Measurement of Adult Antimicrobial Drug Use in Tertiary Care Hospital Using Defined Daily Dose and Days of Therapy

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Widespread overuse and inappropriate use of antimicrobial drugs continues to fuel an increase in antimicrobial resistance and leads to consequent treatment complications and increased healthcare costs. In the present study we aimed to describe antimicrobial drug consumption and predictors and to identify potential targets for antimicrobial stewardship. This was a prospective observational study conducted at adult medicine wards of tertiary care teaching hospital over the period of five months. Antimicrobial drug consumption was measured using days of therapy per 1000 patient days and defined daily dose per 1000 patient days. Additionally, predictors of multiple antimicrobial prescribing were also analyzed. Seven hundred thirty patients were screened and 550 enrolled, receiving 1,512 courses of antimicrobial therapy, mainly intravenously (66%). Most frequently prescribed agents were artesunate (13%), ceftriaxone (11%) and metronidazole (10.5%). Overall consumption was 1,533 days of therapy per 1000 patient days and was mainly attributed to antibiotics (98.3%) for empirical therapy (50%). Median days of antimicrobial drugs prescribing were 3 (inter quartile range 2-5). Most commonly consumed antimicrobials were ceftriaxone (31%, 248.8 g) and artesunate (26%, 29 g). Antimicrobials contributed to 72.5% expense of the total incurred. Multivariate analysis reveals that younger patients (≤45 years) (odds ratio: 1.59, 95% CI 1.14-2.21) were more likely and absence of comorbidities (odds ratio: 0.58, 95% CI 0.42-0.79) and shorter hospital stay (≤ 6 days)(odds ratio: 0.44, 95% CI 0.32-0.60) were associated with less likelihood of prescribing multiple antimicrobial drugs. Estimating antimicrobial drugs use by defined daily dose method will remain open to criticism because the prescribed dosage is not often in agreement with the "usual" daily dose, which depends on location of and susceptibility of pathogenic organisms and metabolic status of the patient.

Key words: Antimicrobial drugs, antimicrobial stewardship, defined daily dose, days of therapy

Appropriate antimicrobial drug (AMD) use is a key factor in limiting the development and spread of resistant bacteria in hospitals and communities^[1]. Several factors such as excessive and unnecessary prescriptions, poor quality, dosing and duration errors, mismanagement of apparent antibiotic failure, non-implementation of infection control practices, dearth of susceptibility testing and surveillance are thought to contribute to the inappropriate use of antimicrobials^[1-3].

Antimicrobial stewardship involves the optimal selection, dosage, and duration of AMD treatment that results in the best clinical outcome for the treatment or prevention of infection with minimal toxicity to the patient and minimal impact on subsequent resistance^[4]. Professional organizations recommend the monitoring of aggregated AMD use at the local and national levels to better understand the relationship between the use of antibacterial drugs and emerging bacterial resistance. The Infectious Diseases Society of America (IDSA) stewardship guidelines recommend using the World Health Organization (WHO) defined daily dose per 1000 patient days (DDD/1000PD) as the measurement unit for antimicrobials^[5]. Certain shortcomings have been recognized with DDD methodology like underestimating antibiotic exposure when the administered daily dose is reduced for a patient with impaired renal function. Secondly, DDD methodology does not apply to pediatric patients. Finally, if the administered daily dosage differs

significantly from the WHO-approved DDD, then DDD methodology will not provide an accurate assessment of the number of days of therapy.

An alternative measure of consumption using days of therapy per 1000 patient days (DOT/1000PD) has been evaluated^[6]. The preferred measurement approach remains unresolved. Suggested advantages of the DOT methodology are that it is not influenced by changes in the recommended DDD, or discrepancies between the DDD and the preferred daily dose and by doseadjustment in renal insufficiency^[7].

AMD use in hospitals has proved to be difficult to measure. Early estimates have simply reported the proportion of patients receiving antibacterials during hospitalization. More recently, the aggregate AMD use has been measured among networks of hospitals in developed countries using standard methodology. Few such data are available in this regard from developing countries, especially the AMD use measurement using DDD and DOT methodology. So evaluation of the usage of antimicrobials is an important step in each setting to complement the effects of increasing the lifespan of these antimicrobials globally^[8]. Given that background, this study is conducted in a tertiary care hospital in India to assess the antimicrobial utilization, consumption using the DOT and DDD methodology.

MATERIALS AND METHODS

This was a prospective observational study conducted in a 28-bed adult medicine (2 male and 1 female) wards of public funded tertiary care teaching hospital. Study initiated following approval from the Institutional Ethics Committee (IEC). All adult inpatients admitted in medicine wards over the 5 months period (between September 2011 to February 2012), were screened for inclusion. Exclusion criteria were incomplete medical records, medico-legal cases or no antimicrobial therapy during the hospital stay. Medico-legal cases were excluded from the study because IEC of the hospital not permitted to review those cases.

Direct patient care was provided by physicians while the study was taking place. During the study period there were no institutional or unit-specific antimicrobial guidelines. Daily chart review and data extraction was performed by investigator, familiar with practice but not involved in the daily care of patients. Included patients were followed until the occurrence of first of three endpoints: discharge, transfer out of the unit or death during the stay.

Patient information was recorded on predesigned data collection form. This included patient demographics, indications for therapy, antimicrobial regimens (agents, doses, frequency and routes) and antimicrobial start/stop dates and times. Length of stay was recorded for all patients admitted to the wards during the study period. The antimicrobials were classified using the World Health Organization Anatomical Therapeutic Chemical (WHO-ATC) classification system^[9].

Outcomes:

The primary outcome of the present study included the percentage use of antimicrobials by class and agent, antimicrobial consumption as measured by DDD/1000PD and DOT/1000PD methods of ten most commonly used antimicrobials. Antimicrobials encompassed systemic antibiotics, antifungals or antivirals prescribed for the purpose of preventing or treating an infection. Percentage use was defined as the number of treatment courses of a particular class and agent divided by the total number of treatment courses. A treatment course referred to any antimicrobial prescribed regardless of the duration of administration. Restarting the same agent up to 48 h after discontinuation was defined a priori as the same treatment course, whereas restarting the same antimicrobial beyond 48 h of discontinuation was considered a new treatment course. DDDs for antimicrobials were computed using standard WHO methodology and normalized per 1000 patient-days to control for differences of hospital census.

Antimicrobial consumption during the study period was expressed as DOT/1000PD, as described by Polk *et al.*^[7]. One day of therapy represented the administration of a single agent on a given day regardless of the number of doses administered or dosage strength. Days of therapy were confirmed by verifying dose administration on the medication record on a daily basis. The length of stay for all patients admitted to the wards during the study period was summed to determine the total number of patient days. Secondary outcome included the assessment of the predictors of multiple antimicrobial prescribing in the inpatients.

Statistical analysis:

Descriptive analysis of primary and secondary outcomes was performed. Values are expressed as numbers with percentages, means with standard deviation (SD), median with inter-quartile range (IQR). Percentage use, WHO DDD/1000PD and DOT/1000PD are calculated as described above. Student t-test and chi-square tests were used to compare demographic variables. Multivariate logistic regression analysis was performed to assess the predictors of multiple antimicrobial prescribing. Data were analyzed using SPSS (version 12.0).

RESULTS

Seven hundred and thirty patients were admitted in the medicine wards during the study period and screened for study eligibility. Five hundred and fifty (75%) patients met the inclusion criteria. Of the 180 excluded patients, 156 did not receive any antimicrobials, 10 incomplete patient records and 14 were medico-legal cases. Of the included patients, 149 (27%) had acute febrile illness, 124 (22.5%) had hypertension, and 116 (21%) had diabetes mellitus as their primary diagnosis. The clinical and demographic characteristics are described in Table 1. Total antimicrobial expenditure varied widely during hospital stay. The total expense on AMDs in all patients was INR 2 061 186 with a mean expense of INR 2919 (579) per patient. The total expense of all drugs was INR 2 844 178 with a mean expense of INR 4029 (624) per patient. Thus, antimicrobials contributed to nearly 72.5% expense of the total incurred on entire medications. Among the prescribed antimicrobials, imipenem was the most expensive antimicrobial agent.

Antimicrobial consumption, percentage use:

Five hundred and fifty (75%) of the admitted patients received at least one AMD. A total of 1,512 courses of AMD therapy were prescribed in 550 patients including 14 antimicrobial classes (Table 2) and 63 agents. Twenty most frequently prescribed agents were analyzed for percentage use and consumption by class (Table 2) and agent (Table 3). Antibiotics resulted in 1,084 (72%) courses, antiprotozoals 397 (26%), antifungals 22 (1.5%) and antivirals 9 (0.5%). The classes of antimicrobials that accounted for greater than 10% of treatment courses in descending order were cephalosporins, penicillins and combinations, antimalarials and antiamoebics (Table 2). Artesunate

197 (13%) was the most commonly prescribed agent followed by ceftriaxone 172 (11%) and metronidazole (10.5%) (Table 3). Each of these agents accounted for greater than 10% of treatment courses. One thousand and four of the 1,512 (66%) antimicrobial courses were initially administered intravenously and only 6% of this transitioned to oral route later.

Antimicrobial consumption, DOT/1000PD:

Overall, it resulted in 5,863 days of therapy with a mean of 3.9 (2.8) days. During the study period there were 3,825 inpatient days. Antimicrobial consumption described as DOT/1000PD was 1,533 with 1,507 (98.3%) of this attributed to antibiotic classes. Antifungals 12.6 (0.8%) and antivirals 13.3 (0.9%) contributed minimally to the overall consumption. The three largest class contributors, in descending order, were cephalosporins, penicillins and antiamoebics (Table 2). In terms of individual agents, metronidazole followed by ceftriaxone and artesunate were the three largest contributors to consumption (Table 3).

Percentage consumption as expressed by DOT/1000PD paralleled percentage use for the majority of antimicrobial classes. Exceptions to this trend included the antimalarial class, for which a lower percentage

Patient characteristics	Values	P value	
Age (years), mean (SD)	42.9 (18.3)		
Males, n (%)	348 (63)		
Age distribution, n (%)			
<30 years	153 (28)	<0.001	
≥30-<60 years	280 (51)		
≥60 years	117 (21)		
Number of drugs prescribed, n (%)			
1-9	335 (61)	<0.001	
≥10	215 (39)		
AMD prescribed, n (%)			
<5	509 (92)	<0.001	
≥5	41 (8)		
Length of hospital stay, n (%)			
<10 days	461 (84)	<0.001	
≥10 days	89 (16)		
Comorbidity*, n (%)			
Absent	296 (54)	0.07	
Present	254 (46)		
System involvement, n (%)			
1	327 (59)	<0.001	
2	165 (30)		
≥3	58 (11)		
Days of AMD prescribing median (IQR)	3 (2-5)		

SD=Standard deviation, AMD=antimicrobial drugs, IQR=inter-quartile range, *comorbidities included diagnoses apart from the primary cause for admission such as hypertension, chronic kidney disease and coronary artery disease of consumption compared to percentage use was most evident (10.5 versus 14.7%). Conversely, antiamoebics demonstrated higher percentage consumption than percentage use (12.6 versus 10.5%) (Table 2). This was supported by trends for individual agents within these classes: metronidazole (14.3 versus 10.5%) and artesunate (10.8 versus 13%) (Table 3).

Antimicrobial consumption, DDD/1000 PD:

Table 4 enlists the 10 most commonly prescribed antibiotics along with their WHO DDD/1000 PD. The most commonly consumed antimicrobials were ceftriaxone (31.2%, 248.8 units consumed in grams) followed by metronidazole (28.9%, 10.5 units consumed in grams).

TABLE 2: ANTIMICROBIAL	USE AN	D CONSUMPTIO	N BY CLASS

Class	Number of courses	% use*	DOT	DOT/1000PD [†]	% consumption [‡]
Cephalosporins	409	27	1,580	413.1	27 (1st)
First generation	1	0.1	4	1.1	0.1
Second generation	10	0.7	43	11.2	0.7
Third generation	373	24.7	1,462	382.2	24.9
Fourth generation	25	1.7	72	18.8	1.2
Penicillin and combinations	230	15.2	899	235.0	15.3 (2nd)
Antimalarials	222	14.7	616	161.1	10.5
Antiamoebics	159	10.5	739	193.2	12.6 (3rd)
Macrolides	105	6.9	393	102.8	6.7
Fluoroquinolones	92	6.1	347	90.7	5.9
Tetracycline	74	4.9	334	87.3	5.7
Penems	34	2.3	209	54.6	3.6
Antitubercular drugs	29	1.9	90	23.5	1.5
Anthelmintics	16	1.1	44	11.5	0.8
Aminoglycoside	15	1.0	61	16.0	1.0
Antifungals	12	0.8	48	12.6	0.8
Antivirals	9	0.6	51	13.3	0.9
Miscellaneous®	106	7.0	452	118.2	7.7

DOT=Days of therapy, PD=patient days, *number of courses per class×100/total courses of therapy (1512); †DOT/1000PD, days of therapy per 1000 patient days (3825); †(DOT/1000PD per class×100)/aggregate DOT/1000PD of all antimicrobials (1532.9) (where relevant, the ranking is given in parentheses); *miscellaneous classes: cholistimethate sodium, clindamycin, lincomycin, linezolide, rifiximine, vancomycin, teicoplanin, nitrofurantoin and sulfamethoxazole/trimethoprim

TABLE 3: ANTIMICROBIAL	LISACE		
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Antimicrobial agent	Number of courses	% use*	DOT	Days of prescribing [§]	DOT/1000 PD [†]	% consumption [‡]
Artesunate	197	13.0	559	2 (1-4)	146.1	10.8 (3rd)
Ceftriaxone	172	11.4	650	3 (2-6)	169.9	12.6 (2nd)
Metronidazole	159	10.5	739	3 (2-6)	193.2	14.3 (1st)
Azithromycin	102	6.7	369	3 (2-5)	96.5	7.1
Amoxicillin+clavulanic acid	100	6.6	369	3 (2-5)	96.5	7.1
Ceftriaxone+Sulbactum	76	5.0	318	4 (2-6)	83.1	6.2
Doxycycline	74	4.9	334	4 (2-6)	87.3	6.5
Piperacillin+Tazobactum	72	4.8	310	4 (2-6)	81.1	6.0
Ciprofloxacin	57	3.8	222	3 (2-5)	58.0	4.3
Cefoperazone	53	3.5	223	4 (2-5)	58.3	4.3
Amoxicillin	43	2.8	162	3 (2-5)	42.4	3.1
Rifaximin	41	2.7	172	3 (2-6)	45.0	3.3
Imipenem+Cilastatin	32	2.1	202	5 (3-7.5)	52.8	3.9
Levofloxacin	32	2.1	110	3 (2-4.5)	28.8	2.1
Cefotaxime	30	2.0	103	2.5 (2-5)	26.9	2.0
Cefepime	25	1.7	72	2 (1-4.3)	18.8	1.4
Vancomycin	24	1.6	110	4.5 (2.5-5.5)	28.8	2.1
Chloroquine	21	1.4	48	2.5 (1.6-2.5)	12.5	0.9
Cefodizime	13	0.9	47	4 (1.8-5)	12.3	0.9
Ampicillin+Cloxacillin	13	0.9	44	3 (2.8-4)	11.5	0.9

DOT=Days of therapy, PD=patient days, *number of courses per class×100/total courses of therapy (1512); 'DOT/1000PD, days of therapy per 1000 patient days (3825); [‡](DOT/1000PD per class×100)/aggregate DOT/1000PD of all 20 antimicrobials (1350) (where relevant, the ranking is given in parentheses); [§]median (IQR) days of prescription

Antimicrobial agent	ATC code	DDD* (g) standard value	Patients prescribed ⁺ (<i>n</i>)	Total units consumed (g)	Cumulative DDD/1000PD [‡]
Artesunate	P01BE03	0.28g, O	73	14.8	57.02
Ceftriaxone	J01DD04	2.00g, P	172	248.8	143.22
Metronidazole	P01AB01	2.00g, O	159	10.5	5.92
Azithromycin	J01FA10	0.30g, O	84	17	66.37
		0.50g, P	18	30.10	59.37
Amoxicillin+clavulanic acid	J01CR02	1.00g, O	38	28.27	32.34
		3.00g, P	62	62.53	22.03
Ceftriaxone+Sulbactum	J01DA63	4.00g, P	76	111	33.39
Doxycycline	J01AA02	0.10g, O	74	7	85.02
Piperacillin+Tazobactum	J01CR05	14.0g, P	72	306	25.02
Ciprofloxacin	J01MA02	1.00g, O	21	16.05	17.65
		0.50g, P	36	0.063	0.141
Cefoperazone	J01DD12	4.00g, P	53	93	29.39

ATC=Anatomical therapeutic chemical classification, DDD=defined daily dose as mentioned by WHO, PD=patient days, O=oral, P=parenteral, g=gram, *DDD= (total units (g) of antimicrobial consumed in one month×1000)/(patient bed days in that month×WHO DDD); [†]total number of patients prescribed with that antimicrobial; [‡]cumulative DDD/1000 bed days=DDD of month 1+DDD of month 2+DDD of month 3+DDD of month 5

Predictors of multiple antimicrobial prescriptions:

Multivariate analysis reveals that younger patients (<45 years) were significantly higher (OR 1.59, 95% CI 1.14-2.21) to be prescribed with multiple AMDs. Similarly, absence of comorbidities (OR 0.58, 95% CI 0.42-0.79) and shorter hospital stay (OR 0.58, 95% CI 0.42-0.79) were associated with less likelihood of prescribing multiple AMDs suggesting non-infectious cause of their hospitalization (Table 5).

DISCUSSION

The present study on antimicrobial usage under the circumstances tested, provides three important characteristics of AMD prescribing: (1) more than half of antibiotics were initially administered parenterally and a switch to oral medication seldom occurred, (2) acute febrile illness is the most common cause of admission and (3) high prevalence of malaria in the region; artesunate was most likely AMD to be prescribed. The trend that emerges from our observations is that AMD use is nonrestrictive but not always characterized by a wide variation in antibiotics used. On the other hand, simultaneous use of more than two AMDs occurred in 50% of the cases.

This type of prospective analysis of antimicrobial consumption is an important component of medical audit, which seeks monitoring, evaluation, and necessary modification in the prescribing patterns of prescribers to achieve rational and cost-effective medical care^[10-12]. by identifying specific targets for the advancement of stewardship. Antibiotic resistance is a major concern worldwide. Selective pressure

TABLE 5: PREDICTORS OF MULTIPLE ANTIMICROBIAL PRESCRIPTIONS (N=706)

Variable	0-2 AMD	>2 AMD	Multivariate analysis		
	(n=428)	(n=278)	OR (95% CI)	P value*	
Age					
≤45	191	160	1.59 (1.14-2.21)	0.007	
>45 years	237	118			
Gender					
Male	226	157	1.06 (0.76-1.49)	0.72	
Female	202	121			
Comorbidity [†]					
Absent	294	160	0.58 (0.42-0.79)	0.001	
Present	134	118			
Hospital stay					
≤6 days	273	122	0.44 (0.32-0.60)	0.001	
>6 days	155	156			

AMD=Antimicrobial agent, OR=odd's ratio, CI=confidence interval, *P value<0.05 is considered significant; [†]comorbidities included diagnoses apart from the primary cause for admission such as hypertension, chronic kidney disease and coronary artery disease

by antimicrobial drugs is by far the most important driving force for the development of such resistance. Antibiotics are among the most commonly prescribed drugs in hospitals and in developed countries around 30% of the hospitalized patients are treated with these drugs^[5]. Prescriptions of 730 consecutive admissions audited over 5-month period to study antimicrobial utilization in the medicine wards revealed that 78% of the patients were prescribed at least one AMD though only 27% patients were admitted with acute febrile illness. This is very high as compared to the reports from developed countries^[8]. The majority of antimicrobials were prescribed for empirical indications, with the most commonly prescribed agent being artesunate followed by ceftriaxone. Penicillins and cephalosporins have continued to be a mainstay of therapy in hospitals because of their broad spectrum of activity, clinical efficacy and favorable tolerability profiles. Unexpectedly, consumption of metronidazole was higher than its percentage use.

Of the 1,512 antimicrobial treatment courses administered in the current study, antibiotics accounted for the majority (72%) compared to antiprotozoals (26%), antifungals (1.4%) and antivirals (0.6%). The antibiotic classes prescribed in greater than 50% of courses were cephalosporins, betalactam / betalactamase inhibitors. This utilization pattern is similar to that described in a survey done in Canada during which cephalosporins were most commonly prescribed (15.4%), followed by fluoroquinolones (13.3%), penicillins (10.9%) and vancomycin (9.4%)^[13]. In that study 2.4% patients were prescribed aminoglycosides, which is similar to 1% of the patients that received aminoglycosides in the present study^[13]. The preference of fluoroquinolones over aminoglycosides point towards a trend of using of less toxic antimicrobial classes.

The calculated value of 1,533 DOT/1000PD in this study exceeds the mean of 855 DOT/1000PD reported in a study from USA capturing aggregate data using electronic claims (ICU, medical and surgical wards)^[14]. The difference in the methodology and study setting make comparisons of the study result problematic. Though the present study is conducted in ward setting, percentage use and consumption were found to parallel each other for the majority of antimicrobials.

For the majority of antimicrobials, percentage use and consumption were found to parallel each other. Discrepancy between these two measures assists in identifying targets for antimicrobial stewardship. The percentage use (14.7%) of antimalarials where was notably higher than the corresponding percentage consumption (10.5%). This difference is attributable to the fact that although artesunate (most common antimalarial prescribed) was used frequently, it was mainly prescribed for fixed short-course of 3 days. For all other AMDs both the measures were comparable. Third generation cephalosporins contributed to the maximum percentage use (24.7%), and consumption (24.9%). Their prolonged and most frequent use is probably because of the fact that maximum number of patients was admitted with gastrointestinal disorders. The above observations

suggest that stewardship initiatives should direct educational efforts to shortening durations of antimicrobial exposure and review of the current approach to empirical prescribing.

Parenteral to enteral conversion is another important stewardship activity^[6]. In our study, 67% of initial treatment courses were given parenterally and only 6% of these were transitioned to the enteral route. Our study was not designed to assess the eligibility and the subsequent conversion to enteral administration. Current clinical practice regarding injection use needs reconsideration.

Majority of the patients in our study were middle aged (40-60 years), and admitted with an empirical diagnosis of acute febrile illness. Thus, they were more likely to receive AMD. While older patients received antibiotics less frequently than younger patients is probably because of the non-infectious cause of their hospitalization. It is more likely that older patients suffer from chronic non-communicable diseases like diabetes and hypertension^[15]. Considering the rising proportion of elderly patients and the fact that typical manifestations of infections may be absent in these patients provide a challenge for the future appropriate antibiotic use in the elderly population^[16]. In our analysis absence of co-morbidities predicts lesser use of AMDs. Similarly, admission due to non- infectious causes may lead to prolonged stay in the hospital and more likelihood of receiving multiple AMDs.

Average number of drugs per prescription is another important index of a prescription audit. It is recommended that the number of drugs per prescription should be kept as low as possible to minimize the risk of drug interactions, development of bacterial resistance, and hospital costs^[17]. In our study, an average of 8.1 drugs were prescribed per patient, which is comparable to the other data reported in literature, ranging from 5.1 to 12^[18,19], according to the type of patient population and the geographical location studied. Considerable efforts have been made in recent years to educate physicians and the public about the importance of minimizing the unnecessary use of antimicrobials^[20,21]. Average hospital stay was 6.6 days in our study cohort which is similar to the available reports from a similar setting^[19,22].

The strength of this study lies in its prospective design which ensures complete data collection

and verification of daily dose administration to accurately determine antibiotic consumption and prescribing patterns. This study also calculated the antimicrobial consumption using DOT/1000PD in inpatient setting. Several strategies have been proposed to facilitate and improve appropriate antibiotic use.

The important limitations this study includes its short observation period. Due to the observational design of the study and desire to preserve prescriber blinding to data collection, no attempt was made to adjudicate or verify the documented indications for therapy. Since residents doctors rotate through the wards on a monthly basis, the study reflects the prescribing patterns of a specific group only. Thus, it might difficult to generalize the results.

In summary, Estimating AMD use by DDD methods will remain open to criticism because the prescribed dosage is not often in agreement with the "usual" daily dose, which depends on location of and susceptibility of pathogenic organisms and metabolic status of the patient. Measurement of AMD use at the national and local levels is recommended by national task forces and WHO that are concerned about the rising rate of bacterial resistance. The acquisition of reliable consumption data in developing countries is in its infancy. The relationships between use and outcomes, such as bacterial resistance, also remain unclear. Thus, additional work must be done before definitive recommendations regarding antimicrobial use and restriction can be made. Furthermore, it provides baseline data against which to measure the success of future interventions and benchmarking data for similar ward settings.

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