Cost and usage patterns of antibiotics in a tertiary care neurosurgical unit

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ABSTRACT

Objectives: The routine use of prophylactic antibiotics in neurosurgery has been shown to significantly reduce surgical site infection rates. The documentation of non-surgical site, nosocomial infections in neurosurgical patients remains limited, despite this being a stimulus for prolific antibiotic usage. The actual quantum of antibiotic use in neurosurgery and its role in infection control remain both undocumented and controversial. The authors address this issue with a cost-effectiveness study using historical controls. **Materials and Methods:** Bacteriologically positive body fluid samples were used to quantify infection rates in the year 2006 and compared with those in the year 1997. Itemized drug lists obtained from dedicated neurosurgical intensive care units and wards were used to quantify antibiotic usage and calculate their costs. Results were compared using both historical and internal controls. The monetary conversion factor used was INR 40=US$1. **Results:** A total of 3114 consecutive elective and emergency neurosurgical procedures were performed during the study period. 329 patients (10.6%) were recorded to have bacteriologically positive body fluid samples, and 100,250 units of antibiotics were consumed costing Rs. 14,378,227.5 ($359,455.7). On an average, an operated patient received 32.2 units of antibiotics valued at Rs. 4,617 ($115.4). The crude infection rates were recorded to have reduced significantly in comparison to 1997, but did not differ between mirror intra-departmental units with significantly different antibiotic usage. **Conclusions:** Antibiotics accounted for 31% of the per capita cost of consumables for performing a craniotomy in the year 2006. This estimate should be factored into projecting future package costs.

Key words: Antibiotics, cost effectiveness, ethics, neurosurgery, nosocomial infection

INTRODUCTION

Antibiotic usage in neurosurgery, though of critical importance, has always remained a grey zone in the past. Universal guidelines that propose which antibiotic(s) to use, the timing and the duration of usage and more fundamentally the qualification and quantification of meningeal infection simply do not exist.[1-16] Though the use of prophylactic antibiotics in clean surgery remains controversial, neurosurgery remains a surgical discipline, where the routine use of prophylactic antibiotics has been clearly shown to decrease infection rates.[2,6,8-10,16] Despite this, studies dealing with nosocomial *extra-neurosurgical site* infections remain few,[14,17-20] as most of the literature deals mostly with cerebrospinal fluid (CSF) bacteriological positivity. Moreover, the quanta of antibiotic usage, cost-effectiveness and proportionate expenditure have been the focus of only one study in the past.[21] The authors present a unique annual audit of nosocomial infections in a series of 3114 consecutive neurosurgical procedures using the gold standard of bacteriological positivity and correlate antibiotic usage patterns and their cost-effectiveness with historical controls.

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MATERIALS AND METHODS

A retrospective analysis of the data sheets of the infection control unit of the department of neurosurgery was performed for the study period extending from January to December, 2006 in an apex referral university hospital. Historical controls from these records were also used from the year 1997 onward. The department of neurosurgery has two mirror units (henceforth referred to as ß and Ω with dedicated intensive care units (ICUs), wards and

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five operation theaters. Thus, contamination of data by patients from other specialties and also attrition of the same due to patient admissions in other wards in the hospital was not an anticipated problem.

Calculating Infection Rates

Infection rates were established by a dedicated staff nurse who would collect all reports of bacteriologically positive CSF, blood, urine, wound swab and tracheal samples derived from patients undergoing neurosurgical procedures on a daily basis from the records maintained by the department of microbiology. These were obtained from patients manifesting clinical or radiological signs of infection such as, fever greater than 100.4°F, tachycardia, wound site inflammation, dysuria, leukocytosis, CSF leak, neck rigidity and productive cough with expectoration and infiltrates on plain chest X-rays. The presence of infection was documented as a bacteriologically positive culture of CSF, blood, urine, wound swab or tracheal aspirate. Positive samples were identified and cross-checked with the names and hospital numbers of patients undergoing neurosurgery as noted in the operation theater registers. Combined statistics based on these data sheets were then reviewed by the consultant neurosurgeons from both units and by the consultant microbiologist on a monthly basis. Infection rates were then calculated for the individual units as well as a grand total for the department.[20]

Historical Controls

For the purpose of this study, historical controls from our records were used from the year 1997 onward as the department of neurosurgery breached the 2000 operations per annum landmark for the first time in its history. At that point in time, all procedures were performed using a perioperative regimen of two doses of ciprofloxacin 500 mg and amikacin 500 mg were administered intravenously every 12 h. In 2000, this was replaced by a comprehensive written antibiotic policy, i.e., antibiotics were administered perioperatively for 24–120 h, starting at the time of induction of anesthesia and stratified according to patient risk factors.[20]

Antibiotic Protocols

In 2006, neurosurgical patients (Class 1) who underwent uncomplicated surgery of less than 4 h duration received 24 h of intravenously administered Chloramphenicol (1g Q6H) and Netilmicin (300 mg Q24H). Class 2 patients who underwent surgery lasting 4–6 h or in whom a breach in sterility was suspected received 48 h of intravenous Chloramphenicol and Netilmicin. Class 3 patients, who underwent procedures lasting greater than 6 h, whose paranasal sinuses were breached, who had redo or emergency operations or implants or were diabetic also received 48 h of intravenously administered Chloramphenicol and Netilmicin. This was followed by oral Chloramphenicol (500 mg Q 6H) and Netilmicin (300 mg Q24 H) administered intramuscularly/intravenously once in every 24 h for 72 h.

Patients who developed signs of sepsis (Class 4) were treated empirically with intravenous antibiotics till the culture reports were made available. Our protocol dictated the use of Cefoperazone-Sulbactam 2 g iv Q12 H along with Netilmycin 300 mg iv Q12 H in these patients typically administered for 10 days.

Documenting Antibiotic Usage

All operations were performed on the basis of a package system which included the cost of all perioperative antibiotics. These were provided to operated patients through the hospital stores. Drug inventories, maintained by the staff nurses in charge of the ICUs and the wards, were accessed to calculate the total antibiotic usage in grams and units as a whole as well as per capita. Antibiotic cost was based on the maximum retail price (MRP) printed on the drug packaging. The manufacturing drug companies had been previously selected on the basis of a tender in which the lowest MRP was the major criterion. The monetary conversion factor used was INR 40=US$1.

The Chi square test was used to determine statistical significance at a P value <0.05.

RESULTS

A total of 3114 routine and emergency procedures were performed during the study period; out of them, 329 patients (10.6%) developed 443 (14.2%) culture-proven bacterial infections [Table 1].

Antibiotic usage data [Table 2] revealed that the total quantum of antibiotics used in the department of neurosurgery for the year 2006 was 82877.6 g (100250 Units) and the cost incurred was Rs. 1,43,78,227.5 ($359,455.7). This translated into a per capita usage of 32.2 units (26.6 g) of antibiotics at a cost of about Rs. 4617 ($115.4) per operated patient [Table 3]. These data were compared to both historical [Figure 1, Table 1] and internal controls [Table 3] from the department.

Though total HAI rates dropped significantly *vis-à-vis* 1997, they did not differ significantly in either unit. It is interesting to note that Unit ß had a statistically higher rate of chest infections (P=0.03) despite greater antibiotic usage as judged by cost (P=0.014, [Table 3]).

The usage of top line antibiotics (Piperacillin-Tazobactam, Meropenem, Vancomycin and Teicoplanin) accounted for about 35% of total cost and only 5% of usage, in terms of units [Table 2, Figure 2]. The ICUs which accounted for 27% of the total bed strength contributed toward 45% of the total antibiotic costs and 43% of the total number of units of antibiotics used [Table 2, Figure 3]. Antibiotics, on an average, accounted for 92.3% of the entire package cost for a ventriculoperitoneal shunt, 46.2% of the cost for a lumbar discectomy and 30.8% of the cost for a craniotomy at our hospital [Figure 4].

DISCUSSION

Acknowledging HAI rates in a high morbidity and mortality branch such as neurosurgery can be delicate as the medicolegal, ethical and professional ramifications are profound. This may explain the paucity of literature dealing with the extra-neurosurgical site nosocomial infections. Only five reports exist[14,17-20] three of which betray an ICU bias. Interestingly, three of these five reports are from our center.[14,18,20] We believe that the documentation of extra neurosurgical site infection is critical as a significantly greater number of patients die

Table 1: Bacteriologically positive body fluid samples derived from neurosurgical patients

Year	Operated patients	Trachea	Wound	CSF	Blood	Urine	HAI	Patient no.
1997	2064	101 (4.9)	66 (3.2)	107 (5.2)	185 (9.0)	174 (8.4)	633 (30.7)	451 (21.9)
2006	3114	144 (4.6)	90 (2.9)	70 (2.3)	69 (2.2)	70 (2.3)	443 (14.2)	329 (10.6)
'*P*'		0.67	0.54	0.00*	0.00*	0.00*	0.00*	0.00*

HAI – Hospital acquired infections; *Significant; Figures in parenthesis are in percentages; Comparative data 1997-2006

Table 2: Antibiotic usage (January-December 2006)

Drug- unit-form	Units ICU	Units ward	Total units	Patient days*	Total amount (g)	Rs/unit	Cost ICU (Rs)	Cost ward (Rs)	Total cost (Rs)
Amikacin 500 mg iv	1125	3259	4384	2192	2192	70	78750	228130	306880
Augmentin 1.2 g iv	2057	2637	4694	2347	5632.8	189	388773	498393	887166
Augmentin 625 mg tab	556	5871	6427	2142.3	4016.9	32	17792	187872	205664
Cefaclor 500 mg tab	2251	6848	9099	3033	4549.5	38	85538	260224	345762
Cefoperazone-Sulbactam 1 g iv	7941	11260	19201	4800.3	19201	106	841746	1193560	2035306
Cefotaxime 1 g iv	207	50	257	85.7	257	90	18630	4500	23130
Cefotaxime-Sulbactum 1.5 g iv	260	567	827	275.7	1240.5	60	15600	34020	49620
Ceftazidime 1 g iv	3234	2250	5484	2742	5484	170	549780	382500	932280
Ceftriaxone 1 g iv	680	644	1324	662	1324	102	69360	65688	135048
Chloramphenicol 1 g iv	10827	6064	16891	4222.8	16891	24	259848	145536	405384
Ciprofoxacin 200 mg iv	423	644	1067	533.5	533.5	20	8460	12880	21340
Ciprofoxacin 500 mg tab	222	3241	3463	1731.5	1731.5	8.5	1887	27548.5	29435.5
Clindamycin 300 mg iv	181	54	235	39.2	70.5	213	38553	11502	50055
Levofloxacin 500 mg iv	817	859	1676	1676	838	103	83018	88477	172628
Meropenem 1 g iv	342	439	781	390.5	781	2450	837900	1075550	1913450
Metronidazole 500 mg iv	4797	3526	8323	2774.3	4161.5	16	76752	56416	133168
Netilmycin 300 mg iv	4427	4821	9248	9248	2774.4	385	1704395	1856085	3560480
Piperacillin-Tazobactam 4.5 g iv	899	1045	1944	648	8748	699	628401	730455	1358856
Teicoplanin 400 mg iv	0	120	120	120	48	890	0	106800	106800
Vancomycin 500 mg iv	2208	2597	4805	1201.3	2402.5	355	783840	921935	1705775
Total	43454	56796	100250	40865.1	82877.6		6489023	7888071.5	14378227.5

iv – Intravenous; *Total number of units/number of units used per day; Tab – tablet

Table 3: Bacteriologically positive body fluid samples derived from neurosurgical patients in Units ß and Ω

Unit	Operated patients	Chest (%)	Wound (%)	CSF	Blood	Urine	HAI	Patient no.	Abx usage (units)	Per capita usage	Per capita cost (Rs)
Unit ß	1563	86 (5.5)	44 (2.8)	35 (2.2)	33 (2.1)	23 (1.5)	221 (14.1)	168 (10.8)	51820.1	33.2 Units	4868.7
Unit Ω	1551	58 (3.7)	46 (3.0)	35 (2.4)	36 (2.3)	47 (3.0)	222 (14.3)	161 (10.4)	48429.9	31.2 Units	4363.9
'*P*'		0.02*	0.81	0.97	0.69	0.003*	0.95	0.74		0.80	0.014*

Abx – Antibiotics; HAI – Hospital acquired infections; *Significant

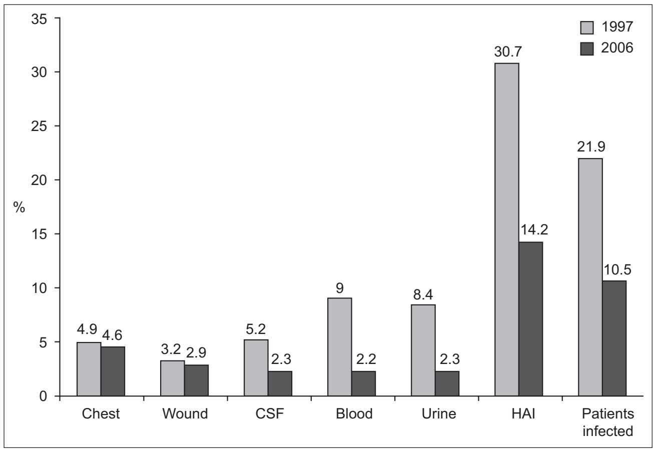

Figure 1: Bar diagrams indicating the significant decrease in the incidence of bacteriologically positive infections from the chest, wound, cerebrospinal fluid (CSF), blood, urine, total number of hospital acquired infections (HAI) and the total number of patients infected during the period 1997–2006

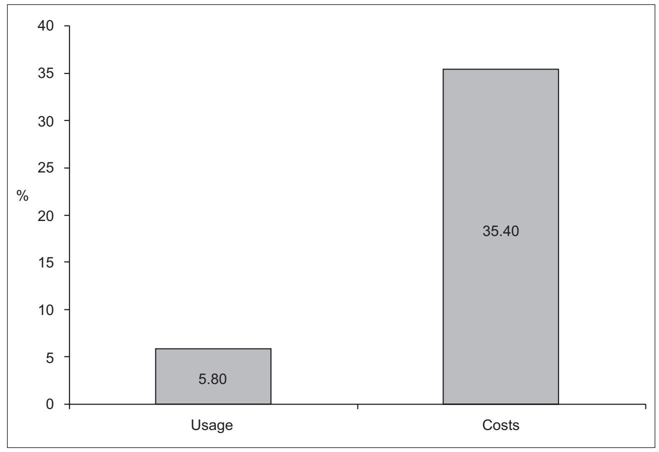

Figure 2: Bar diagrams depicting the relative usage and costs of Piperacillin-Tazobactam, Meropenem, Vancomycin and Teicoplanin vis-à-vis total use and expenditure on antibiotics

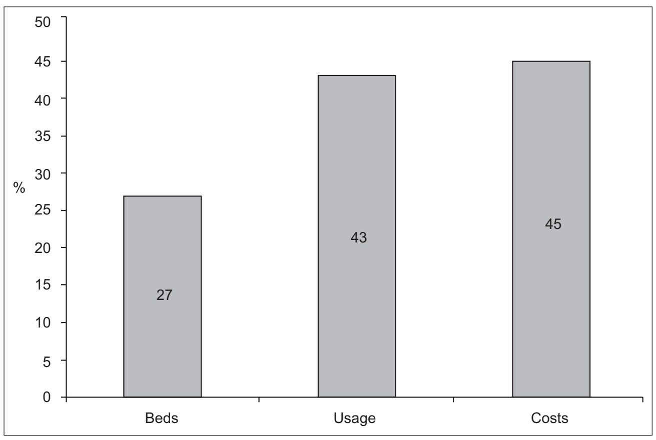

Figure 3: Bar diagrams depicting the relative contribution of the intensive care units to bed strength, antibiotic use and expenditure

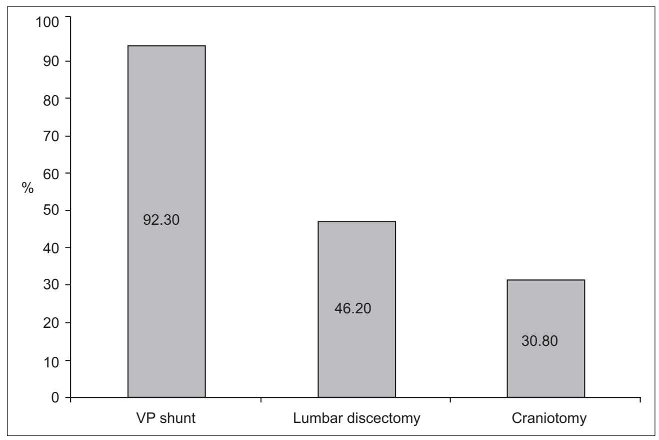

Figure 4: Bar diagrams projecting the relative proportion of per capita cost of antibiotics vis-à-vis total package costs for common surgical procedures. Key: VP - ventriculoperitoneal

of ventilator acquired pneumonia and septicemia than of meningitis.[20]

Additionally, there is no data that deals with the quantum and pattern of antibiotic usage in neurosurgery or its cost effectiveness other than a single report by Alleyne *et al*. (2000) which estimated a saving of about $80,000 per annum by discontinuing the routine use of prophylactic antibiotics for external ventricular drains.[21]

Rationale for Prophylaxis

Though most neurosurgical procedures are considered clean, the routine use of antibiotics may be helpful in decreasing the rate of CSF and wound site infections. The duration of antibiotic usage is controversial with some authors believing that antibiotic coverage should be prolonged to account for the transdural escape of CSF into the subgaleal/subcutaneous compartment, while others believe in a single dose or very limited perioperative cover.[2,6,10,16] We believe that the antibiotic coverage is justified in prolonged surgery perioperatively, as ours is a national quaternary care referral center dealing with some of the most difficult and complicated cases of brain and spinal pathology that can be found in a developing country. Their treatment typically requires prolonged and complex surgery involving multiple units of blood transfusions, instrumentation, high dose steroids and elective ventilation. It is also our hypothesis that perioperative antibiotics may not only reduce the incidence of CSF and surgical site infections but also counteract infections in the bloodstream, urine, incision site and chest. Perhaps, this may partially account for the decline in the overall HAI rate (1997–2006) by more than half from 30.4% to 14.5% [Figure 1] despite a 50% increase in the number of surgical procedures [Table 1]. Moreover, despite a workload exceeding 3000 operations per annum, the rate of CSF infection remained 2.3%, which compares with available statistics from western literature.[10,20]

Per Capita Cost and Usage

In this study, per capita usage was noted to be 32.2 units of antibiotics (26.6 g) valued at a cost of about Rs 4617 ($115.4) per operated patient [Table 3]. The average cost per unit was Rs 143.4($3.6). There are no data to compare these values with.

This study was made possible by the fact that we have dedicated operation theaters, ICUs and wards, a universal prophylactic antibiotic policy, an antibiotic policy to deal with the empirical treatment of septicemia/pneumonia/meningitis, an active in-house infection control unit and a general package system which includes the cost of all antibiotics dispensed in the entire department following neurosurgery. We also have an established infection control program which has documented its findings in peer reviewed literature since 1993.[4,5,22,23]

Given that the package cost of a craniotomy in our center is Rs 15,000 ($375), antibiotic usage accounted for nearly 31% of the total cost of surgical consumables [Figure 4].

Patterns of Usage

Antibiotic patient days

In this study, the total number of antibiotic units used was 100,250. This is slightly misleading, yet all encompassing term as every generic antibiotic has a different dosing frequency. Thus, the total usage may be skewed by drugs which need to be given more frequently on a daily basis to maintain therapeutic serum levels. To counteract this bias, we calculated a variable that we termed antibiotic patient days (total number of units used/dosing frequency per day; [Table 1]). This variable enabled us to determine biological equivalence between the several different antibiotics that were used during this study period. Thus, eight units of Ciprofloxacin (Q12 H dosing) accounts for four antibiotic patient days while eight units of Chloramphenicol (Q 6H dosing) accounts for two antibiotic patient days. The cumulative antibiotic patient days in this study was calculated to be 40,865.1 [Table 1] or 112 years. To put this in perspective, the entire quantum of drugs used in this study could provide a single patient with 112 continuous years of any antibiotic (irrespective of dosing frequency) adequate to support therapeutic serum levels. More practically, this variable enabled us to directly compare the usage of antibiotics with varying pharmacokinetics and related dosing frequencies. Top line antibiotics such as Teicoplanin (120 patient days), Meropenem (391 patient days), Piperacillin-Tazobactam (648 patient days) and Vancomycin (1201 patient days) were sparingly used [Table 1, Figure 2] and accounted for only 5.8% of usage but 35.4% of all costs.

Not surprisingly, the ICUs accounted for slightly less than half of the total antibiotic cost and usage despite housing only a quarter of the total available beds [Figure 3].

Use/abuse - The grey zone

The quantum of antibiotics (32.2 units) received by the average operated patient was 50% more than what we would have expected even if all the operated patients had received the standard, maximal, five-day protocol (Class 3 patients; 22 units per capita; [Table 4]) given for the most complicated cases. It is also imperative to note that as per our data, only 10.6% of operated patients had a bacteriologically positive body fluid sample that definitely justified the use of broad spectrum/extended duration antibiotic cover. Thus, it is evident that antibiotic usage was being skewed by patients who required prolonged antibiotics for meningitis, pneumonitis, urinary tract or wound infections.

We devised hypothetical situations to explain this [Table 4]. Actual per capita usage, cost and average cost per antibiotic unit recorded in this study were compared to projected values in groups with an increasing proportion of Class 4 patients with clinicoradiological signs of sepsis who received broad spectrum antibiotics. This gave us an estimate of the number of patients treated over and above those who received antibiotics prophylactically and on the basis of culture reports documenting severe infection. The first scenario envisaged a group (standard protocol- SP) with zero infections in which only prophylactic antibiotics were used. Demographically, the SP group contained Class 1,

Table 4: Projections of antibiotic costs, units used and cost per unit as a variable of increasing proportion of Class 4 patients

Patient class	Coverage duration (hours)	ABx units	Total cost (Rs)	Cost per unit (Rs)
Class 1	24	5	481	96.2
Class 2	48	10	962	96.2
Class 3	120	22	2459	111.8
Class 4	240	60	11940	199
Hypothetical groups				
Standard protocol 1/3 (Class 1+2+3)	64	12.3	1300.7	105.8
Group A 10.6% (Class 4)+89.4% (SP)	82.6	16.4	1940.2	118.3
Group B 20% (Class 4)+80% (SP)	99.2	20.2	2600.5	128.7
Group C 30% (Class 4)+70% (SP)	116.8	24.5	3405.4	139.0
Group D 40% (Class 4)+60% (SP)	134.4	28.9	4306.5	149.0
Group E 50% (Class 4)+50% (SP)	152	33.6	5326.3	158.5

ABx – Antibiotic

2 and 3 patients in an equal mix. Group A most closely reflected the cohort depicted, albeit simplistically, in this data. Thus, Group A had 10.6% Class 4 patients treated for sepsis (a 10 day course of antibiotics) while the rest 89.4% patients received only prophylactic antibiotics (SP group). Groups B, C, D and E were cohorts representing an increasing proportion of Class 4 patients with compositions varying from 20 to 50%. A best fit hypothesis indicates that antibiotic consumption in this study lies somewhere between that projected for groups D and E. Extrapolating this data to the current study raises several possibilities. Either 40–50% of the entire surgical cohort had clinicoradiological evidence of sepsis (Class 4) and received empirical treatment for only 10 days, or that roughly 10% of the cohort with bacteriologically positive body fluid samples was treated for the same for 40–50 days each. A middle path implies that approximately 20–25% of patients were Class 4 and received treatment for 20 days each on average. In this last model, the clinicoradiological indications of sepsis as defined by an intention to treat may have exceeded bacteriological positivity by a factor of 100–125%.

It must be clarified that these are assumptions and have been made as this retrospective study could not document the proportion of patients in classes 1-4 and the duration of antibiotics prescribed for each of the 3114 patients operated on during the course of the study.

The threshold to increase the duration and/or spectrum of antibiotics in a febrile postoperative patient is generally low. This is especially so when the qualification of CSF infection in the postoperative period is uncertain but the consequences of under treatment potentially deadly. This dilemma exists even in the clinical setting of a septicemic/pneumonitic process. To withhold the timely and judicious use of broad spectrum antibiotics, with all the wisdom of hindsight, may be indefensible in a patient who succumbs from the same. However, if the same patient was to survive and all body fluid cultures were eventually found negative (which could also be a consequence of the act of starting broad spectrum antibiotics in time) the attending surgeon could be criticized for using antibiotics indiscriminately.

Inter Unit Variations

Though the departmental antibiotic policy was applicable to both units, the cost and usage of antibiotics in Unit ß exceeded that of Unit Ω [Table 3]. The former was significantly greater (P=0.014). Yet, the total number of HAI and the patients infected did not achieve statistical difference. Thus, internal controls suggest that an increase in antibiotic usage may not help in controlling infections. Conversely, the excess spending in unit ß may perhaps be explained by a statistically higher rate of chest infections which may have mandated the use of more expensive antibiotics for a longer duration of time.

Ethical Considerations

There exist very relevant ethical dilemmas regarding the widespread use of prophylactic antibiotics (18). It may be argued that, after all, only 37 patients who do suffer CSF infections were salvaged (the difference in 1997–2006 CSF infection rates, [Table 1]). However, overall costs for the rest of the patients increase and a selection pressure is then exerted, which helps in breeding of multi-drug resistant super bugs. We would disagree as our historical controls suggest that the use of antibiotics has decreased overall HAI rates by nearly 50% despite an increase in patient load by 50% in the decade 1996–2006 (22). Perhaps, prophylactic antibiotics guard not only against CSF and wound infections but also against microbial colonization of the trachea, bloodstream and urine. Infections of these last three systems accounted for 64% of all HAI in this study.

CONCLUSIONS

HAI may affect nearly 11% of all patients undergoing routine and emergency neurosurgery in a center with a turnover exceeding 3000 procedures per annum. Protocol-based risk stratified prophylactic antibiotics may have helped in decreasing infection rates by 50% when compared to historical controls. On an average, an operated patient received 32.2 units of antibiotics valued at Rs. 4617 (($115.4). This accounted for about 31% of the cost of a craniotomy in the year 2006. Greater antibiotic usage was not associated with a decrease in infection rates within the two units of the department.

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