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Cost analysis of dalbavancin versus standard of care for the treatment of acute bacterial skin and skin structure infections (ABSSSIs) in two Italian hospitals

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Objectives: Thanks to its long half-life, dalbavancin qualifies as an optimal drug for saving costs. We aimed to assess the cost and effectiveness of dalbavancin versus the standard of care (SoC).

Patients and methods: We conducted a multicentre retrospective study, including all hospitalized or outpatients diagnosed with ABSSSIs at Padua University Hospital, Padua and San Paolo Hospital, Milan (1 January 2016 to 31 July 2020). We compared patients according to antibiotic treatment (dalbavancin versus SoC), the number of lines of dalbavancin treatment, and monotherapy or combination (dalbavancin in association with other antibiotics). Primary endpoints were direct medical costs and length of hospital stay (LOS) associated with ABSSSI management; Student's *t*-test, chi-squared test and one-way ANOVA were used.

Results: One hundred and twenty-six of 228 (55.3%) patients received SoC, while 102/228 (44.7%) received dalbavancin. Twenty-seven of the 102 (26.5%) patients received dalbavancin as first-line treatment, 46 (45.1%) as second-line, and 29 (28.4%) as third- or higher-line treatment. Most patients received dalbavancin as monotherapy (62/102; 60.8%). Compared with SoC, dalbavancin was associated with a significant reduction of LOS (5 ± 7.47 days for dalbavancin, 9.2 ± 5.59 days for SoC; $P < 0.00001$) and with lower mean direct medical costs (3470 ± 2768€ for dalbavancin; 3493 ± 1901€ for SoC; $P = 0.9401$). LOS was also reduced for first-line dalbavancin, in comparison with second-, third- or higher-line groups, and for dalbavancin monotherapy versus combination therapy. Mean direct medical costs were significantly lower in first-line dalbavancin compared with higher lines, but no cost difference was observed between monotherapy and combination therapy.

Conclusions: Monotherapy with first-line dalbavancin was confirmed as a promising strategy for ABSSSIs in real-life settings, thanks to its property in reducing LOS and saving direct medical costs.

Introduction

Acute bacterial skin and soft tissue infections (ABSSSIs) are a heterogeneous group of clinical manifestations involving epidermidis, derma and subcutaneous tissue[1] and range from erythema, oedema and cellulitis up to necrotizing fasciitis; the severity of the clinical presentation depends on the number of structures involved and on the extension of the infectious process.[1,2] ABSSSIs are still among the most common infections in the general population;[2] over time many classifications of ABSSSIs have been proposed, but the most common one distinguishes uncomplicated and complicated infections. The former include either superficial (impetigo) and deep (erysipelas, cellulitis, folliculitis, abscesses) infections, while the latter include acute or chronic wound infections, traumas, animal bites, diabetic foot infections and ulcers.[3–5] A further, easier classification has

also been proposed by IDSA, dividing ABSSSIs into purulent and not-purulent forms.[5]

The most common causative agents are Gram-positive organisms, including *Staphylococcus aureus* (either MSSA or MRSA) and *Streptococcus pyogenes* in 80%–85% cases, whereas *Pseudomonas aeruginosa*, *Escherichia coli* and other bacteria are observed in up to 20% of cases. Drug-resistant pathogens, such as MRSA, are usually acquired in hospital settings; however, there is growing evidence of infections caused by community-acquired MRSA.[3–5]

Incidence of ABSSSIs is constantly increasing, leading to an increased rate of hospitalizations, especially among elderly and frail patients, and resulting in a huge amount of costs for the healthcare systems.[6–8]

Possible risk factors for ABSSSIs are advanced age, white ethnicity, comorbidities (especially diabetes, obesity, vascular insufficiency, immunodepression and recent surgery) [6,7] and being colonized by MRSA.[9] These factors and especially the presence of multiple comorbidities may affect a greater probability of relapse and a worse outcome.[10] The outcome is also influenced by diagnostic delay and inappropriate empirical treatment, which may cause additional days of hospitalization, higher risk of readmission, mortality and higher costs.[11]

In the presence of risk factors for MRSA infection, treatment of ABSSSIs should include an antibiotic active against MRSA. To date, the standard of care (SoC) for such infections is vancomycin or daptomycin, which need daily IV administration in the hospital setting.[12] Linezolid is another valid option for ABSSSIs, thanks to its non-inferiority to vancomycin; however, it could require monitoring of plasma concentrations in order to reduce its possible side effects, mainly in elderly, nephropathic or critically ill patients.[13] Indeed, in almost 50% of patients diagnosed with ABSSSIs who require hospital admission, the only reason for hospitalization is the need to receive an IV antibiotic treatment[12] and the median length of antibiotic therapy may range from 5 days up to 4 weeks.[14]

Most recently, new agents have been approved for ABSSSIs, such as dalbavancin.[12,14,15] Dalbavancin is a long-acting lipoglycopeptide that has bactericidal activity against Gram-positive microorganisms, including MRSA. It can be administered as a single dose or with a loading dose followed by a second dose after 1 week, allowing physicians to either discharge patients early or to avoid hospitalization in patients who are clinically stable.[3,16] In a randomized controlled trial enrolling more than 1200 patients, once-weekly IV dalbavancin was not inferior to twice-daily IV vancomycin followed by oral linezolid for the treatment of ABSSSIs.[4] Since its introduction, dalbavancin proved effective and safe in several real-life experiences,[17–25] not only in the treatment of ABSSSIs, but also in off-label indications, as well as bone and joint infections and endocarditis.[26,27] This drug is thus an interesting option for patients who still need IV therapy, but can be managed in outpatient services. Furthermore, dalbavancin has demonstrated not only efficacy and safety comparable to SoC in randomized clinical trials, but was also associated with significant cost savings, especially when SoC also needs to cover MRSA;[28–30] this antibiotic in fact allows a shorter length of hospitalization and a reduced number of procedures that are required for the administration of daily IV treatments, such as implantation of intravascular catheters.[28–34] Further, hospital admission could even be avoided in some patients, since dalbavancin is an excellent candidate for outpatient parenteral antimicrobial therapy (OPAT).[35,36]

Despite such interesting and promising properties, in clinical practice in Italy, dalbavancin is still used after several lines of other antibiotic treatments or in combination with other antibiotics and thus its economic advantages are often offset by the direct drug-related cost.[24,37]

In this context, the objective of our multicentre retrospective analysis was to compare the cost and effectiveness (indirectly measured in terms of days of hospitalization) of dalbavancin versus SoC in the treatment of ABSSSIs.

Materials and methods

Study population

This multicentre retrospective observational analysis was conducted in two Infectious and Tropical Diseases Units in Northern Italy (Infectious and Tropical Diseases Unit, Padua University Hospital and Clinic of Infectious Diseases, ASST Santi Paolo e Carlo, University of Milan).

All adult patients, older than 18 years of age, diagnosed with ABSSSIs between 1 January 2016 and 31 July 2020 at the two centres were consecutively included.

The study was conducted according to principles of good clinical practice and the Declaration of Helsinki and received ethical approval (42031/2018). Patients' informed consent was waived due to the retrospective nature of the study (Italian Drug Agency note, 20 March 2008; GU Serie Generale no. 76, 31 March 2008).

Patients were divided into three groups: subjects treated with SoC (all other antibiotics for the treatment of ABSSSIs excluding long-acting antibiotics); patients treated with dalbavancin; and patients who received both SoC and dalbavancin. In the latter group, we recorded the line of treatment in which dalbavancin was used (i.e. first line, second line, third line or higher, depending on whether dalbavancin was used as first antibiotic or after a first antibiotic or after two or more consecutive antibiotics, respectively; antibiotic switch was for any reason depending on physician's choice). We also collected whether patients were hospitalized or outpatients.

For each subject we collected the following data: gender, age at ABSSSI diagnosis, comorbidities, hospital ward, date of hospital admission and discharge, date of ABSSSI diagnosis, therapies for ABSSSI management (start and end dates), adverse events (type, procedures for the management and treatment of the adverse event, such as blood tests, specialist examinations, radiological procedures, therapies), pre-treatment C-reactive protein (CRP) and estimated glomerular filtrate rate (eGFR), outcomes (healing, death, relapse without new hospitalization, relapse with new hospitalization, not known/self-discharge), date of outcome and infection-related monitoring activities (diagnostics, outpatient activities, day hospital admissions, other therapies).

Statistical analyses

Means, SDs, medians, minimum, maximum, first quartile and third quartile values were used to summarize countable and continuous variables. Percentage and number of patients were used to summarize categorical variables, as appropriate.

The three statistical comparisons across the groups of interest were performed using Student's *t*-tests on the equality of means for continuous variables and dichotomous variables, while Pearson's chi-squared was used for categorical variables. Additionally, for continuous variables and polytomous variables, the comparisons across the groups of patients were carried out using one-way ANOVA. A P value of ≤ 0.05 was set up to define statistical significance.

The primary endpoints of the analysis were direct medical costs related to ABSSSI management, assuming the hospital perspective, and the number of days of hospitalizations due to ABSSSIs.

The direct medical costs related to ABSSSIs were calculated considering the following aspects: daily hotel and care costs (350€, provided by the hospital financial office); antibiotic costs (based on the number of days and posology of each treatment); adverse event management costs (based on the activities performed); and post-discharge monitoring costs. The hospitalization costs were calculated by considering the number of days of hospitalization related to ABSSSIs (from the diagnosis of ABSSSI until healing from the infection or death or discharge). The costs of the outpatient services are based on the national tariffs for specialist outpatient assistance services currently in use in Italy. The costs of treatments are based on the cost data provided by the hospitals and, if not available, to the median ex-factory price reimbursed by the Italian National Health Service, as reported by the Italian Drugs Agency in the class A and H drug lists (updated to July 2020). Cost data refers to the year 2020.[38,39]

Results

Clinical characteristics of the study population

Over the study period, 228 patients were diagnosed with ABSSSIs in the two study centres. Overall, the mean age was of 59 (SD± 17.6) years, and 128/228 (56%) were male. Among 228 patients, 126 (55.3%) received SoC and 102 (44.7%) received dalbavancin. Among patients who received dalbavancin, 27 (26.5%) received the drugs as first-line treatment, 46 (45.1%) as second-line, 29 (28.4%) as third-line or higher, and in 62 (60.8%) patients dalbavancin was prescribed as monotherapy. The main antibiotics used in association with dalbavancin were: β-lactams (amoxicillin/clavulanate, ampicillin/sulbactam, piperacillin/tazobactam); cephalosporins (ceftriaxone, cefazolin); fluoroquinolones (levofloxacin, ciprofloxacin); lincosamides (clindamycin); tetracyclines (doxycycline); glycopeptides (vancomycin); cyclic lipopeptides (daptomycin); and carbapenems (imipenem/cilastatin, meropenem, ertapenem).

The full clinical characteristics of the study population are presented in Table 1. Most patients in both groups (SoC and dalbavancin) had two or more comorbidities (93% and 95%, respectively). Patients treated with dalbavancin were more commonly female compared with patients receiving SoC ($P < 0.001$); higher levels of CRP were observed in the SoC group compared with dalbavancin, dalbavancin in second line of treatment and in combination with other antibiotics (Table 1).

In terms of clinical outcome, we did not observe any statistically significant differences between SoC versus dalbavancin, with a clinical efficacy being reached in 91% and 94% of dalbavancin and SoC groups, respectively (Table 1).

Comparison of length of hospital stay and costs between dalbavancin and SoC

Results from the comparison between SoC and dalbavancin in terms of days of hospitalization and costs are depicted in Table 2.

The mean number of days of hospitalization was significantly lower for the dalbavancin group compared with the SoC group (5 ± 7.47 versus 9.2 ± 5.59; $P < 0.001$). The mean direct medical costs were 3470€ (±2768) for dalbavancin and 3493€ (±1901) for the SoC group, with no statistically significant difference ($P = 0.9401$).

Comparison of length of hospital stay and costs between dalbavancin and SoC, according to treatment lines

Considering the line of treatment in which dalbavancin was administered, the mean number of days of hospitalization were 2.3 (±3.21) in the dalbavancin first-line group, 5.1 (±7.28) in the dalbavancin second-line group and 7.5 (±9.65) in the dalbavancin third-line group, with a statistically significant difference ($P < 0.001$) for all comparison groups.

Interestingly, the mean direct medical costs increased with increasing treatment lines: 2402€ (±1190) in the dalbavancin first-line group; 3501€ (±2728) in the dalbavancin second-line group; and 4415€ (±3511) in the dalbavancin third- or higher-line group ($P = 0.014$).

Comparison of length of hospital stay and costs between dalbavancin and SoC, according to monotherapy and combination therapy

Regarding the dalbavancin regimen administered to patients (dalbavancin monotherapy or dalbavancin associated with other antibiotics), the mean number of days of hospitalization were 4.7 (±6.86) in the dalbavancin monotherapy group and 5.6 (±8.39) in the dalbavancin associated with other antibiotics group, with a non-statistically significant difference ($P = 0.629$).

The mean direct medical costs were similar between the dalbavancin monotherapy group (3327€, ±2441) and the combination group (3690€, ±3230; $P = 0.521$).

Discussion

Our study adds important data about cost and effectiveness of dalbavancin versus SoC regimens for the treatment of ABSSSIs in a real-life setting. ABSSSIs are a frequent reason of hospital admission and nearly 10% of all hospital antibiotic therapy is attributed to ABSSSIs, with a consequent relevant healthcare system burden.[40] Indeed, the management of ABSSSIs is complex given the frequent association with comorbidities such as obesity, diabetes mellitus and peripheral vascular disease, which may complicate the choice of the appropriate empirical antibiotic therapy.

The current study enrolled 228 patients with ABSSSIs, 102 patients treated with dalbavancin and 126 patients with the SoC. Patient demographics and clinical characteristics were well balanced according to age, number of comorbidities, severity of infection and renal function. Only the gender distribution was significantly different, with fewer males in the dalbavancin group; however, we believe this difference can be related to the retrospective nature of the study. In addition, second or higher lines of treatment and monotherapy with dalbavancin were used more commonly in patients with higher systemic inflammation (CRP), showing that clinicians were confident in using this new long-acting agent even in patients with several comorbidities and often as a salvage therapy.

Indeed, in our real-life study, dalbavancin was confirmed as an effective treatment for ABSSSIs. The overall cure rate was as high as >90% in both dalbavancin and the SoC. These results are similar to those reported by Phase 3 clinical trials, which displayed clinical success in patients infected by *S. aureus* of 90.6%

Table 1. Characteristics of the study population

Parameters	Total population (*N* = 228)	SoC (*N* = 126)	Dalbavancin (*N* = 102)	*P* value (SoC versus dalbavancin)	First line (*N* = 27)	Second line (*N* = 46)	Third or higher line (*N* = 29)	*P* value (SoC versus first-line dalbavancin versus second-line versus third- or higher-line)	Dalbavancin monotherapy (*N* = 62)	Dalbavancin with other antibiotics (*N* = 40)	*P* value (SoC versus dalbavancin alone versus dalbavancin with other antibiotics)
Age, mean (±SD)	58.92 (±17.60)	59.09 (±18.34)	58.72 (±16.73)	0.874	57.59 (±17.54)	57.66 (±19.43)	60.04 (±14.57)	0.488	60.42 (±17.12)	56.08 (±15.97)	0.366
Female, *n* (%)	100 (44)	49 (39)	51 (50)	0.001	14 (52)	23 (50)	14 (48)	0.407	33 (53)	18 (45)	0.417
Comorbidity, *n* (%)				0.828				0.738			0.467
1 comorbidity	13 (6)	8 (6)	5 (5)		19 (70)	3 (7)	2 (7)		4 (6)	1 (3)	
2 comorbidities	138 (61)	79 (63)	59 (58)		6 (22)	23 (50)	17 (59)		33 (54)	26 (65)	
≥3 comorbidities	77 (33)	39 (31)	38 (37)		2 (8)	20 (43)	10 (4)		25 (40)	13 (32)	
eGFR (mL/min/ 1.73 m2), *n* (%)	*N* = 213	*N* = 124	*N* = 89	0.084	*N* = 24	*N* = 43	*N* = 22	0.346	*N* = 54	*N* = 35	0.740
<60	47 (22)	34 (27)	13 (15)		3 (13)	8 (19)	2 (9)		9 (17)	4 (11)	
≥60 and <90	65 (31)	35 (28)	30 (34)		10 (42)	13 (30)	7 (32)		17 (31)	13 (37)	
≥90	101 (47)	55 (44)	46 (52)		11 (46)	22 (51)	13 (59)		28 (52)	18 (51)	
CRP (mg/L), mean (±SD)	89.26 (±64.07)	81.68 (±57.58)	100.03 (±71.26)	0.064	88.56 (±71.59)	93.70 (±69.90)	124.16 (±17.25)	<0.0001	95.86 (±70.73)	106.05 (±72.60)	0.047
Outcomes, *n* (%)											
Healing		118 (94)	93 (91)	0.765	27 (100)	42 (91)	24 (83)	0.107	55 (89)	38 (95)	0.519
Death		0 (0)	0 (0)		0 (0)	0 (0)	0 (0)		0 (0)	0 (0)	
Relapse without new hospitalization		3 (2)	5 (5)		0 (0)	1 (2)	4 (14)		4 (6)	1 (3)	
Relapse with new hospitalization		2 (2)	2 (2)		0 (0)	2 (4)	0 (0)		1 (2)	1 (2)	
Not known/ self-discharge		3 (2)	2 (2)		0 (0)	1 (2)	1 (3)		2 (3)	0 (0)	

Numerical variables are presented as mean (±SD), categorical variables as absolute numbers (percentages). *P* values for comparison among groups (SoC versus dalbavancin; SoC versus first-line dalbavancin, second-line dalbavancin, third- or higher-line dalbavancin; SoC versus dalbavancin monotherapy or dalbavancin associated with other antibiotics) by Student's *t*-test or chi-squared test, as appropriate.

Table 2. Results of the analysis

Parameters	SoC (*N* = 126)	Dalbavancin (*N* = 102)	*P* value (SoC versus dalbavancin)	First line (*N* = 27)	Second line (*N* = 46)	Third or higher line (*N* = 29)	*P* value (SoC versus first-line dalbavancin versus second-line dalbavancin versus third- or higher-line dalbavancin)	Dalbavancin monotherapy (*N* = 62)	Dalbavancin with other antibiotics (*N* = 40)	*P* value (SoC versus dalbavancin alone versus dalbavancin with other antibiotics)
Days of hospitalization, mean (±SD)	9.2 (±5.59)	5.0 (±7.47)	<0.0001	2.3 (±3.21)	5.1 (±7.28)	7.5 (±9.65)	<0.0001	4.7 (±6.86)	5.6 (±8.39)	0.629
Costs (€), mean (±SD)	3493 (±1901)	3470 (±2768)	0.94	2402 (±1190)	3501 (±2728)	4415 (±3511)	0.014	3327 (±2441)	3690 (±3230)	0.521

Numerical variables are presented as mean (±SD), categorical variables as absolute numbers (percentages). *P* values for comparison among groups (SoC versus dalbavancin; SoC versus first-line dalbavancin, second-line dalbavancin, third- or higher-line dalbavancin; SoC versus dalbavancin monotherapy or dalbavancin associated with other antibiotics) by Student's *t*-test, one-way ANOVA or chi-squared test, as appropriate.

with dalbavancin and 93.8% with vancomycin/linezolid,[4] and by real-life settings.[19,23,24,41]

Furthermore, the 30 day recurrence rate was similar to the conventional therapy and no deaths were recorded in the two groups. Serious adverse outcomes of ABSSSIs are in fact rare, and mortality is extremely low, less than 5% among hospitalized patients, suggesting that the current hospitalization rates may be excessive and somewhat overused at many centres.

The significant costs related to ABSSSIs seem to be associated with hospitalizations, which could affect up to 70% of the total costs for the management of these infections.[42] Furthermore, a UK study demonstrated that 97% of hospital costs are due to direct inpatient bed day costs and the remaining 3% to the non-bed day costs, including drug acquisition, administration and monitoring costs.[43]

We hereby show that the dalbavancin-based treatment significantly reduced the length of hospital stay compared with the SoC, especially when dalbavancin was used as a single agent and as first-line treatment. Consequently, dalbavancin provided an overall cost reduction of 1099€ and 2013€ when used as a first-line treatment compared with a second- or third-line treatment, respectively. Our results are in accordance with previous studies showing a significant and considerable reduction of more than 4–7 days in the hospital length of stay for patients treated with dalbavancin, which would allow cost offsets higher than the cost of dalbavancin itself. Of note, considering that the maximum benefit of dalbavancin was obtained with its early use (first- or second-line treatment), we suggest that dalbavancin should be recommended as an early treatment rather than for compassionate use after failures of multiple other antibiotics, as it happened for the use of other 'new' antibiotics.

From a microbiological point of view, it is well known that the main pathogens causing ABSSSIs are Gram-positive bacteria, with the most common being *S. aureus*, both MSSA and MRSA. Even though in the EU/EEA the mean MRSA prevalence is decreasing significantly, from 19.6% in 2014 to 16.7% in 2021, MRSA is still frequently isolated in several Mediterranean countries, as in Italy, with a prevalence up to 40%. This MRSA prevalence could be responsible for the high rate of clinical failure of conventional first-line therapy of ABSSSIs, often characterized by suboptimal coverage of MRSA with the empirical treatment that was in fact modified in more than 60% of patients, as reported in a recent European survey.[40] In this setting, dalbavancin is active against most MDR Gram-positive bacteria, including MRSA. However, we suggest that the use of dalbavancin, also in the outpatient setting, may be evaluated in a coordinated antimicrobial stewardship programme to improve the appropriate use of empirical treatments, reserving anti-MRSA antibiotics for in the presence of known MRSA risk factors or local epidemiological issues. These programmes have been shown to save resources, optimize treatment duration, preserve antibiotic efficacy in the long term and avoid the spread of antimicrobial resistance patterns.[44]

We must also highlight that the cost of the long-acting agent is often offset by an earlier discharge made possible by dalbavancin, thanks to the reduction of the endovascular device-associated infections, which are not needed for dalbavancin administration. These data have been confirmed by the budget-impact analysis developed by Marcellusi *et al.*[30] in three European countries (Italy, Spain, Austria) in which the increased early use of dalbavancin

could significantly reduce both hospitalization rates and lengths of hospital stay in non-severe ABSSSI patients.

Interestingly, our results also reflect the current mode of reimbursing dalbavancin in a hospital perspective and an exclusive 'intra-diagnosis-related group (DRG)' dalbavancin financial model; a probable evolution of reimbursing dalbavancin is its OPAT use (also for second or later infusion) that may substantially reduce costs and increase effectiveness.

A therapeutic pathway allowing for early patient discharge has been of particular interest, mainly during the current SARS-CoV-2 pandemic, when shortages of available hospital beds and the risks of in-hospital infections have been critical factors in the management of patients with ABSSSIs. A close telehealth follow-up may further help clinicians to safely administer dalbavancin in the Emergency Department (ED) setting, as reported in a pre-pandemic study in which recurrences of infections were similar between patients included in the telehealth programme and control patients.[45]

Our study has the following limitations: first, this was a retrospective study with a relatively small sample size; recurrence rates were potentially underestimated given that we did not have data about possible recurrences not managed at our centres, although we arranged follow-up for most enrolled patients; only two Italian centres were involved in the study, so generalization of the data may not be feasible since dalbavancin availability and costs could vary in other settings.

Notwithstanding the limitations mentioned above, we believe our study has several strengths and originality with respect to the published literature; the inclusion of two large Italian hospitals, a homogeneous setting that improves representativeness and reflects the real-life situation of many acute care hospitals; finally, the analysis of multiple outcomes (both hospital stay and costs).

In conclusion, our study demonstrated that the long-acting lipoglycopeptide dalbavancin is able to facilitate early discharge, simplifying ABSSSI treatment. It thus represents an interesting therapeutic opportunity aimed at reducing the frequency of antibiotic administration and the length of hospital stay of patients diagnosed with ABSSSIs, with a desirable consequence of overall cost savings and improvement of quality of patient care. Further studies are needed to determine specific clinical pathways in which patients with strict selection criteria may be safely discharged and followed in the outpatient setting.

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Author contributions

G.M. and A.M.C. conceived the study. F.B., M.M. and F.R. were involved in the clinical care of the patients and collected data for the study. U.R., D.C., G.M. and A.M.C. supervised the study. S.S. and U.R. performed the statistical analyses. F.B., M.M., S.S. and U.R. wrote the manuscript. All the authors revised the manuscript.

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