3. Methodology

3.1. Development of indicators for identifying ADEs


3.1.2. Study setup: Medicine units of tertiary care teaching hospital

3.1.3. Development of Indicator list

This section of the work uses the terminology ADE since the screening of medical records will help to identify ADEs. After performing causality assessment, these ADEs are documented as ADRs.

An initial list of ADE indicators was prepared based on published literature (Institution of Health Improvement, 2005; de Wet & Bowie 2009; Matlow et al. 2005; Morris & Cantrill 2002; Morris et al. 2002; Szekendi et al. 2006; Takata et al. 2008). These indicators were reviewed by a panel of 3 experts (Two clinical pharmacists and a clinician). The indicators which were relevant to the study set up were selected. The indicators relevant to general medical practice were kept in the list whereas the indicators related to other specialties like psychiatry, ICU and surgery were deleted. The review team collectively decided on whether to keep or delete a particular indicator from the list. This exercise was carried out to concise the list, so that Delphi panel can work on it for the development of final set of indicators.

3.1.4. Delphi panel review

A Delphi panel was formed with three clinicians and two clinical pharmacists. The members evaluated the indicator list anonymously and scored it. The panel members rated each item of the list on a Likert scale, which represented a score from 1 to 5 (Armitage & Colton). During this review panel members were asked to suggest any additional indicators which could be added to the list. At the end of first review, the scores were summarized and it was presented to the panel members along with their own scores.

In the second review panel members were encouraged to reassess their opinion in light of scores given by other members. Additional indicators were added to the list for review. After the second review, the mean score for each item was calculated. The mean score of 3 and above out of 5 was considered as criteria for inclusion into the list. For the newly added
indicators one more review was conducted and mean scores were calculated. The final comprehensive list was divided into four categories namely (1) Abnormal changes in clinical condition. This is the category of indicator where the clinical condition observed in the patient points to the possibility of drug involvement (2) changes in patient care process. This is the category of indicator where the modifications of patient care process give some clue on ADE (3) drug related alterations. This is the category of indicator where the use of certain drugs raises the suspicion of ADEs (4) changes in lab parameters. This is the category of indicator where the alterations in certain lab parameters pointing to the drug related problems.

After the preparation of comprehensive list of indicators, they were used to screen the case reports of previously identified and documented ADEs. These adverse events were identified by clinical pharmacists from medicine wards during their rounds with clinicians. Case reports of the period between February to November 2008 was considered for this screening process. During this period a total of 509 reports were documented. Since this screening is exploratory in nature, it was decided to screen around 20% of records and therefore 100 records were reviewed. Systematic sampling procedure was used to select the samples, wherein every fifth record was selected for review. These reports contained complete details of the case which included medical history, diagnosis, lab investigations, therapy and ADE. Reports were reviewed for the presence of any indicators from the prepared list. Following four factors were then assessed viz: mean number of indicators per case report, commonly identified indicators, total number of identified indicators and indicators that were not identified in any of the case reports.
3.2. Intensive monitoring of ADRs in medicine department


3.2.2. Study setup: The study was carried out in one unit of the medicine department of the study hospital.

3.2.3. Patients and data

All patients admitted to the study wards during the data collection period were included in the study. The researcher reviewed drug charts, medical and nursing notes of all the patients admitted in the study ward. The review was conducted to screen case records for the presence of any evidence of ADRs. Objective markers of ADRs, e.g. laboratory results, were identified from the case notes and the hospital computer system and the subjective markers of ADRs like headache, nausea and rash were identified through patient progress notes, discussion with the medical team and patient interview. After completion of data collection, case note analysis was performed to assess patient outcomes and to ensure that all the available details regarding the ADR had been collected. The ADRs were defined according to WHO definition and was in accordance with the adverse effects listed for each drugs in their summary of product characteristics and the hospital formulary. The collected data is documented separately in ADR documentation form for further assessment. An ADR alert card was provided to those patients who experienced such ADRs which by their nature cautions against re-exposure of the suspected drug. All ADRs were assessed by a panel of experts including the investigator. The panel consisted two clinical pharmacists and two clinicians and they met periodically to assess the ADRs. The panel assessed the causality, predictability and preventability using appropriate scales given in section 3.3.4.b. When there is a disagreement between the members of panel consensus was arrived after discussion. Opinion of treating physicians was also considered in arriving at a consensus.

Inclusion criteria:
- Adult patients of either sex who developed an ADR

Exclusion criteria:
- Patients who developed an ADR due to intentional or accidental poisoning
- ADR to fresh blood/ blood products
- ADR due to drug overdose
- Patients with drug abuse and intoxication
3.2.4. Evaluation of data

Reported ADRs were evaluated to identify the pattern with respect to patient demographics, nature of the reactions, characteristics of the drugs involved and outcome of the reactions. Causality, severity, preventability and the presence of predisposing factors for the reactions were assessed.

a). Patient characteristics

Patient's age and gender were considered for evaluation. Patients were divided into five groups: young adults (16-30 years), adults (31-45 years), older adults (46-60 years), elderly adults (61-75 years) and very elderly adults (>75 years) for age categorization. Children of 15 years or less were excluded from the study. The age categorization was based on a classification reported by Gallelli et al (Gallelli et al. 2002).

b). Reaction characteristics and drug characteristics

The incidence rate of ADRs were calculated based on the number of patients developed ADRs divided by total number of patients monitored during the study period of six months. ADRs were also classified as either type A (dose-dependent) or type B (idiosyncratic) according to the system introduced by Rawlins and Thompson in 1977 (Dollery & Rawlins 1977). Drugs which were commonly responsible for ADRs were classified according to WHO Anatomical Therapeutic Chemical (ATC) classification based on WHO-ATC Index 2008 (WHO, 2008). Reactions were further classified depending on the organ system affected using WHO Adverse Reaction Terminology (ART) (WHO, 2003).

c). Management and outcome

Management strategies employed for the ADRs were categorized as drug withdrawal, dose reduction, additional treatment for ADR and no change in regimen without any additional treatment. Outcomes of all ADRs were categorized after dechallenge, rechallenge and as well as the final outcome of the event. Patient outcomes were reported as fatal, fully recovered (patient fully recovered during hospitalization), recovering (patient recovering, but not fully recovered during hospitalization) and unknown (not documented after initial report in chart).
d). Analysis of ADRs

i. Causality - In order to assess the likelihood that a drug has caused the reaction, causality was assessed using Naranjo’s ADR probability scale whereby the ADRs were classified into certain, probable, possible and unlikely to be drug induced depending upon the level of association (Naranjo et al. 1981).

ii. Preventability - ADRs were categorized into definitely preventable, probably preventable and not preventable using the modified criteria of Schumock and Thornton by Lau et al. (Lau, Stewart & Dooley 2003).

iii. Severity - Depending upon the severity, ADRs were classified into mild, moderate and severe reactions using the criterion developed by Hartwig et al. for severity assessment (Hartwig, Siegel & Schneider 1992)

iv. Onset of ADRs - Based on the onset of ADRs, they were classified into acute (< 1 hour), sub-acute (1-24 hour) and late onset (>48 hours) (Edwards IR. 1997).

v. Predisposing factors - Factors which could have predisposed to the occurrence of ADRs in the individual reports were evaluated. Predisposing factors studied were: age, gender, multiple and inter-current disease states and poly pharmacy (Parthasarathi, 2004). Age above 60 years and below 18 years was considered as a predisposing factor under ‘age’ criteria. Polypharmacy was considered as minor (2-3 drugs), moderate (4-5 drugs) or major (>5 drugs) based on the classification by Veehof et al (Veehof et al. 2000). Gender of the patient was considered as a factor only if there was previous information that the gender of the patient is known to predispose for the reaction in question. Multiple disease state was considered if more than two coded diseases have been diagnosed in the patient at the time of reaction and inter-current disease is considered if they are known to alter the response to the drug in question and predispose the patient to the ADR.

3.2.5. Statistical analysis

Frequencies with percentage were used to summarize gender, diagnosis, number of drug dispensed, frequency, drugs involved, organ system involved and severity of ADRs. Mean with 95% confidence interval was used to summarize age, length of stay. Chi square test
was used to find the association between age and gender. Spearman correlation was used to find the correlation between numbers of drugs and length of stay with ADRs. A p value of less than 0.05 was considered statistically significant.

3.3. Development and evaluation of a prediction model for the cost of management of ADRs

3.3.1. Study duration: March to August 2008 for the cost modeling.

3.3.2. Patients and data The patient data of intensive monitoring program (Section. 3.2) was used.

Analysis of whether the ADR directly increased the length of stay was quantified after clinical assessment of the condition in consultation with treating medical team. The costs involved in the management of ADRs were collected from hospital patients’ administrative system (HPAS). Items utilized in the cost function for each patient were: additional hospital stay, medication, clinical investigation charges, additional procedures and other costs like professional and nursing charges. This analysis used the perspective of the payers in making these estimates.

3.3.3. Model development and evaluation

Frequencies with percentage were used to summarize gender, diagnosis, number of drugs taken, length of stay, drugs & organ system involved and severity of ADRs. Mean with 95% confidence interval was used to summarize age, length of stay. Cost model was developed after identifying variables contributing to the cost of managing ADRs using univariate analysis. Stepwise backward elimination procedure was used for selection of variables. The 5% significance level was used when assessing factors for inclusion in the model.

A three step data analysis was designed to develop the prediction model. Univariate analysis was used to identify statistically significant factors. Variables with p value more than 0.2 were excluded from the model. Finally, all eligible covariates identified in the univariate analysis were considered in final model. Generalized Linear Model (GLM) with normal distribution and log link models was used to model total cost to be obtained in the final model (Diehr et al. 1999) The level of p<0.05 was considered as statistically significant.
3.3.4. Validation of fitted model

The developed prediction models were assessed by performing mean absolute error (MAE) as mean of absolute difference between observed and predicted cost, root mean square error (RMSE) as predicted cost minus observed, square of the difference, mean of the squared difference and square root of this value, residual analysis and Intra-correlation coefficient (ICC). Residual analysis was carried out to detect violations of the assumptions in the fitted model. Histogram and scatter plots of residuals were plotted for the evaluating the model assumptions (Diehr et al. 1999; Lindsey & Jones 1998; Shrout & Fleiss 1979) (Miles, 2005).

3.4. Development and validation of a prediction model for severity of ADRs

3.4.1. Study duration: November 2007- April 2008

3.4.2. Data source: All data for the study were extracted from the intensive monitoring study (Section 3.2).

3.4.3. Statistical analysis

Frequencies with percentage were used to summarize gender, diagnosis, number of drugs taken, length of stay, drugs involved, organ system involved and severity of ADRs. Mean with 95% confidence interval was used to summarize age, length of stay. Spearmen correlation was used to correlate the number of drugs taken, gender, number of ADRs, length of stay and severity of ADR. The associated risk factors for severity of ADR were obtained by means of a multiple logistic regression model (Generalized Linear Model). Backward elimination procedure was used for selection of variables. Hosmer& lemeshow test and area under the Receiver Operating Characteristic curve (AUROCC) was used to test the goodness of fit of the model (Lemeshow & Hosmer 1982). The 5% significance level was used when assessing factors for model inclusion.

A three-step data analysis was designed to develop the prediction model. Univariate analysis was used to identify significant factors. Variables with a p value more than 0.25 were excluded from the model. Finally, all eligible covariates identified in the univariate
analysis were entered in the multivariate logistic regression analysis to obtain the final model. The significance level of p<0.05 was considered for interaction evaluation and the final model building analysis.

Before proceeding to the model validation phase, the ability of the new model to discriminate between true positives and false positives was determined via construction of AUROCC. To achieve this, the true-positive ratio (sensitivity) and false-positive ratio (1-specificity) for 0.1 increments of predicted hospital readmission risk were calculated and plotted. This ROC curve was compared with that produced when the original ten variable models was applied to the model-building study population. The model that produced an area under the AUROCC nearest to a value of 1 was regarded as the most effective in discriminating true and false positives (Hanley & McNeil 1982; Knottnerus 1995).

3.5. Study of clinical Characteristics of patients with Anti tubercular therapy induced hepatotoxicity (ATT-IH)

Background:

The medicine unit involved in this study had clear protocols for initiation, follow-up and withdrawal of ATT drugs.

Diagnosis of ATT-IH

Liver function tests (LFT) were monitored by measuring the serum level of AST, ALT, ALP, bilirubin (total and direct), total protein, and albumin. Pretreatment LFTs were conducted. After initiating the drug therapy, LFTs were performed after a week, then biweekly for at least two months. LFTs were repeated later whenever symptoms suggestive of hepatotoxicity like nausea, anorexia, malaise, vomiting, organomegaly or jaundice occurred. Patients were kept under close observation and were instructed to report any unusual signs and symptoms experienced during their treatment period. In the patients developing hepatotoxicity, medications were stopped immediately and serum transferases were measured twice weekly, until symptoms resolved and the transferases level decreases down to 2 × ULN. This unit also had a criterion of not starting ATT therapy when the patients are diagnosed with Hepatitis B & C.
**Management of ATT-IH**

Whenever patients were diagnosed with ATT-IH, usual regimen was discontinued. After discontinuation of the hepatotoxic drugs an alternative regimen including ethambutol (15 mg kg\(^{-1}\)), ciprofloxacin (500-750 mg, b.i.d.) and an aminoglycoside antibiotic (Streptomycin 5 mg kg\(^{-1}\)) were substituted temporarily. Alternative regimen was continued until normalization of serum transaminases levels. The anti-TB drugs including isoniazid, rifampin, pyrazinamide and ethambutol were reintroduced gradually in a stepwise manner to all patients. After normalization of serum transaminases, small dose of isoniazid (50 mg) was reintroduced and gradually increased to recommended daily dose over one week. This procedure was repeated by adding rifampin and pyrazinamide respectively. Reintroduction of anti-TB drugs is an accepted method. (Snider, 1992; Mahashur, 1991) Also information regarding the drugs, dosage and duration of treatment were noted. BMI was considered to identify patients who were under weight and who are normal weight. BMI of > 19 kg/m\(^2\) was considered as normal weight.

3.5.1. **Study period:** July 2003 to July 2006.

3.5.2. **Study setup:** One unit of general medicine department of the study hospital.

3.5.3. **Study Design:** Retrospective observational study

3.5.4. **Inclusion of cases for review**

Records were reviewed to identify patients who developed ATT-IH. The inclusion criterion was the elevation of LFTs beyond three times the basal value. Those records which met this criterion were selected for thorough review and assessment of clinical characteristics and risk factors.

3.5.5. **Data Collection**

A total of 941 records of TB patients who were treated during the study period were screened for clinical and biochemical data. ATT-IH was defined as increased levels of liver transaminases more than three times above the normal value (< 40UL\(^{-1}\) for AST and ALT) with or without any other clinical signs and symptoms. Case records in which the LFTs were elevated to the level expected for the diagnosis of hepatotoxicity were identified through this
screening process. Descriptive statistics was used to express the clinical characteristics of patients who developed ATT-IH.

3.6. Economic impact of management of cutaneous ADRs (cADRs) in hospitalized patients

3.6.1. Study period: June 2008 to December, 2008

3.6.2. Study setup: One unit of a dermatology department and units of other departments where dermatologists managed the referred cases.

3.6.3. Patients and data analysis:
The data of in-patients of one unit of the department of dermatology and the in-patients referred from other departments due to cADRs were included in the study. The diagnosis of the cADR was made by the dermatologist based on clinical and morphological grounds. The identification of cADR, causality assessment, management, documentation of outcome and screening for predisposing factors was carried out using standard procedure as explained in section 3.2.4

The cost incurred in managing the documented cADRs was calculated based on the total amount spent on the patients with cADR divided by total number of patients with ADRs. In the cases where the offending drug was stopped and where the treatment was continued without any change, the cost of treatment was considered as nil. All the cases which involved expenditure on drugs, laboratory tests, consultation, hospital stay etc., were considered for the calculation of the cost incurred for the hospital. If the patient was transferred to the intensive care unit from the ward to which he/she was admitted in order to manage cADRs, this additional cost of care was added to the total cost. Only direct costs were included for the cost calculation.

3.6.4. Statistical analysis

Rates of cADR occurrence during the hospital stay were calculated as percentage of inpatient population treated. Student t-test was used to compare means. For other variables, the $\chi^2$ test was used. A two tailed p value of less than 0.05 was considered statistically significant.
3.7. ADRs in hospitalized patients treated with cardiovascular drugs

3.7.1. Study period: Feb 2009 to Sep 2009

3.7.2. Study setup: One unit of cardiology department of tertiary care teaching hospital

A prospective intensive monitoring study was conducted in a unit of department of cardiology of study hospital. All patients admitted in the cardiovascular unit during an eight month (Feb 2009 to Sep 2009) period were evaluated for cardiovascular drug induced ADRs. Patients who were previously using or newly started on cardiovascular drugs were monitored and followed for detecting and recording ADRs.

The identification of ADR, causality assessment, management, documentation of outcome and screening for predisposing factors was carried out using standard procedure as explained in section 3.2.4. The length of stay for each patient was recorded using HPAS.

3.7.4. Statistical analysis

Frequencies with percentage were used to summarize gender, diagnosis, number of drug dispensed, frequency, drugs involved, organ system involved and severity of ADRs. Mean with 95% confidence interval was used to summarize age and length of stay. Chi square test was used to find the association between age group, gender, length of stay with ADRs.

The data were hierarchically structured, in that multiple ADR episodes can occur with multiple admissions. To compare ADR incidence between patients with and without ADRs, a generalized estimating equation (GEE) (Brown & Prescott, 1999) with compound symmetry was used to account for the within-patient correlation. This was considered more appropriate than a random effects model when there are small numbers of observations within patients (Brown & Prescott, 1999).

For all other analyses, where a patient had multiple admissions or multiple ADRs, a patient’s first ADR episode was used for analysis at the patient level. The first ADR episode was used to assess the affected patient population and their risk factors (age, gender and number of drugs) were identical or assumed to be broadly similar for patients who had multiple admissions. Binary outcomes were compared between groups using the chi-square
statistic for assessing significance. Comparisons between groups with respect to continuous measures were made using the t-test or the Mann-Whitney U-test, depending on skewness, for assessment of statistical significance. The 5% level was used for assessing significance.

Risk factors for ADRs were identified by investigating the effects of age, gender and number of drugs prescribed on the time to ADR. Regression analysis was used to identify the predictors. Results are given in terms of the Odds ratio (OR) for a particular factor with accompanying 95% confidence interval. The 5% significance level was used when assessing factors for model inclusion.

All analysis was performed using Statistical Package for Social Studies (SPSS) for window 15 (SPSS Inc., South Asia, Bangalore).