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Original Article

Length of preoperative hospital stay is the dominating risk factor for surgical site infection in neurosurgery: A cohort data-driven analysis

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ABSTRACT

Background: The number of days of preoperative hospital stay (PHS) is a modifiable variable that has shown contradictory surgical site infection (SSI) risk factor results in neurosurgery. We sought to pinpoint the day of PHS length related with a marked increase of risk of SSI.

Methods: From a tertiary teaching hospital, January 2015–December 2017, prospectively collected nonpercutaneous neurosurgery procedures with standard antibiotic prophylaxis and 1-year follow-up were evaluated. SSI risk factors were assessed through multiple logistic regression models with different thresholds of PHS.

Results: A total of 1012 procedures were included in the study. Incidence of SSI was 4.4%. The median PHS was higher in those with SSI than in those without (1 day, interquartile range [IQR]: 7 vs. 0 days, IQR: 1, respectively, $P = 0.002$). By the amount of six days of PHS, this exposure risk past the threshold of significance for impact on wound infection (OR 2.8; CI 1.23–6.39, P = 0.014). Operative time past 4 h (OR 2.11; CI 1.12-3.98; $P = 0.021$), and in some models, previous surgery at same admission were also identified by multivariate analysis as increasing postoperative SSI risk.

Conclusion: The gradual increase of the SSI OR associated with longer PHS days was the highest risk factor of SSI in our cohort of patients. Studies directed to reduce this complication should consider the PHS.

Keywords: Antibiotic prophylaxis, Hospitalization, Neurosurgery, Preoperative period, Risk factor, Surgical site infection

INTRODUCTION

The U.S. News and World Report rankings of Best Hospitals list minimization of hospital-acquired infection 7 times in its criteria.[21] Neurosurgical studies report surgical site infection (SSI) incidence of 3.5–6.2%, related to morbidity and mortality, making prevention of SSI a high priority.[1,14,17] Surgical antibiotic prophylaxis is well known in preventing SSI, thus is common practice.[2,9] However, some found no benefit, and others even a negative role, possibly related to the antibiotic resistance patterns.[10,24]

Although the length of preoperative hospital stay (PHS) is factored in some neurosurgery SSI studies and has been related to this complication,[1,17,31] the specific number of days of PHS is less well understood, with mixed findings.[3,8,11,13,19,23,25,27,29,33,36-38,40,41] Moreover, to the knowledge of the authors, there are no prior characterizations of PHS as a quantitative variable for the determination of the point at which it is become a relevant risk factor for SSI.

Hospital stay has been associated with changes in the bacteria flora,[4,18] increasing the amount of isolated pathogens resistant to antibiotics used in surgery that targets common community-acquired bacteria. This colonization may cause increased risk of SSI for patients with longer PHS, as it is widely documented in the literature of different surgical specialties.[7,34,35,39] In the present study, the number of days of the PHS is evaluated for its possible role as a SSI risk factor in those undergoing open neurosurgical procedures with standard antibiotic prophylaxis against community usual bacteria.[28]

MATERIALS AND METHODS

The Institutional Research Ethics Committee approved the study. According to the STROBE guideline, retrospective analysis of the institutional neuroanesthesia database consecutive cohort was conducted. All the nonpercutaneous procedures perform by the neurosurgery or orthopedic spine surgery divisions between January 2015 and December 2017, classified by the surgeon as clean wound, and received antibiotic prophylaxis with cefazolin or clindamycin were selected, including those of the same patient. Surgeries to anatomical areas with on-going local infections or with positive microbiological isolates from samples taken during the procedure were excluded, as well as those cases with SSI wherein the clinical infection signs appeared after the exposure of inert prosthetic or fixation material through the skin during the ambulatory follow-up. Data were also extracted from the prospectively recorded neuroanesthesia database and the patient's electronic medical records. Several variables were collected, including age, sex, diagnosis, surgery, antibiotic prophylaxis, emergency procedure, previous surgery during the same hospital admission, previous surgery on the same anatomical area, operative time, maximum number of people in the operating room, American Society of Anesthesiologists classification (ASA), aseptic product for skin preparation, training level of the physician closing the wound, intraoperative transfusion, ICU stay during the admission, ICU stay before the surgery during the same hospital admission, history of diabetes mellitus, and days of PHS.

SSI cases were identified from the database with up to 1 year postoperative follow-up and from the institutional epidemiology group register. Afterward, the data were verified by manual review of the clinical records according to the Centers of Disease Control and prevention criteria[30] and the study exclusion criteria. Included patients received 2 g of intravenous cefazoline or 600 mg of clindamycin if they had history of allergy, administered within 1 h before incision. In those with operative time longer than 4 h or need of transfusion, a half the dose was repeated. Outcomes of positive cultures at the time of SSI diagnosis were gathered for further analysis. The bacteria were classified as cutaneous origin (*Staphylococcus aureus*, coagulase-negative staphylococci, and *Propionibacterium acnes*) and noncutaneous origin (*Escherichia coli*, *Pseudomonas aeruginosa*, *Acinetobacter* spp., streptococci, enterococci, and Gram-positive bacillus) similarly to Korinek *et al*.[24]

Statistical analysis

Data were analyzed using STATA® software version 16. A univariate analysis was carried out to describe the characteristics of the patients included. Categorical data are presented as percentages and were analyzed using the Chi-square test. For continuous data, the median (interquartile range [IQR]) and mean (standard deviation [SD]) are presented. Comparisons of continuous data were performed using the Mann–Whitney U-test for nonnormally distributed variables.

As the main goal of the study was to characterize the odds of SSI in function of the PHS, 15 logistic regression models were made, each one of them using its own dichotomized variable PHS with a different cut point of time in days, from 0 to 15+ days. The characteristics identified as potential risk factors based on univariate analysis underwent the multivariate logistic regression analysis, and $P \leq 0.05$ represented statistical significance.

RESULTS

[Table 1] summarizes the results of the univariate analysis of patient-related factors and their association with SSI. A total of 1441 consecutive surgeries were identified, and 1012 nonpercutaneous surgeries passed the inclusion and exclusion criteria. No differences were found in the demographic variables between the cases with and without SSI. Mean age was 51.6 [SD 22.8] years (ranged 0–97 years) and 51.8% (*n*: 524) were female. Diabetes mellitus was found in 7% (*n*: 71) of the cases and 19.5% ($n = 197$) had the antecedent of prior surgery at the same anatomical localization, not necessarily performed during the same hospitalization. The most frequent diagnostic category was nontumoral spine disorders 40.1% (*n*: 406) and the most frequent ASA class was 3 with 49.2% (*n*: 498).

Table 1: Demographics and bivariate analysis according to surgical site infection event.

Variables	Total, *n* (%) *n*=1012	SSI		*P*-value†
		Yes, *n* (%) *n*=45	No, *n* (%) *n*=967	
Sex				
Female	524 (51.8)	25 (55.6)	499 (51.6)	0.604
Male	488 (48.2)	20 (44.4)	468 (48.4)	
Age (years)				
Median (IQR)	56 (32)	51 (39.5)	56 (32)	0.248
Diagnosis				
Tumoral	285 (28.2)	15 (33.3)	270 (27.9)	0.115
Vascular	104 (0.3)	9 (20)	95 (9.8)	
Traumatic brain injury	117 (1.6)	2 (4.4)	115 (1.9)	
Traumatic or degenerative spine disease	406 (40.1)	15 (33.3)	391 (40.4)	
Other	100 (9.8)	4 (8.9)	96 (9.9)	
ASA				
1	85 (8.4)	1 (2.2)	84 (8.7)	0.090
2	343 (33.9)	11 (24.4)	332 (34.3)	
3	498 (49.2)	26 (57.8)	472 (48.8)	
4	79 (7.8)	7 (15.6)	72 (7.5)	
5	7 (.7)	0	7 (.7)	
Previous surgery at same admission	43 (4.2)	7 (15.6)	36 (3.7)	<0.001*
Previous surgery in equal location	197 (19.5)	12 (26.7)	185 (19.1)	0.212
History of diabetes mellitus	71 (7)	3 (6.7)	68 (7)	0.925
ICU stay during hospitalization	549 (54.2)	28 (62.2)	521 (53.9)	0.272
PHS				
Mean	1.5 (3.1)	3.8 (5.7)	1.4 (2.9)	
Median (IQR)	0 (1)	1 (7)	0 (1)	0.002*

*$P \leq 0.05$ considered statistically significant difference. †*P*-values are calculated from Chi-square test; Fisher's exact; and Mann–Whitney U, as appropriate. SSI: Surgical site infection, IQR: Interquartile range, SD: Standard deviation, ASA: American Society of Anesthesiologist classification of physical state, ICU: Intensive care unit, PHS: Preoperative hospital stay

The overall SSI rate was 4.4% (*n*: 45) and positive cultures at the time of SSI identification were obtained in the 84.4% (*n*: 38) of the cases. The most frequent isolated microorganism was *Staphylococcus epidermidis* in 34.2% (*n*: 13) followed by *S. aureus* 26.3% (*n*: 10). In 11 cases, out of those 38 (26.3%) positive culture cases, more than 1 microorganism species was isolated and 55.3% of the times, at least one microorganism was among the defined as noncutaneous origin bacteria. Cefazolin was used as antibacterial prophylaxis in 94.3% of the cases, while clindamycin just in the 5.7%, without having a statistical difference on their relation to SSI ($P = 0.704$).

The overall median preoperative hospitalization time was 0 (IQR 1) days, 0 (IQR 1) for non-SSI, and 1 day (IQR 7) for SSI cases ($P = 0.002$). ICU stay during the hospitalization was observed in a 54.2%. However, only in 10.6% was the ICU stay preoperative, which was associated with SSI in the bivariate analysis (OR 2.2; CI 1.04–4.74; $P = 0.035$). Intraoperative transfusion (OR 2.1; CI 1.07–4.22; $P = 0.027$), surgical time ≥4 h (OR 2.3; CI 1.27–4.24; $P = 0.005$), and any previous surgery during the same hospital admission (OR 4.76; CI 1.99–11.3; $P < 0.001$) were also associated with SSI. Bivariate analysis of the other variables, type of surgery ($P = 0.124$), emergency surgery ($P = 0.538$), asepsis product ($P = 0.871$), level of training of the professional closing the wound ($P = 0.546$), maximum number of persons in the operating room ($P = 0.316$), ASA score ($P = 0.09$), and diabetes mellitus ($P = 0.925$) showed no difference in the SSI rate [Tables 1 and 2].

The multivariate regression analysis of the significant variables is shown with adjusted OR in [Table 3]. The identified independent risk factors were surgical time ≥4 h (OR 2.107; CI 1.12–3.98; $P = 0.021$) and PHS (OR 1.13; CI 1.05–1.22; $P = 0.001$). The 15 time points' logistic regressions of the PHS centered analysis are summarized in [Table 4 and Graph 1]. They reveal a gradual increase of the PHS OR for SSI from 1.71 (CI 0.87–3.37; $P = 0.123$) to 13.26 (CI 3.94–44.63; $P < 0.001$), reaching and maintaining the significance at 6 days. Most of the variables have consistent values across the models with different threshold of PHS, except for previous surgery in the same hospitalization which starts with an OR of 3.1 at day 1 and ends with an OR of 1.68 in the logistic regression with PHS dichotomized at 15 days. Furthermore, the SSI association of this last variable was not significant in any of the models with PHS cut point at 6 days or more.

Table 2: Surgical factors and bivariate analysis according to surgical site infection.

Variables	Total, *n* (%) *n*=1012	SSI		*P*-value†
		Yes, *n* (%) *n*=45	No, *n* (%) *n*=967	
Type of surgery				
Noninstrumented spinal surgery	201 (19.9)	4 (8.9)	197 (20.4)	0.124
Instrumented spinal surgery	254 (25.1)	12 (26.7)	242 (25.0)	
Posterior fossa and craniocervical junction surgeries	54 (5.3)	5 (11.1)	49 (5.1)	
Supratentorial surgeries excluding Groups 5 and 6	272 (26.9)	15 (33.3)	257 (26.6)	
Drainage of extracerebral collections, skull fracture reductions and decompressive craniectomies	132 (13.0)	3 (6.7)	129 (13.3)	
Implant or revision of noninstrumentation devices, extracranial surgeries, and cranioplasty	99 (9.8)	6 (13.3)	93 (9.6)	
Operative time>2 h	725 (71.6)	36 (80)	689 (71.2)	0.203
Operative time>4 h	304 (30.1)	22 (48.9)	282 (29.2)	0.005*
Emergency surgery	253 (25)	13 (28.9)	240 (24.8)	0.538
Antibiotic prophylaxis				
Cefazolin	954 (94.3)	43 (95.6)	911 (94.2)	0.704
Clindamycin	58 (5.7)	2 (4.4)	56 (5.8)	
Antiseptic product for skin preparation				
Iodine soap and solution	561 (55.4)	27 (60)	534 (55.2)	0.871
Chlorhexidine soap and solution	234 (23.1)	8 (17.8)	226 (23.4)	
Iodine povacrylex 0.7% and isopropyl alcohol 74% (DuraPrep, 3M)	208 (20.6)	10 (22.2)	198 (20.5)	
Other	9 (.9)	0	9 (.9)	
Intraoperative transfusion	153 (15.1)	12 (26.7)	141 (14.6)	0.027*
Preoperative ICU stay	107 (10.6)	9 (20)	98 (10.1)	0.035*
Person who closed the wound				
Medicine intern	10 (0.99)	0 (0)	10 (0.99)	0.546
Younger resident	389 (38.44)	15 (33.3)	374 (38.7)	
Older resident	519 (51.28)	28 (62.2)	491 (50.8)	
Attending neurosurgeon	94 (9.29)	2 (4.4)	92 (9.5)	
Maximum number of people in the operating room				
Median (IQR)	10 (4)	9 (3.5)	10 (4)	0.316

†*P*-values are calculated from Chi-square test; Fisher's exact; and Mann–Whitney U, as appropriate. **P*≤0.05 considered statistically significant. SSI: Surgical site infection, ICU: Intensive care unit, IQR: Interquartile range

Table 3: Multivariate analysis of patient-related factors for surgical site infection.

Variables	Odds ratio (adjusted)	95% confidence interval	*P*-value†
Operative time>4 h	2.107	(1.118–3.975)	0.021*
Intraoperative transfusion	1.398	(0.651–3.000)	0.390
Previous surgery at same admission	1.743	(0.587–5.174)	0.317
Preoperative ICU stay	1.012	(0.527–1.943	0.971
PHS	1.132	(1.051–1.218)	0.001*

†*P*-value is from logistic regression analysis. **P*≤0.05 considered statistically significant. ICU: Intensive care unit, PHS: Preoperative hospital stay

DISCUSSION

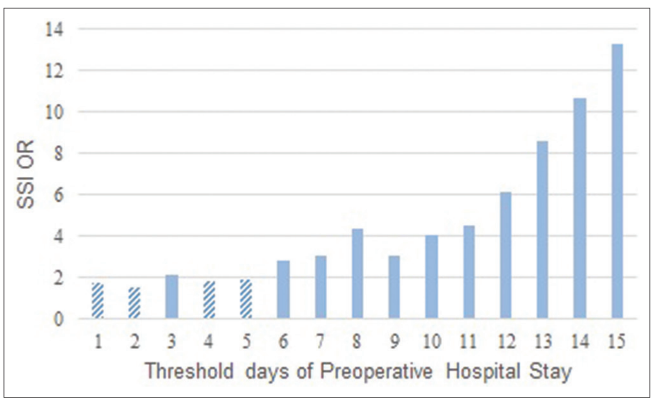
To the best of our knowledge, this study is the first study in neurosurgery to include a quantitative analysis to describe how the PHS gradually increases the SSI risk. Herein, SSI risk factors are identified for a specific but representative fraction of neurosurgical patients, with clean wounds, without late prosthetic material exposure, and with antibiotic prophylaxis directed to community acquired flora, aiming to standardize the grade of wound contamination and antibiotic selective pressure. The time of exposure to the hospital environment before surgery is shown to be the most relevant factor for this surgical complication among the factors studied in this cohort.

Delays in surgical schedule for neurosurgical patients might be common in many environments due to the requirement of multiple specialized studies and careful planning of these procedures, even though the patient is coursing with a condition that motivated an emergency consult and are not seemingly suited for discharge. Even though systematic evaluation of the length of PHS has not been previously studied, its relevance has been implicated in different surgical specialties[7,26,32,34] and identified as

Table 4: Threshold-dependent surgical site infection risk factors.

PHS (days)	Previous surgery at same admission			Preoperative hospital stay		
	OR (adjusted)	95% CI	*P*-value†	OR (adjusted)	95% CI	*P*-value†
1	3.10	(1.16–8.29)	0.024*	1.71	(0.87–3.37)	0.123
2	3.26	(1.19–8.92)	0.022*	1.51	(0.75–3.07)	0.251
3	2.61	(0.94–7.24)	0.065	2.12	(1.04–4.33)	0.039*
4	2.86	(1.02–8.05)	0.046*	1.83	(0.86–3.93)	0.120
5	2.82	(0.99–8.04)	0.053	1.91	(0.85–4.30)	0.117
6	2.27	(0.79–6.52)	0.129	2.80	(1.23–6.39)	0.014*
7	2.17	(0.74–6.37)	0.159	3.07	(1.30–7.26)	0.011*
8	2.09	(0.74–5.93)	0.167	4.37	(1.89–10.11)	0.001*
9	2.63	(0.94–7.37)	0.066	3.03	(1.18–7.74)	0.021*
10	2.42	(0.86–6.86)	0.095	4.03	(1.55–10.46)	0.004*
11	2.35	(0.82–6.69)	0.111	4.51	(1.73–11.81)	0.002*
12	2.19	(0.76–6.13)	0.147	6.13	(2.28–16.45)	<0.000*
13	1.81	(0.59–5.54)	0.297	8.57	(2.99–24.6)	<0.000*
14	1.59	(0.50–5.08)	0.438	10.70	(3.55–32.27)	<0.000*
15	1.68	(0.52–5.36)	0.386	13.26	(3.94–44.63)	<0.000*

†*P*-value is calculated from logistic regression analysis. **P*≤0.05 considered statistically significant difference. OR: Odds ratio, CI: Confidence interval, PHS: Preoperative hospital stay



Graph 1: OR of surgical site infection (SSI) according to preoperative hospital stay threshold. Solid bars represent $P < 0.05$.

an increased risk factor of SSI resistant to the standard antibiotic prophylaxis[15] and other types of infectious complications.[39] The previous studies highlight the importance of PHS in neurosurgery.[8,13,19,27] However, the time thresholds were reportedly chosen based on clinical expertise, rather than data driven, or only included central tendency measures. Moreover, others did not find PHS to be an independent SSI risk factor.[3,11,23,33,37,38,40] These divergent results could be due to variability in patient selection, prophylaxis protocols, institutional care, statistical methods, or time thresholds.

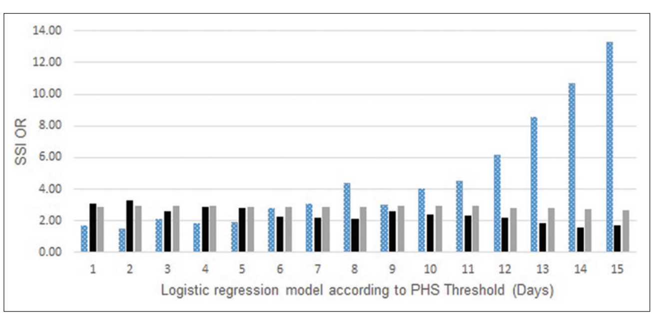
Accordingly, this study aimed to address these methodological gaps and improve the characterization of PHS to SSI risk relationship. As such, PHS, evaluated as a quantitative variable, had significant OR in relationship to SSI. However, length of PHS as a potentially large discrete variable that could be nonlinear still needs further clarification. Thus, as the binary outcome is evaluated with respect to given time frame, but also with a risk factor of variable degree of exposure, a logistic regression model was chosen over Cox proportional hazards. Moreover, considering the low incidence of infection, the relatively short follow-up period and the assumption that its relative risk could not be constant, there are no advantages from the Cox model.[8] As such, multiple logistic regression models including the PHS as a dichotomous variable with progressive time points, led to the cumulative risk threshold characterization, and was more informative than Cox regression or a single logistic regression model, resulting in specific cumulative day odds ratio [Graph 1].

By applying these methods, it became possible to show that the day of PHS-SSI OR that reaches the threshold transition is between the 5th and 6th days, and the PHS-SSI OR relationship was continuous and consistent with time progression. This may be particularly helpful in light of the prior mixed findings in which some found antibiotic prophylaxis effective,[5,25] no benefit,[12] or yielding higher risk of meningitis by prophylaxis of resistant microorganisms.[24] Because the number of days patients is admitted to the hospital before surgery in many circumstances can be modified, this study's approach was to determine at what point PHS seems to put patients at higher risk of postoperative infection. Thus, this work may inform on the explicit risk and the drop of effectiveness of the studied prophylactic antibiotic selection for patients with PHS ≥6 days, possibly associated with higher risk of complications and worse outcomes, in the context of the difficulties in isolation of bacteria from the central nervous system.[6]

Operative time ≥4 h was a SSI risk factor in this study's multivariate analysis, consistent with prior work.[12,33] Further, this time doubled the risk of infection, despite institutional protocols reinforcement prophylactic antibiotic dosages at the ≥4 h time point, and other standard transoperative measures including preheating intraoperative infusions, and forced patient heating to maintain transoperative normothermia. Our institutional antibiotic redosing protocol recommends half the dose initially administrated, because at 4 h provides adequate antibiotic levels based on pharmacokinetic estimates.[20]

The previous surgery during the same hospital admission also was found to be related to SSI and was significant in some of the logistic regression models. Counterintuitively, unlike the PHS-SSI relationship that increased markedly after day 5, the antecedent of surgery during the same hospital admission SSI across different time thresholds demonstrated decreasing strength with time [Graph 2]. Indeed, in all the logistic regression models, where one of these two variables showed statistical significance in relation to SSI, the other one failed to do so. This suggests that both variables are time related and participate as moderating variables of each other. However, it is still yet to be determined how they are related to explain this relationship. Even though the previous surgery during the same hospital admission was associated with higher median PHS ($P < 0.001$), it cannot be rule out that an impact from secondary surgical inflammatory responses or the administration of antibiotics for the prior intervention is causative.

As this was a retrospective cohort study of consecutively and prospectively collected clinical cases without control, the results are Level 3 evidence that PHS ≥6 days is a risk factor for PHS in those undergoing neurosurgery with clean wounds, without late prosthetic material exposure, and antibiotic prophylaxis directed to community-acquired flora, according to Oxford Centre for Evidence-Based Medicine.[22] For nonpercutaneous clean neurosurgical interventions, alternative SSI prevention strategies than antibiotic prophylaxis with cefazolin or clindamycin are a consideration for those patients in whom reaching six or more hospital days could not be avoided (recommendation Grade B).[16]



Graph 2: OR for surgical site infection by each logistic regression model. Dotted blue: Preoperative hospital stay. Black: Previous surgery during the same hospitalization. Gray: Operative time longer than 4 h.

Limitations

The primary limitation of this study was the inability to guaranty the follow-up of some wound infection-related factors including radiation therapy or cerebrospinal fluid leak that has shown a higher risk of infection for neurosurgical patients.[21,24] Furthermore, the influence of bacterial colonization risk from the nosocomial environment could not be confirmed by this study.

Future work

Further studies are needed to determine if similar PHS-SSI risk applies to patients receiving perioperative antibiotics other than cefazolin or clindamycin, which may cover a wider spectrum of microorganisms and were out of the scope of this work, as well as those with prolonged wound healing during the stay outside the nosocomial environment. Studies evaluating nosocomial bacterial colonization relation to PHS-SSI risk and selection of antimicrobial prophylaxis are indicated. Prospective and multicenter PHS-SSI studies would increase formal prophylaxis recommendations strengths in neurosurgery.

CONCLUSION

For nonpercutaneous clean neurosurgical procedures with antibacterial prophylaxis directed against community cutaneous flora, the odds of SSI gradually increase in relation with the amount of days of PHS, as pass threshold for significance at 6 or more days. Surgical time longer than 4 h and previous surgical interventions during the same hospital admission were also found as independent risk factors in our cohort of patients. Future studies are indicated for specific antibiotic prophylaxis recommendations in neurosurgery for patients with prolonged PHS.

Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

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Conflicts of interest

There are no conflicts of interest.

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