



Universal versus Risk-Based Management of Unknown Group B Streptococcus Status at Term

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Abstract

Keywords

- ▶ early-onset Group B streptococcus (EOGBS)
- ▶ intrapartum antibiotic prophylaxis
- ▶ risk-based management of GBS
- ▶ universal management of GBS
- ▶ neonatal sepsis
- ▶ prelabor rupture of membranes
- ▶ maternal intrapartum fever

Objectives This article estimates and compares public health costs of universal versus risk-based intrapartum antibiotic prophylaxis (IAP) administration for women with unknown Group B streptococcus (GBS) status at term.

Study Design The annual number of women in the U.S. who are: unscreened for GBS, without risk factors, delivering vaginally, multiparous, and eligible for discharge within 24 hours was estimated. Under the risk-based strategy, women and neonates were assumed to stay another day for observation and incur the cost of an additional 24-hour stay. With universal IAP administration, women delivering without complications were assumed to be discharged within 24 hours, with an incurred cost of penicillin.

Results The estimated cost for the risk-based management of unscreened women at term without rupture of membranes (ROM) > 18 hours ranged from \$468,886,831 to \$850,556,179. Similarly, the cost of managing unscreened women without maternal intrapartum fever (MIF) ranged from \$742,024,791 to \$919,269,233. Alternatively, universal IAP administration costs ranged from \$470,107,674 to \$568,359,086.5. Cost comparisons yielded an equivalence or up to a 33.2% reduction in cost, and 36.6 to 38.2% reduction in cost for women without ROM > 18 hours and MIF, respectively.

Conclusions Universal IAP may be cost saving due to the reduction in extended hospitalizations for neonates and healthy mothers.

Since its emergence in the 1970s as a prominent infectious cause of mortality and morbidity in neonates,^{1–4} maternal colonization of Group B streptococcus (GBS) remains a frequent cause of secondary sequelae, including sepsis, pneumonia, and meningitis.^{2,5,6} The current recommended strategy for management of GBS colonization is selective intrapartum antibiotic prophylaxis (IAP) for screen-positive mothers, following a universal antepartum rectovaginal culture at 35 to 37 weeks' gestation and for women with risk factors for GBS

transmission to the infant.^{1,7} This strategy has been shown to be effective in decreasing the incidence of GBS colonization in infants and preventing early-onset GBS (EOGBS)-related illness, which is defined as disease onset before the 7th day of life.^{1,5,8} Since the implementation of universal antepartum screening and the use of IAP for GBS management, the incidence of EOGBS is currently reported at an all-time low of between 0.23 and 0.37/1,000 births in the United States.⁹ Current cases of EOGBS are uncommon in patients who

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Table 1 Economic costs of hospitalization for women without ROM > 18 hours at term who do not receive intrapartum antibiotic prophylaxis (IAP)

Population	Calculation	Results
# of births in the U.S. in 2016		3,877,317 ¹⁶
# of births to women at term with GBS unknown status	$n \times 10.7\%^{14}$	414,873
# Women without PROM	$n \times (61.8\%^{10} - 91.6\%^{11})$	256,391–380,024
# Women that deliver vaginally	$n \times 68.1\%^a$	174,603–258,796
# Women from this population that are multiparous	$n \times (47.8\%^4 - 58.5\%^{14})$	83,460–151,396
Cost of a 48-h hospitalization for this population WITHOUT IAP	$n \times \$5,618.1^b$	\$468,886,831–\$850,556,179

Abbreviations: GBS, Group B streptococcus; PROM, premature rupture of membranes; ROM, rupture of membranes.

^aInferred estimated of number of women that deliver vaginally based on cited estimate of 31.9%^{15,17,19,36} of women that deliver via cesarean section.

^b► **Table 5** shows the calculations used to determine the cost of a 24- and 48-hour hospitalization used in these calculations.

screened positive during their antenatal course and who received adequate IAP; cases of sepsis can be attributed to the transient nature of GBS infection (culture-negative patients in the antenatal course who then go on to deliver infected neonates) and untreated, unscreened mothers for whom GBS colonization had not been determined before labor and for whom IAP was not administered.^{4,10,11}

Currently, women with unknown GBS statuses who are at least 37 weeks' gestational age and who have no risk factors are not recommended to receive IAP.^{1,7} On the pediatric side, babies born to these women who are GBS positive or GBS status unknown at term and who did not receive IAP are observed for up to 48 hours following delivery.^{2,12} Therefore, with respect to unknown GBS status at term, there appears to be a conflict between the bodies governing obstetrics and gynecology versus pediatrics. To address this conflict, the primary aim of this study was to compare two strategies for the management of unknown GBS status at term in women without risk factors. The first strategy is the current American College of Obstetrics and Gynecologists' (ACOG) recommended strategy of withholding IAP for women with unknown culture status unless the patient has specific risk factors.¹ The second strategy is to give IAP regardless of the presence or absence of risk factors, based on the recommendation that the lack of antibiotics during labor will result in infant hospitalizations for the currently recommended

48-hour observation period. Our focus was exclusively on the economic cost to society associated with each strategy.

Methods

This study was an economic analysis that aimed to compare two strategies for managing women with unknown GBS status at term without risk factors. Our methodology for determining the cost of not administering IAP because of the current risk-based administration of prophylaxis for the management of unknown GBS status at term is outlined in ► **Tables 1** and **2** for women presenting without prolonged rupture of membranes (ROM) and maternal intrapartum fever (MIF), respectively. These clinical schemas were chosen because they are the most frequently encountered exclusionary criteria for withholding antibiotics in labor and employing the risk-based strategy; thus, patients with prolonged ROM or MIF would receive IAP. Our methodology for determining the cost of managing GBS status unknown at term with universal prophylaxis is outlined in ► **Table 3**. The prior publications used to obtain the data needed for our cost estimates are displayed in ► **Table 4**.

We performed a limited sensitivity analysis to estimate the public health costs for the universal and risk-based strategies of GBS management by determining the minimum, average, and maximum incidences of MIF, premature ROM, and multiparity among women. We estimated the

Table 2 Economic costs of hospitalization for women without MIF at term who do not receive intrapartum antibiotic prophylaxis (IAP)

Population	Calculation	Results
# of births in the U.S. in 2016		3,877,317 ¹⁶
# of births to women at term with GBS unknown status	$n \times 10.7\%^{14}$	414,873
# Women without MIF	$n \times (97.8\%^{10} - 99\%^{15})$	405,746–410,724
# Women that deliver vaginally	$n \times 68.1\%^a$	276,313–279,703
# Women that are multiparous	$n \times (47.8\%^4 - 58.5\%^{14})$	132,078–163,626
Cost of a 48-h hospitalization for this population WITHOUT IAP	$n \times \$5,618.1^b$	\$742,024,791–\$919,269,233

Abbreviations: GBS, Group B streptococcus; MIF, maternal intrapartum fever.

^aInferred estimate of number of women that deliver vaginally based on cited estimate of 31.9%^{15,17,19,36} of women that deliver via cesarean section.

^b► **Table 5** shows the calculations used to determine the cost of a 24- and 48-hour hospitalization used in these calculations.

Table 3 Economic costs for universal IAP

Population	Calculation	Results	
# of births in the U.S. in 2016		3,877,317 ¹⁶	
# of births to women at term with GBS unknown status	$n \times 10.7\%^{14}$	414,873	
	Cost of PCN for all women during labor course	# of births to women at term with GBS unknown status \times \$75.18 ¹⁸	\$31,190,146 to be added to total cost of hospitalization
# Women that delivery vaginally	$n \times 68.1\%^a$	282,528	
# Women that are multiparous	$n \times (47.8\%^4 - 58.5\%^{14})$	135,049–165,279	
# Women that deliver WITH complications	$n \times 15.7\%^{19}$	21,203–25,949	
# Women that deliver WITHOUT complications	$n \times 84.3\%^{19}$	113,846–139,330	
Cost of a 48-h hospitalization for women that deliver WITH complications	$n \times \$5,618.1^b$	\$119,118,499–\$145,783,101	
Cost of a 24-h hospitalization for women that deliver WITHOUT complications	$n \times \$2,809.05^b$	\$319,799,028–\$391,385,840	
Total economic costs of hospitalizations when implementing universal IAP	Sum of costs of hospitalization & PCN for all women during labor course =	\$470,107,673.5–\$568,359,087	

Abbreviations: GBS, Group B streptococcus; IAP, intrapartum antibiotic prophylaxis; PCN, penicillin.

^aInferred estimate of number of women that deliver vaginally based on cited estimate of 31.9%^{15,17,19,36} of women that deliver via cesarean section.

^b► **Table 5** shows the calculations used to determine the cost of a 24- and 48-hour hospitalization used in these calculations.

public health costs by grouping incidences for each calculation, such that the minimum incidence values were used to determine the minimum societal cost estimate for both strategies of GBS management. This same method of grouping was used to determine the average and maximum societal cost estimates.

The Consolidated Health Economic Evaluation Reporting Standards checklist for reporting standards was adhered to in the economic analysis.¹³

Van Dyke et al evaluated the efficacy of universal screening and management of GBS in women during pregnancy. In this large study of over 7,000 women, the percentage of women who presented at term with unknown GBS status was 10.7%.¹⁴ This percentage was used as the basis of all our calculations. We obtained an estimate of the total number of women in the United States with GBS status unknown at term by multiplying 10.7% by the total number of women who gave birth in 2016.^{14,15}

Table 4 Referencing source used for cost estimate calculations

Data point	Referencing source
% of women who present at term with Group B streptococcus status unknown	Van Dyke et al (2009)
# of babies born in the United States in 2016	Martin et al (2018)
% of singleton births in the United States in 2016	Martin et al (2018)
% of women who present with rupture of membranes > 18 hours	Zuppa et al (2014) and Gilson et al (2000)
% of women who present with maternal intrapartum fever	Zuppa et al (2014) and Makhoul et al (2007)
% of women who deliver via cesarean section	Pasko et al (2018) and Martin et al (2018)
% of women who are multiparous	Picchiassi et al (2018) and Van Dyke et al (2009)
% of women who deliver vaginally with complications/ no complications	Podulka et al (2011)
Cost of one-night hospitalization for mother	Podulka et al (2011)
Cost of one-night hospitalization for infant	Kowlessar et al (2013)
Cost of intrapartum antibiotic prophylaxis (penicillin)	Lexicomp (2019)

Strategy 1: Determining the Societal Cost of Risk-Based Administration of IAP to Women Who Present at Term with GBS Status Unknown and No Known Risk Factors

The total population of women who present at term with unknown GBS status was further stratified for the presence or absence of risk factors. As outlined in **Table 1**, the percentage of women who present at term without ROM > 18 hours ranged from 61.8¹⁰ to 91.6%¹¹ in previous studies. As outlined in **Table 2**, the percentage of women who present at term without MIF ranged from 97.8¹⁰ to 99%¹⁶ in previous studies. These percentages were used to determine the proportion of the total population of women giving birth in the United States annually who would not have been treated based on the current ACOG guidelines.

This population of women untreated for GBS status unknown at term was further stratified based on delivery method. Based on the 31.9% national cesarean delivery rate,^{15,17} we estimated that the vaginal delivery rate would be 68.1%. According to the current ACOG guidelines, the women who had GBS status unknown at term without risk factors and who delivered vaginally would not qualify for IAP.

The total population of untreated women per ACOG guidelines was analyzed further based on parity, due to an assumption that multiparous women are typically eligible for discharge within 24 hours postpartum. The percentage of multiparous women, based on 1 previous live birth, was determined through an analysis of multiple studies. The percentage of multiparous women ranged from 47.8⁴ to 58.5%.¹⁴ Without IAP, these women, who were multiparous and delivered vaginally with GBS status unknown and no known risk factors at term, would not be discharged within 24 hours and,

instead, would incur an additional 24-hour hospitalization while their infant was observed for the potential development of GBS disease.¹² The cost of a 2-day hospitalization for both mother and infant was applied to this total stratified population of women to estimate the total economic cost of the current risk-based management of GBS status unknown at term without risk factors. To determine the cost of a 48-hour hospitalization, the cost of hospitalization for neonate and postpartum mother were summed and then multiplied by 2 (**Table 5**).

Strategy 2: Determining the Societal Cost of Universal Administration of IAP to Women Who Present at Term with Unknown GBS Status

Strategy 2 assumed that the total population of women who presented at term with unknown GBS status would be prophylactically treated, regardless of the presence or absence of risk factors. The population of women who presented at term with GBS status unknown was assumed to receive penicillin G at least 4 hours prior to delivery, consistent with the current recommendations for prophylactic treatment of GBS colonization.^{1,3,5,7} We assumed this treatment would include the initial loading dose of 5 million units, with at least 1 subsequent dose of 2.5 million units of penicillin G. The combined cost of the single loading dose and subsequent dose, was estimated by averaging a composite resource reported value of \$37.95 and multiplying by 2 (**Table 5**), to arrive at an average of \$75.18 for IAP during labor per patient.¹⁸ Two doses were chosen in lieu of one dose as 55% of laboring women will require more than 4 hours of antibiotics, meaning an additional dose would need to be administered in addition to a loading dose to cover

Table 5 Calculations for the estimated values used to further determine the total estimated cost of hospitalization for Strategies 1 and 2

Value	Calculation	Estimated total
Estimated cost of 24 h hospitalization for infant in 2016 ^a	The cost was \$941.176 in 2011 ³⁶ ; with cumulative inflation of 6.7%, ³⁷ the cost in 2016 would be =	\$1,004.23
Estimated cost of 24 h hospitalization for mother in 2016 ^b	The cost was \$1,619.047 in 2008 ¹⁹ ; with cumulative inflation of 11.5%, ³⁷ the cost in 2016 would be =	\$1,804.82
Estimated cost of 24 h hospitalization for mother and infant pairs	\$1,004.23 + \$1,804.82	\$2,809.05
Estimated cost of 48 h hospitalization for infant	\$1,004.23 × 2	\$2,008.46
Estimated cost of 48 h hospitalization for mother	\$1,804.82 × 2	\$3,609.64
Cost of 48 h hospitalization for mother and infant pairs	\$2,008.46 + \$3,609.64	\$5,618.1
Average cost of 1 dose of penicillin	(\$33 + \$42.18) ¹⁸ / 2	\$37.59
Average cost of 2 doses of penicillin	\$37.59 × 2	\$75.18

^aCost of 24-hour hospitalization was estimated using the average hospital cost for all live births which was \$3,200 divided by the average length of stay (days) of 3.4 to generate an estimate of \$941.176 per day in 2011.³⁶ Costs were further adjusted for inflation to the year 2016, to standardize dates for birthing statistics and health care costs.

^bCost of 24-hour hospitalization was estimated using the mean cost per stay of vaginal delivery without complication of \$3,400 divided by the mean length of stays (days) of 2.1 to generate an estimate of \$1,619.047 per day in 2008.¹⁹ Costs were further adjusted for inflation to the year 2016, to standardize dates for birthing statistics and health care costs.

Table 6 Economic cost to society of women who present at term without rupture of membranes > 18 hours

Estimates used in calculations	Universal cost of IAP (\$)	Cost of current standard of care (\$)	Variation of cost with IAP (%)
Minimum values of estimates	470,107,673.5	468,886,831.4	0.25% cost increase
Average values of estimates	519,233,380	647,068,557.4	19.2 cost reduction
Maximum values of estimates	568,359,086.5	850,556,178.9	33.2 cost reduction

Abbreviation: IAP, intrapartum antibiotic prophylaxis.

4+ hours. This number was used to estimate the total cost of prophylactically treating the entire population of women who presented with GBS status unknown at term. This cost was added to the total cost of hospitalization for mother–infant pairs postpartum to compare against the estimated total cost of the risk-based management of GBS status unknown at term.

As outlined in ►Table 3, the hospitalization costs for Strategy 2 were estimated by further stratifying the total population of women with GBS status unknown at term based on delivery method, complications associated with delivery, and parity. Of women delivering vaginally, we assumed 84.3% would deliver without complications and, therefore, were eligible for discharge within 24 hours postpartum, while the remaining 15.7% of women delivering vaginally with complications were assumed to be discharged within 48 hours.¹⁹ The cost of hospitalization was estimated per mother–infant pairs, based on length of stay, and was then summed to determine the total economic cost of hospitalization for Strategy 2. The total cost of hospitalization was then summed with the cost of penicillin G administration to estimate the total societal economic cost of universal prophylaxis for all women who presented at term with unknown GBS status.

Determining the Cost Reduction of Universal Prophylactic Management versus Risk-Based Prophylactic Management of GBS Status Unknown at Term

The total economic cost to society of the risk-based management of GBS status unknown at term for women presenting without ROM > 18 hours or MIF versus universal prophylaxis are compared in ►Tables 6 and 7, respectively.

Results

We estimated the societal cost of universal prophylactic management of GBS status unknown at term to range from

\$470,107,674 to \$568,359,087 (►Table 3). The estimated economic cost to society for the risk-based management of women who present at term with GBS status unknown and the absence of ROM > 18 hours ranged from \$468,886,831 to \$850,556,179 (►Table 1). When these cost estimates were compared with that of the universal IAP for treatment of unknown GBS status, a cost increase of 0.25% was calculated for the lower end estimate of universal prophylaxis, while a 33.2% cost reduction was calculated for the higher end of universal prophylaxis (►Table 6).

In addition, the estimated economic cost to society for the risk-based management of women who present at term with GBS status unknown and the absence of MIF ranged from \$742,024,791 to \$919,269,233 (►Table 2). When these cost estimates were compared with that of universal prophylaxis, a cost reduction that ranged from 36.6 to 38.2% was observed (►Table 7).

Discussion

Appropriate timing of discharge for the healthy term neonate is a delicate balance for the providing pediatrician. One component of this evaluation, given its prevalence and morbidity, is evaluation for EOGBS. Roughly 95% of infants with invasive GBS disease will present with symptoms within the first 24 hours of life, prior to the earliest anticipated discharge.²⁰ A 2012 cost analysis by Berger et al suggests that delayed hospital discharge at 48 hours for women treated with IAP results in similar mean expected quality-adjusted life years (QALYs) but greater mean hospitalization costs, estimated at \$1,170.96.¹² Currently, early discharge is generally offered to women who deliver vaginally and who receive adequate IAP in labor or to infants born to culture-negative mothers.²¹ Those women with unknown culture status who do not receive IAP are excluded from early discharge, due to a delay period for observation for EOGBS in the neonate, which amounts to considerable potential cost expenditures in maternal and neonatal delayed discharges in a substantial subset of the population.¹⁴

Table 7 Economic cost to society of women who present at term without maternal intrapartum fever

Estimates used in calculations	Universal cost of IAP (\$)	Cost of current standard of care (\$)	Reduction of cost with IAP (%)
Minimum values of estimates	470,107,673.5	742,024,791.4	36.6
Average values of estimates	519,233,380	830,137,497.4	37.5
Maximum values of estimates	568,359,086.5	919,269,232.7	38.2

Abbreviation: IAP, intrapartum antibiotic prophylaxis.

In our study, we compare the cost effectiveness of two management strategies for the management of the GBS-unknown patient in labor at term: universal IAP versus the current more commonly practiced risk-based IAP. The results suggest a considerable population-based cost savings associated with universal IAP for unscreened women in labor at term, due to decreased need for extended postnatal hospitalization for term infants and their healthy mothers during a period of monitoring for GBS sepsis after delivery. Cost analysis from the independent models yielded equivalence in total costs or up to a reduction in cost by 33.2% and reduction in costs by 36.6 to 38.2% for women without ROM > 18 hours and MIF, respectively.

Thus, we conclude that universal IAP for unscreened patients at term without risk factors may be cost saving due to the reduced need for extended hospitalization for observation of neonates and mothers otherwise meeting criteria for early discharge.

An alternatively proposed strategy to the currently recommended culture-based and risk-based strategy for the GBS unknown patient, is the adoption of rapid intrapartum polymerase chain reaction testing for all patients in labor and the subsequent IAP administration based on such results.²² This strategy would also obviate unnecessary prolonged hospitalization for GBS observation periods for healthy neonates born to healthy term women; however, the major drawbacks include test processing of nearly an hour, inability to test for clindamycin resistance for penicillin allergic patients, and furthermore, high costs associated with the tests at this time.

Cost savings aside, risk-based prophylaxis may be insufficient or inadequate in the GBS-unknown population, and this population remains at risk. Neonatal GBS sepsis cases today remain most common in term infants, despite the 2002 recommendation for universal GBS screening,^{14,23} and the 2009 study by Van Dyke et al suggests that patients with unknown GBS status account for 13.4% GBS disease at term. Universal IAP for these patients may result in further reductions in early neonatal sepsis cases, particularly given known efficacy of chemoprophylaxis at reducing attack rate of EOGBS by 80 to 95%.^{24,25}

The Centers for Disease Control and Prevention published 2000 to 2006 data for EOGBS disease burden within the United States and 178 cases of EOGBS were recorded in 2006 from a population of 450,000 reported the year before (11% of the national population).²⁶ This leads to an estimated 1,614 cases per year within the U.S. population at that time, 72% of cases which occurred in term neonates.²⁶ GBS status was known for 93% patients with babies resulting in EOGBS. This leaves a calculated 81 patients that year in the U.S. population for whom GBS would have been unknown who would otherwise not have received IAP under the currently recommended guidelines for whom therapy may have been beneficial in preventing EOGBS.

IAP for a larger, unscreened population is not without potential risks. Hypersensitivity reactions still remain an important cause of adverse reactions with penicillin therapy.

A cited 5 to 10% of patients experience a reaction to penicillin treatment.²⁷ Anaphylaxis is the most severe manifestation of these hypersensitivity reactions, seen in 1-5/10,000 cases²⁸ and can lead to cardiovascular collapse, laryngeal edema, and, rarely, death. IAP would expose an additional 414,873 unscreened individuals to these potential hypersensitivity reactions. Patients with a low risk for anaphylaxis can receive cefazolin for the management of GBS colonization, while patients with a high risk for anaphylaxis can receive vancomycin or clindamycin for GBS colonization management depending on culture sensitivities.²⁹ Public health cost estimates for the prophylactic management of GBS colonization with cefazolin, vancomycin, and clindamycin were not included in our analysis, because the cost of cefazolin, vancomycin, and clindamycin is \$0.11,³⁰ \$0.32,³¹ and \$0.31,³² respectively, for the initial dose of prophylactic management.²⁹ Such antibiotic costs are markedly reduced in comparison to penicillin. Additionally, as the percentage breakdown of penicillin-allergic patients using each respective agent is unknown, an estimate to reflect each cost scenario is not technically feasible. Instead, we have chosen penicillin as an upper limit estimate of cost for universal prophylaxis.

An additional risk with more widespread administration of IAP, is a potential to increase multidrug resistance to penicillins. Already, GBS has demonstrated resistance to aminoglycosides, macrolides, and fluoroquinolones.³³ Along these lines, some studies have suggested an association between exposure to IAP and non-GBS sepsis, or infection with Gram-negative pathogens, and ampicillin-resistant *Escherichia coli* infection.^{34,35} Given these considerations, universal administration of penicillin during labor to facilitate early discharge should be deferred until appropriate recommendations from governing bodies.

Our study was limited by the body of evidence available to guide recommendations about the early discharge of mother and baby at 24 hours after routine vaginal delivery; the majority of these studies on early discharge are based on noninferiority and do suggest that further randomized control trials would be beneficial to guide clinical recommendations. However, our study aligns with a prior economic analysis by Berger et al that suggests a financial benefit and noninferior practice, as measured by similar QALYs in favor of early discharge for neonates and mothers without evidence of GBS infection in the event of uncomplicated delivery.

In addition, our study was also limited by the number of prior publications focused on unknown GBS status management in the United States. This resulted in data obtained from study populations of varying countries being used to estimate the cost of GBS management in the United States. Lastly, we acknowledge a slight underestimation in the total number of women who present at term with unknown GBS status. This underestimation is the result of the categorization of 31 births in 2016 in the United States¹⁵ being coupled as quintuplet and higher-order pregnancies, which prevented the determination of the exact number of mothers for these births.

Conclusion

In conclusion, IAP for the unscreened population may allow for early discharge of otherwise healthy mother and baby, as the time needed for in-house GBS sepsis observation would be eliminated. On a population scale, this would allow for a significant decrease in health care costs, when compared with the currently employed risk-based prophylaxis algorithm. Thus, our recommendation would be to begin implementation of routine IAP for patients with uncomplicated pregnancies and who are GBS culture-unknown at term without contraindications to prophylaxis.

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Conflict of Interest

The authors have no conflicts of interest.

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