. According to them drug remained in good physical properties when accumulates for one year in normal circumstances.

Stella et al., (2012) have tackles the question of the instruments of drug discharge from Cyclodextrin compounds. Further particularly, they enforced to respond the question whether drug release from aqueous formulations is sluggish or deficient? An appraisal of the text, their own employment and assorted imitations recommended that drug release from Cyclodextrin composites is quick and quantitative in most belongings.

Turk et al., (2012) deliberate micronization of pharmaceutical matters by the quick development of supercritical solutions (RESS) process and optional it as a capable technique to advance bioavailability of inadequately soluble pharmaceutical agents. According to them, RESS process facilitates the micronization of thermally labile equipment and the configuration of subdivisions of less than 500 nm in width. Their research intended towards an enhanced sympathetic of the association between development limitations and subdivision individuality and to discover novel region of submission for nanoscale subdivisions. From investigational conclusion they demonstrate that the RESS dispensation of Griseofulvin escorts to a appreciably better dissolution rate of the drug consequential in an enhanced bioavailability. Furthermore, stable postponements of nanoscale subdivision of β-Sitosterol were formed by the swift development of a supercritical mixture throughout a capillary nozzle into aqueous solutions. The element sizes of β-Sitosterol in the aqueous solution were slighter or equivalent to those fashioned by RESS into air lacking the surfactant solution.

Hecq et al., (2013) equipped and distinguished nanocrystals for inspect solubility and termination rate improvement of Nifedipine. In organize to augment these distinctiveness; the grounding of nifedipine nanoparticles was attained via elevated or high pressure homogenization (HPH). They optimized homogenization practice in observe to element extent and range distribution. They performed crystalline state assessment ahead of and subsequent particle size decrease throughout differential scanning calorimetry (DSC) and powder X-ray diffraction (PXRD) to indicate ultimate

alteration to amorphous state throughout the homogenization progression. Throughout this revision, they have exposed that preliminary crystalline state is preserved subsequent particle extent diminution and that the dissolution distinctiveness of nifedipine nanoparticles were considerably amplified in observed to the profitable product. Supercritical antisolvent (SAS) progression, examining to progress the aqueous solubility and the disbanding rate of drug, thus elevating its bioavailability. They accomplished that SAS progression could be a practical technique for the research of the enclosure multifaceted of drug with HP- -CD and its solubility, dissolution extent and hypolipidemic commotion is considerably amplified by complexation among SV and HP- -CD.

Turner et al., (2013) in their revision finished utilize of artificial neural networks (ANNs) forthe forecast of clearances, per potion vault to plasma proteins, and quantity of distribution of a sequence of structurally assorted compounds. A numeral of hypothetical descriptors was produced from the drug arrangements and mutually automatic and physical clipping were worn to obtain finest subsets of descriptors for quantitative structure-pharmacokinetic relationship models. The mixture of descriptor production, ANNs, and the alacrity and achievement of this method evaluated with conservative techniques shows strapping potential for exploit in pharmaceutical product expansion.

Yap et al., (2013) elected 503 composites with recognized CLtot explained in the journalism to ascertain quantitative structure–pharmacokinetic associations for medicine clearance by discovering three arithmetical knowledge techniques, general regression neural network (GRNN), support vector regression (SVR) and k-nearest neighbor (KNN) for modeling the CLtot of all of these recognized composites. Six dissimilar sets of molecular descriptors, DS-MIXED, DS-3DMoRSE, DS-ATS, DS-GETAWAY, DS-RDF and DS-WHIM, were appraised for their convenience in the forecast of CLtot. QSPkR models urbanized by via DS-MIXED, a compilation of legitimate, geometrical, topological and electro topological descriptors, usually give enhanced forecast accuracies than those urbanized via other descriptor sets. These consequences recommended that GRNN, SVR, and their agreement model are potentially helpful for forecasting QSPkR properties of remedy leads.

RESEARCH METHODOLOGY

AIMS

The main aim of the paper is to increase the knowledge regarding antibiotic prescribing patterns and prevalence of resistance using two hospitals in Rohtak, Haryana, India as examples. The knowledge and methods will be used to identify targets for intervention to improve clinical practice with regards to antibiotic prescribing in this and similar settings.

Patients And Methods

Study Design

All the five studies of the paper were cross-sectional using quantitative methods. The first two studies were conducted to understand the prescribing pattern for common infections or infectious disease complaints in outpatient clinics (Paper I) and the prescribing patterns for common infections using “foci of infection” approach among admitted patients (Paper II) in the two hospitals in Rohtak, India. Another of the studies (Paper III) was performed to estimate the adherence to treatment guidelines for acute diarrhea, a common infection among children. Paper IV and V were microbiological studies. The study in Paper IV was performed to estimate the prevalence of nasal carriage of S. aureus, its resistance pattern and factors associated with nasal carriage in children below five years of age.

The Paper V was done to define the magnitude of resistance among pathogenic bacteria isolated from patients with suspected infections. For papers I, II, IV and V the data was collected repeatedly over 15 months, from November 2007 to February 2009. Data was first collected at the teaching hospital and then at the non-teaching hospital for 45 days in each hospital. To allow time for appropriate data management a period of15 days was introduced between the two hospitals and the two seasons. Data was thus collected four times for 45 days each in the two hospitals. For paper III data was collected from 1st June to 14th August 2009.

Study Settings

Rohtak district is situated in the eastern part of state Haryana, India. This regionis popularly known as main Haryana, with agriculture as the main source of income. The districthas population of about 374292. Rohtak city is the administrative center of Rohtak District.(Census of India 2011).

Health care infrastructure in Rohtak

The city hosts the Pandit Bhagwat Dyal Sharma Health University under under which PGIMS is running and there is a Civil Hospital both are funded by state Govt. There are also various privately operated medical facilities.

The Health University, Rohtak is situated at a distance about 240 Km from the State Capital Chandigarh and about 70KM from Delhi on Delhi-Hisar-Fazilka National Highway No-10.The PGIMS, Rohtak is the only major Institute for Medical Education and Research and a teritiary care center for specialized health care services not only to the people of state of Haryana, but also to those from Punjab, Western Utter Pradesh, Rajasthan and Delhi. This institute was started under the name of Medical College, Rohtak in the year of 1960.

Today this institute is a famous Institution not only for medical education but also for the health care facilities both at the nation and international level. Under this university the following Institution are serving the people successfully PGIMS (1260 bedded), PGIDS, SIMH, Nursing college, Pharmacy college.

There are three community health centers, two in a rural area and one in urban area. A network of 20 primary health centers and 50 sub-centers caters to the rural population. In urban areas, there are five civil dispensaries serving the same purpose as primary health centers in rural areas. This city is health care hub, with Ayurvedic medical college hospital. Apart from the above public health infrastructure there are many large private hospitals(having at least 100 beds), In Rohtak district, there are around 1000 qualified doctors working in different health care facilities.

Many of the practitioners in government hospitals are allowed to work in private clinics outside of their official hours of work. Practitioners from other formal systems of medicine mainly, Ayurveda and Homeopathy (around 110 in number) and informal health-care providers (around 800 in number) outnumber the allopathic practitioners. Most (82%) of the informal health-care providers are based in the rural areas (De Costa et al. 2009, Deshpande et al. 2004). The health-care workers trained in AYUSH are not allowed to prescribe allopathic medicines but many of them do so.

Partial Least Squares

Partial least squares (PLSs) assumes a linear relationship between feature vector, X, and target property, ^y, but unlike MLR, PLS is more appropriate when the number of features greatly exceed the number of samples and when features are highly collinear. It is to note that advancement has brought about methods like quadratic-PLS and kernel-PLS for nonlinear systems, multiway-PLS, unfolding-PLS, hierarchical-PLS, three-block bifocal PLS, and so on. These will not be discussed here and interested readers can refer to the review by Hasegawa et al.

PLS works on the assumption that the examined system is subjected to the influ-ence of just a few causal factors, termed latent factors or latent variables. PLS avoids the problem of collinear features by extracting these latent factors that can explain the variations of the molecular descriptors while simultaneously models the response of the target property.

PLS was also interpreted as the initialism for “Projection to Latent Structure”. As illustrated in Figure 1.2, the latent factors can be estimated through X-scores and Y-scores, which are extracted from the molecular descriptors and desired compound properties, respectively. Subsequently, the X-scores are used to predict the Y-scores, which in turn can be used to predict the compound properties. The number of latent factors used in PLS is an important consideration for QSAR modeling, and it is usually obtained through the use of cross-validation methods like n-fold cross-validation and leave-one-out methods, where a portion of the samples is used as training set, while the other portion is set aside as testing set to validate the model that was built from the training set.

PLS has been applied on various QSAR studies like toxicity of quaternary ammonium compounds on Chlorella vulgaris, angiotensin II AT1 receptor antagonists, CYP11B2 binding affinity and CYP11B2/CYP11B1 selectivity, toxicity to Daphnia magna, and nonpeptide HIV-1 protease inhibitors prediction. PLS is also used as an analysis method in the popular 3D-QSAR technique,

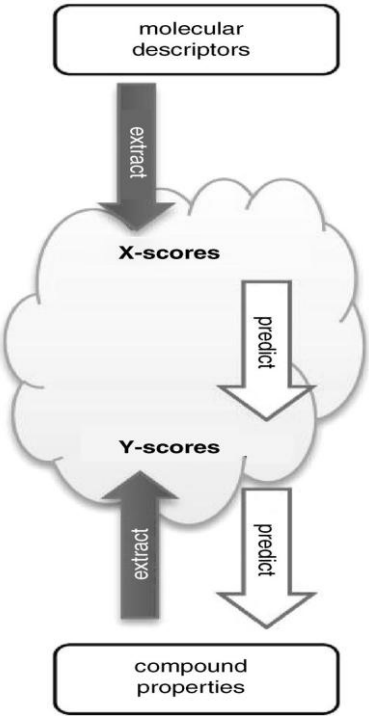

Figure 1: Extraction of latent factors from molecular descriptors and compound properties.

DATA ANALYSIS

For all studies data were entered in Epidata software (Version 3.1,Epidata software Association, Odense, Denmark) and transferred to Stata version 10 (Stata Corp., College Station, TX, USA) for further analysis. The data was double entered and checked. The five research questions of the paper were investigated in fivepapers. The outcome in paper I was antibiotic prescribing calculated as DDD per TP Damong patients with suspected infections attending outpatient clinics. Antibiotic prescribing among admitted patients calculated, as DDD per HPD was the outcome in paper II.

The primary outcome in paper III was ORS prescribing rate. The secondary Outcomes were (a) prescribing of "ORS together with zinc" and (b) antibiotics". For paper IV the outcome was prevalence of nasal carriage of S. aureus in children below five years of age and prevalence of antibiotic resistance among isolates of S. aureus. For paper V the outcome was prevalence of antibiotic resistance among pathogens cultured from admitted patients with suspected patients.

Descriptive statistics were presented as mean, median and (or) proportion (Paper I to V).Two-by-two tables were made to calculate crude odds ratio (OR) using Chi square test. The P-value smaller than 0.05 were taken to define statistical significance. The test of significance was two-sided. Odds ratios and their 95% confidence intervals (CI) were also computed (Paper I, III, IV and V).Logistic regression models were fitted for studies in papers III and IV to determine the factors associated with the outcome (as defined above). In paper IV a given variable was entered in the final multivariate logistic model if the bivariate analysis yielded a P valueless than 0.1. All the variables were adjusted for age and sex. A complete case series analysis was used. A post-hoc power calculation was done for the study in paper IV and was found to be 0.98.In paper III two multivariate stepwise logistic regression models, one for each secondary outcome variable, were computed.

The outcome variables were controlled for design effect due to intra cluster correlation (ICC). Covariates found significant in bivariate analysis using Chi-square test at a level of $P < 0.20$ were included in the model and removed using a backwards stepwise method (Wald test with removal level of significance of $P < 0.10$). Bonferroni correction was applied for OR's because of the double comparison of independent variables with two outcomes. A value of $P < 0.05$ was considered statistically significant in the final models.

Serum protein binding

Serum protein binding (%SPB) affects the drug disposition as well as the pharmacodynamic effect of the drugs. %SPB in the present QSPkR investigations was found to depend upon various electrostatic parameters *viz.* PNSA, RNCG, PPSA-1, RPCS-1, MPC(Qmin), PNSA-1, HDSA-1, Hypnotic-80, etc. The quantitative prognosis was further fortified by encompassing its dependence on constitutional parameters *viz.* RNCA, RNTB, RNHA, nHet, nCIR and topological parameter *viz.* CIC-2, CATS2D and geometrical parameter *viz.* KSI-3, SssO, etc. Its positive dependence on such descriptors indicates that hydrogen bonding and van der Waals' interactions play a stellar role in governing protein binding. %SPB does not seem to have any dependence on lipophilic parameters indicating that the hydrophobic and ionic bonding of antibiotic drugs is negligible.

The study of the results as shown in table 6, indicated that correlations of %SPB with various descriptors were statistically significant ($p<0.001$) with good prediction power of (R^2=0.9949, Q^2=0.9957). Logarithmic transformations (R^2=0.9395, Q^2= 0.8091) tends to decrease the degree of correlations. Fig. 13depicts the linear plots (governing the line through the origin) and the residual plots between the values of %SPB as reported in literature and those predicted using multi-parameter QSPKR studies for a series of 17 antibiotic drugs Fig. 14 shows the corresponding plots for log-transform of %SPB.

Table 1: Significant linear, logarithmic relationships for a series of 17 antibiotic drugs using %SPB as pharmacokinetic parameter

Equation(s)	M	R^2	Q^2	S^2	F	P<
%SPB = -11.5787 + 22.7063 SpMax8_Bh(s) -27.9160 – C-040 +7.3276 HDSA-1 + 8.32 32 – SssO - 1.2316 PNSA	5	0.9939	0.9866	11.4452	358.21	0.001
%SPB = -5.5920 +14.7195 - SpMax8_Bh(s) -20.1195 - C-040 +6.0875 HDSA-1 + 5.46 77 – SssO - 1.2413 RNCA	5	0.9939	0.9863	11.4232	358.90	0.001
%SPB = -11.9612 + 30.9943 - SpMax8_Bh(s) -15.6891 - C-040 + 4.9318 HDSA-1 + 8.18 21 – SssO - 1.6579 –Hypnotic – 80	5	0.9944	0.9880	10.4198	393.67	0.001
%SPB= -5.8130 + 22.1221Sp Max8 _ Bh(s)-20.7064 C-40 + 7.1357 HDSA-1 + 8.9819 SssO+1.7633X1Av	5	0.9946	0.9888	10.1533	404.06	0.001
%SPB = 5.7413 + 22.9908Sp Max8 _Bh(s) - 13.0678 RNTB - 22.1188 RPCS-13.384 1nHet + 7.5330 HDSA-1	5	0.9949	0.9357	9.6266	426.30	0.001
Log %SPB = -1.4954 +8.1158 PPSA-1 -8.3921 CIC-2 + 2.21 23 RNHA - 3.2234 KSI-3 + 2.8228 MPC(Qmin)	5	0.9100	0.7869	0.0055	22.24	0.001
Log %SPB = 1.8530 +7.8401 PPSA-1-8.2490CIC-2 -2.2140 - PNSA-1 - 2.0898 KSI-3 + 1.4422 MPC(Qmin)	5	0.9100	0.7879	0.0055	22.26	0.001
Log %SPB = 1.4385 + 8.2122 - PPSA-1 -9.5852 CIC-2 - 3.84 25 - PNSA-1 -2.1127 KSI -3 + 1.5529 - P_VSA_s_5	5	0.9123	0.7767	0.0053	22.88	0.001
Log %SPB = 11.5412 -10.87 64 + 6.6845 - CATS2D _09 _LL + 4.2233 – nCIR -6.5874 PNSA-1 -2.8669 – RNCG	5	0.9395	0.8091	0.0037	34.14	0.001

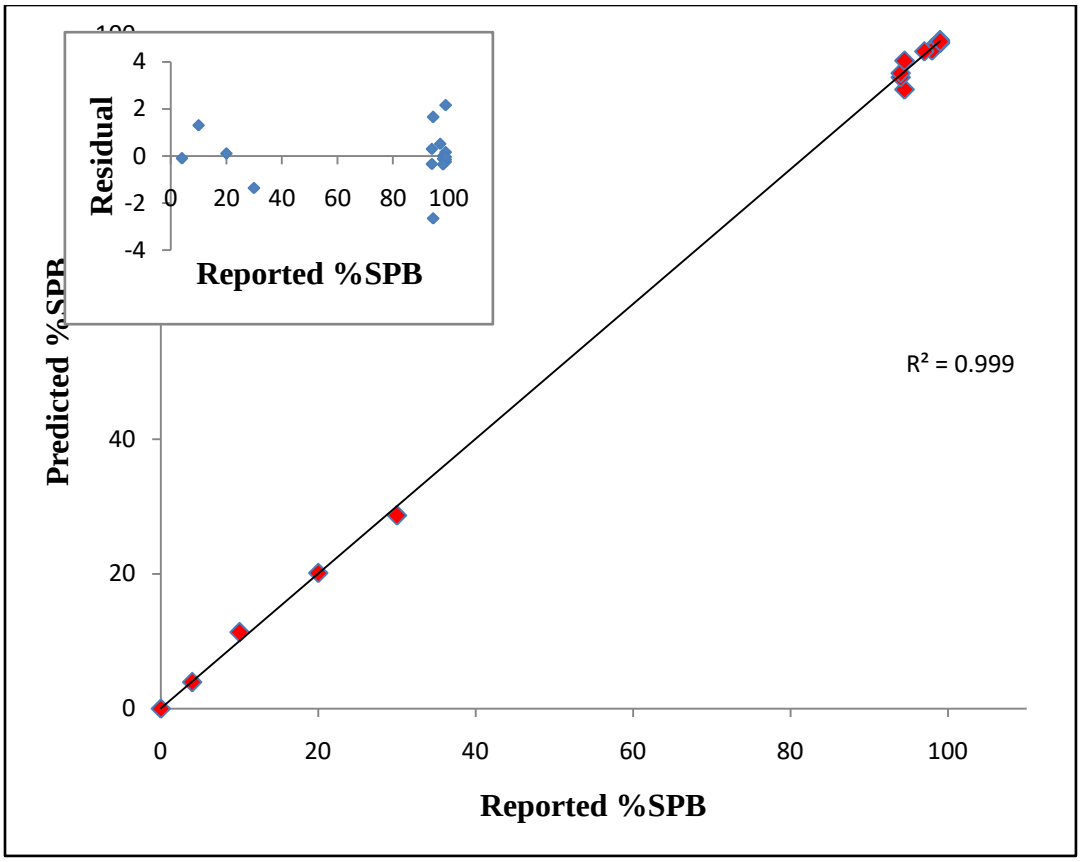

Fig. 2: Plot between the predicted and reported values of %SPB for QSPkR of antibiotic drugs. The inset shows the corresponding residual plot

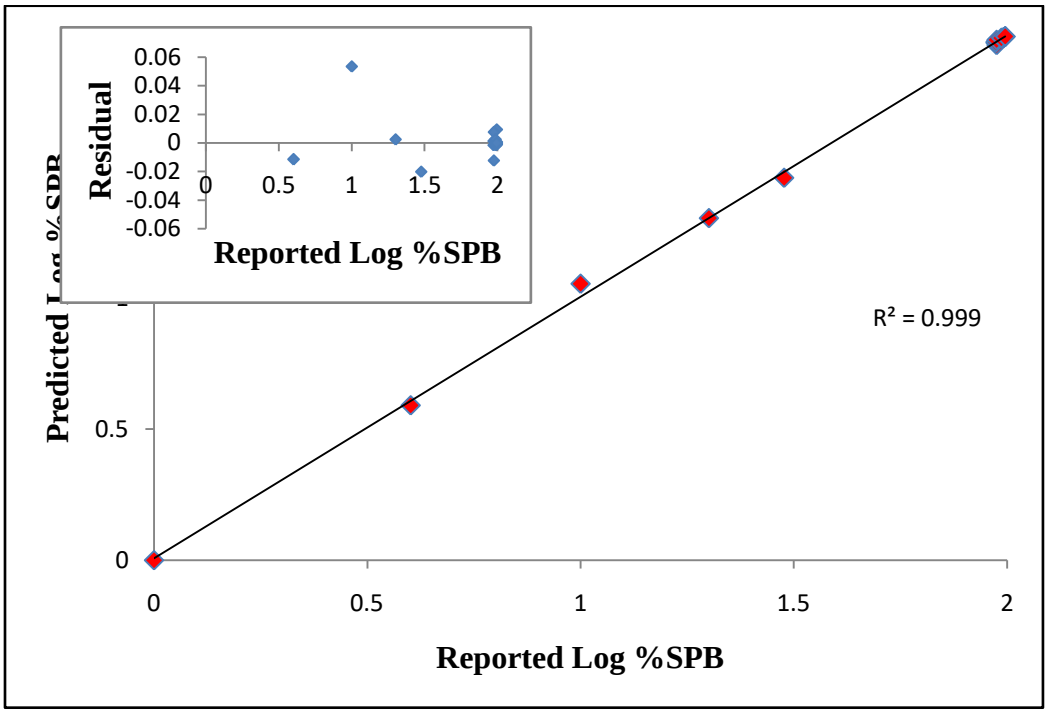

Fig. 3: Plot between the predicted and reported values of Log %SPB for QSPkR of antibiotic drugs. The inset shows the corresponding residual plot

DISCUSSION

In Paper I an overall antibiotic prescribing rate of 66% was documented in the outpatient diagnosis-prescribing study. In a study in Delhi using the exit interview methodology it was found that 39% of the patients attending public clinics and 43% of the patients attending private health-care facilities were prescribed antibiotics (Kotwani and Holloway2011). However, that study was done among all patients attending outpatients and nonspecifically among patients suspected to have an infectious aetiology as in our study. Therefore, the proportion of patients receiving antibiotics is not strictly comparable. In another study done in secondary level hospitals in Maharashtra in outpatient attendees using the WHO core prescribing indicators, 35% of the prescriptions contained an antibiotic and 25% of the prescriptions contained an injection (Potharaju and Kabra 2011).

In our outpatient clinics injectable antibiotics were prescribed to 1.2% of the patients. This low rate could be due to the fact that our study involved only antibiotics and not all drugs ina prescription. Also, our study was done with only the specialist practitioners and not all practitioners. A study done among the Paediatric outpatient clinics of a tertiary care set-up found a rate of 29% for antibiotic prescribing among all children attending outpatients(Dimri et al. 2009).

In contrast a study done in primary and secondary health-care facilities in Uttar Pradesh, India found a high prescribing rate (81.8%) of antibiotics (Kumar et al. 2008). That study also noted differences in antibiotic prescribing between health care facilities at different levels. Lower prescribing rates were found in government hospitals compared to the private hospitals. Practitioners doing specialty practice prescribed fewer antibiotics compared togeneral practitioners. In Paper I facility level differences in the antibiotic prescribing were found, with less prescribing (by 11 percent points) in the teaching hospital as compared to the non-teaching hospital.

This could be due to better opportunities of continuous professional development for the teaching hospital staff. Also, it is possible that the physicians at the teaching hospitals face less pressure because of a policy of restricting the pharmaceutical company representatives. Similar effects of the policy of restricting the academic detailing by the pharmaceutical company representatives have been observed in European hospitals (Jack 2011). No comparison of antibiotic prescribing between teaching and non-teaching hospital have been published from India before. In Europe however, a lower prescribing rates in outpatients of teaching hospitals have been observed (Zarb and Goossens 2011).

Higher rates of antibiotic prescribing have been noted in the rural areas compared to the urban areas (Kumar et al. 2008). In our study however, the non-teaching hospital located in the urban setting had a higher prescribing rate of antibiotics compared to teaching hospital located in the rural setting (Paper I). The only earlier published study conducted in the province of Madhya Pradesh was done in primary heath centers of Bhopal district and found that 63.5% of the prescriptions contained antibiotics (De Costa et al. 2008).Seasonal variations in antibiotic prescribing have not been well studied in India. A study conducted in Delhi found very little seasonal variation in antibiotic prescribing, but observed slightly higher consumption of fluoroquinolones in winter (Kotwani et al. 2009).

However, seasonal variation in outpatient antibiotic prescribing is well documented in studies from Europe (Ganestam et al. 2003, Abell et al. 1999, Adriaenssens et al. 2011).These studies show that antibiotic-prescribing peaks occur in Europe during the winter season and correlate well with the peaks of influenza season (Ganestam et al. 2003,Molstad et al. 2008). This may be due to more frequent diagnostic dilemmas of the physicians during the influenza season but nevertheless represents inappropriate antibiotic important, but nonetheless give us important information on the diagnostic uncertainties faced by the physicians in the study area. The variation in antibiotic prescribing according to seasons deserves to be studied in future studies on outpatient antibiotic prescribing in India.

In Paper II, 92% of the admitted patients with suspected bacterial infections were prescribed antibiotics. There is no similar published study from India using the WHOATC/DDD methodology and “focus of infection” approach to study antibiotic prescribing. ESAC has carried out three point-prevalence surveys on hospital antibiotic use in Europe (Zarb and Goossens 2011). These surveys were carried out in the second quarter of the year2006 (Ansari et al. 2009), 2008 (Amadeo et al. 2010) and 2009 (Zarb et al. 2011). Higher antibiotic prescribing rates among the admitted patients in the teaching hospital compared to the non-teaching hospital were observed in our study. This finding is consistent with three point-prevalence surveys conducted in Europe (Zarb and Goossens 2011) and one study in the United States (Pakyz et al. 2008). The differences in the antibiotic prescribing observed between the teaching and the non-teaching hospital can to some extent be explained by the differences in the case-mix.

Surgical Prophylaxis Among Admitted Patients

In paper II it was observed that about one third of all antibiotic prescribing was for surgical prophylaxis. The proportion of patients receiving surgical prophylaxis in our study (34%)was higher than that recorded by the ESAC surveys (13 to

15%) (Zarb and Goossens2011). The problem of continued prophylaxis for duration of more than 24 hours is an area of concern. In our study 86% of the patients receiving surgical prophylaxis received it for more than 24 hours, which is inappropriate as most guidelines recommend surgical

prophylaxis as a single dose sixty minutes before surgery (Dellinger et al. 1994). Surgical prophylaxis of inappropriate duration is also a problem in Europe, where between 53 to69% patients received inappropriately long prophylaxis (Zarb and Goossens 2011). Lack of stop orders once the surgical prophylaxis is begun or the fears of high infection rate in the unit are the main reason cited for long prophylaxis (Zarb and Goossens 2011).

So, antibiotics are being prescribed to compensate for a poor actual or perceived hygiene(environmental or hand hygiene). In a study on perceptions of hand hygiene done in outreaching hospital important motivational and infrastructure barriers were identified for introducing hand hygiene practices (Joshi et al. 2012). The duration of surgical prophylaxis need to be reduced. Work is ongoing to identify possible methods for this.

CONCLUSIONS

This paper provides much needed information on antibiotic prescribing linked to the diagnosis of individual patients in an Indian setting. It also provides information on antimicrobial resistance among bacteria (both commensal and pathogens) from two hospitals in Rohtak, India. I believe that the findings can be useful for planning antibiotic stewardship programs in other similar settings throughout the world. The paper identified several key areas that call for interventions.

• Outpatient antibiotic prescribing was found to be less frequent in the teaching hospital compared to the non-teaching hospital. Broad-spectrum antibiotics were prescribed more often in the non-teaching hospital irrespective of diagnosis and age group.

• High antibiotic prescribing rates were observed for self-limiting diseases like diarrhea and upper respiratory tract infection.
• A high rate of quinolone prescribing in outpatients is a cause of concern and treatment guidelines are needed to define such use for common infections.

• The method for surveillance adapted for the outpatient diagnosis prescribing study appears suitable for busy outpatient settings like ours in India and might be tried in other low and middle-income countries.

• The targets identified for interventions in the surveillance study among admitted patients were: higher antibiotic prescribing in a teaching hospital compared with anon-teaching hospital, longer than recommended duration of prophylaxis and lack of distinction between prophylaxis and therapy among surgical patients, irrational antibiotic prescribing in gastroenteritis, overuse of quinolones and lack of use of penicillin in pneumonia, overuse of quinolones and lack of use of doxycycline and macro ides in genital infections, and overreliance on antibiotics in treating skin and soft tissue infections.

• Even the specialist paediatricians did not adhere to standard treatment guidelines for diarrhea among children. So, developing guidelines alone is not enough. Research, advocacy, political commitment and public health campaigns are needed for implementing the guidelines along with training of healthcare workforce.

• Antimicrobial susceptibility testing and surveillance among the healthy individual's commensal bacteria also suggests importance of prudent antibiotic prescribing.

• High rate of antibiotic prescribing among admitted patients, especially of 3rd generation cephalosporin's and quinolones together with high rates of ESBL producing pathogens, shows urgent need to curb antibiotic use when there is no indication for it. The therapeutic armament against the ESBL producing Gram- negative bacteria is very limited. Thus, to preserve the effectiveness of current antibiotics we urgently need antibiotic stewardship programs. The situation islike "the lull before the storm". The time to act is now!

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