

# Bisphosphonate-associated Osteonecrosis of the Jaw in Ontario: A Survey of Oral and Maxillofacial Surgeons

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**ABSTRACT. Objective.** Osteonecrosis of the jaw (ONJ) in association with use of bisphosphonate (BP) has been described primarily in cancer patients receiving high-dose intravenous BP. The frequency of the condition in patients with osteoporosis appears to be low. We evaluated the frequency of BP-associated ONJ in Ontario in the cancer population and in those receiving BP for osteoporosis and metabolic bone disease.

**Methods.** A survey developed by representatives of the Ontario Society of Oral and Maxillofacial Surgeons was mailed to Ontario oral and maxillofacial surgeons (OMFS) in December 2006, asking oral surgeons to provide information on cases of ONJ seen in the previous 3 calendar years (2004 to 2006). OMFS were subsequently contacted by telephone if they had not responded or if they had reported cases of ONJ. The frequency of ONJ in association with BP use was estimated from the number of patients with filled prescriptions for BP in Ontario between 2004 and 2006. The cumulative incidence of ONJ was calculated separately for patients using intravenous (IV) BP for cancer treatment and for patients using oral or IV BP for osteoporosis or other metabolic bone disease.

**Results.** Between 2004 and 2006, 32 ONJ cases were identified. Nineteen patients received IV BP for cancer treatment and 13 patients received oral or IV BP for osteoporosis or metabolic bone disease. Over a 3-year period the cumulative incidence of BP-associated ONJ was 0.442% of cancer patient observations (442 per 100,000) and 0.001% of osteoporosis or other metabolic bone disease observations (1.04 per 100,000). The relative risk of low dose IV/oral BP-associated ONJ was 0.002 (95% CI 0.001, 0.005) compared to high-dose IV BP. Other risk factors for ONJ were present in all cases in whom detailed assessment was available. The median duration of exposure to BP was 42 months (range 36 to 120 mo) and 42 months (range 11 to 79 mo) in osteoporosis patients and cancer patients, respectively.

**Conclusion.** Over a 3-year period, the cumulative incidence for BP-associated ONJ was 0.442% of cancer patient observations (442 per 100,000) and 0.001% of osteoporosis or metabolic bone disease observations (1.04 per 100,000). This study provides an approximate frequency of BP-associated ONJ in Canada. These data need to be quantified prospectively with accurate assessment of coexisting risk factors. (First Release April 15 2011; J Rheumatol 2011;38:1396–402; doi:10.3899/jrheum.100221)

## Key Indexing Terms:

BISPHOSPHONATE  
ONTARIO

OSTEONECROSIS  
SURVEY

JAW  
OSTEOPOROSIS

Osteonecrosis of the jaw (ONJ) was first reported with use of bisphosphonate (BP) in 2003<sup>1</sup>. These early reports described dental lesions seen in cancer patients receiving high-dose intravenous (IV) BP<sup>2</sup>. ONJ is characterized by accumulation of dead exposed necrotic bone in the oral cavity<sup>3</sup>. Over the

previous century, ONJ was associated with tissue damage following head and neck irradiation in cancer patients. Other risk factors for development of osteonecrosis include underlying malignancy as well as local infection, chemotherapy, or steroid use<sup>4</sup>. Data evaluating the inci-

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dence of BP-associated ONJ are largely from case series and other retrospective observational data, with very limited prospective data<sup>3,4,5,6,7,8,9,10,11,12,13,14,15</sup>. The frequency of the condition in those receiving high doses of BP for cancer-related skeletal disease has been estimated to be between 1% and 15%<sup>16,17,18,19,20</sup>. In cancer patients, the incidence appears to be related to dose and duration of BP therapy<sup>21,22</sup>. In osteoporosis patients, a causal link between BP use and ONJ has not been confirmed<sup>3,4</sup>. The estimated incidence of BP-associated ONJ in osteoporosis patients varies between 40 in 100,000<sup>23</sup> to less than 1 in 100,000 per years of exposure<sup>24</sup>.

In Canada, Jadu and colleagues found a 3.2% incidence of pamidronate-related bone necrosis in myeloma patients at Princess Margaret Hospital, a tertiary care cancer center in Toronto<sup>15</sup>. That study was a retrospective review of dental records at a single center, the cases were not adjudicated, and they were not necessarily referred to an oral surgeon. It is also possible that cases of lingual mandibular sequestration were identified and were also identified in this figure.

As BP use has become the cornerstone in the management of osteoporosis and other metabolic bone diseases, even a very low incidence of BP-associated ONJ in the osteoporosis population is important to quantify. Our primary objective was to estimate the frequency of BP-associated ONJ in Ontario in both the cancer population and in those with osteoporosis or other metabolic bone disease. Our secondary objective was to describe the frequency of known risk factors in patients diagnosed with BP-associated ONJ and also to describe the location of the lesions and current management of the condition in Ontario.

## MATERIALS AND METHODS

*The survey.* In Ontario, all oral and maxillofacial surgeons (OMFS; with the exception of those who have recently moved their practice into or out of Ontario) are members of the Ontario Society of Oral and Maxillofacial Surgeons (OSOMS). The ONJ survey was developed with representatives of OSOMS. The study was approved by the McMaster University Research Ethics Board and was mailed out to the OSOMS membership in December 2006. OMFS were contacted by telephone if they had not responded or if they identified seeing cases of ONJ in the calendar years of 2004, 2005, and 2006. ONJ was defined as being an oral cavity lesion characterized by one or more spots of bare alveolar or hard palate bone in the absence of local malignancy or radiation therapy to the head or neck and with no evidence of healing after 6 weeks of appropriate evaluation and dental care. If the oral surgeons did not reply to the survey they were contacted by telephone and were asked if they had seen cases of ONJ in the 3 calendar years 2004 to 2006. All Ontario oral surgeons were contacted up to 5 times to confirm if cases had been seen by them. Surgeons were asked to complete a survey questionnaire for each recalled case corresponding to the given definition of ONJ. The questionnaire requested information regarding ONJ risk factors including diagnosis of malignancy, history of radiation therapy, corticosteroid use, and exposure to oral or intravenous BP therapy. Information about the location of the ONJ lesion and treatment received were also requested (Figure 1).

Surgeons reporting a case were asked to obtain informed consent from their patients for a chart review. Data were subsequently collected from the charts utilizing a standardized data abstraction form, which included infor-

mation on demographic data, risk factors for ONJ, duration and type of BP exposure, location of the lesion, and the management strategies implemented. Table 1 provides a list of the risk factors assessed through chart review.

*Adjudication of ONJ cases.* The diagnosis of ONJ was adjudicated by 2 authors (LR, EP), who were blinded to BP exposure. Adjudication required that all the following diagnostic criteria were met: (1) presence of bare alveolar or hard palate bone in the mandible or maxilla persisting for more than 6 weeks; (2) absence of history of head and neck irradiation; and (3) absence of malignancy in jaw biopsy specimens when these were available. As some patients may have been evaluated by more than one surgeon, demographic data and clinical characteristics were carefully evaluated to exclude duplicated cases.

*Estimation of the cumulative incidence of BP-associated ONJ in Ontario.* The number of BP-associated ONJ cases diagnosed between January 2004 and December 2006 (i.e., the 3-year period) was used as the numerator to calculate the cumulative incidence of ONJ in the province of Ontario for this time period. Cases occurring in the context of high dose of IV BP therapy for cancer were considered separately from those occurring in patients receiving low dose of IV or oral BP treatment for osteoporosis or other metabolic bone diseases.

The sum of unique patients who filled at least one prescription for a BP over the period 2004–2006 in Ontario was used as the denominator for calculation of the cumulative incidence. This information was obtained from the Brogan Incorporated (Kirkland, QC, Canada) prescription dynamics data sets. This database identifies 100% of patients on the Ontario Drug Benefit Plan and 83% of patients on private drug plans who have filled a prescription for BP. Patients who paid cash for the medications are not identified by the database and it is estimated that this population accounts for 7%–10% of the total numbers of individuals filling prescriptions for BP in Ontario<sup>25</sup>.

The denominator for patients with osteoporosis took into consideration individuals exposed to alendronate, risedronate, etidronate, and zoledronic acid marketed under the name Aclasta<sup>®</sup>. The denominator for patients receiving BP for cancer-related complications included individuals exposed to pamidronate, IV clodronate, and zoledronic acid marketed under the name Zometa<sup>®</sup>.

Finally, to estimate the potential risk difference by dosage exposure (high-dose IV BP versus low-dose IV/oral BP), a relative risk calculation is reported. To compute the relative risk, we computed the cumulative incidence (which is synonymous with incidence proportion, a measure of risk) for each group by dividing the total number of incident cases by the total number of drug observations. The relative risk is the risk for group “X” (low-dose IV/oral BP) divided by the risk for group “Y” (high-dose IV BP). The limits of the 95% confidence interval of the natural log of the relative risk were obtained (e.g., upper/lower limit =  $\ln(\text{relative risk}) \pm 1.96 \times \text{standard error}$ ) and then exponentiated back to the original scale ( $\exp(\log \text{limit})$ ).

*Data analysis.* Data were analyzed using Stata SE 11.0 for Macintosh (Stata, College Station, TX, USA). Logic checks were completed using cross-tabulations for key variables. Data were summarized using descriptive statistics. Categorical data were reported as numbers and percentages. Continuous variables were expressed as median, minimum (min), and maximum (max). Since clinical information obtained for many cases was incomplete, the number of observations is reported for each variable. The proportion of responders was calculated as the percentage of surgeons responding by mail or telephone confirming that they had seen a case of ONJ in the period 2004 to 2006.

## RESULTS

*The survey.* Figure 2 illustrates the process of the survey. There were 185 oral surgeons in active practice in Ontario in 2006. One hundred seventy oral surgeons responded to the mailed survey form and faxed in their response or confirmed

- Have you seen any cases of ONJ in the past 3 years? YES \_\_\_\_\_ NO \_\_\_\_\_
- Was there a coexisting diagnosis of malignancy – ca breast or multiple myeloma?
- History of radiation?
- History of prednisone use?
- Has the patient been exposed to bisphosphonates oral? IV? Duration and type?
- How has your patient been treated (antibiotics? debridement? hyperbaric oxygen?)

ONJ definition: an oral cavity lesion characterized by 1 or more spots of bare alveolar or hard palate bone in the absence of local malignancy or radiation therapy to the head or neck with no evidence of healing after 6 weeks of appropriate evaluation and dental care

Please describe the location of the lesion(s) on the chart below

	Anterior	Posterior
Maxilla – palatal		
Maxilla – buccal		
Both		
Mandible – lingual		
Mandible – buccal		
Both		

Figure 1. The ONJ questionnaire for information regarding ONJ risk factors including diagnosis of malignancy, history of radiation therapy, corticosteroid use, exposure to oral or intravenous BP therapy, location of the ONJ lesion, and treatment.

Table 1. Risk factors assessed through chart review.

Assessment of Known Risk Factors
1. Cancer history current or past, not active
2. Chemotherapy current or previous
3. Radiotherapy current or previous
4. Diabetes mellitus: yes or no
5. Smoking status: past, current, nonsmoker
6. Glucocorticoid use past or current
7. Oral hygiene rated by surgeon
8. Dental procedures completed within 6 months of diagnosis
9. Dental risk factors: periodontal disease, tori, local infection, denture trauma
10. Current medications
11. Bisphosphonate use, oral or intravenous, and frequency: never, current, within 6 months of diagnosis of osteonecrosis of the jaw
12. Name and dosage of bisphosphonate and duration of exposure

by telephone if they had seen cases. There were 15 nonresponders; 11 were unreachable or not willing to participate and 4 surgeons remembered cases but were not able to provide any further information. One hundred forty-five surgeons confirmed that they had not seen any cases of ONJ in Ontario in calendar years 2004 through 2006. Twenty-five surgeons provided information about 41 possible cases and completed the survey questionnaire for each possible case. Of these 41 possible cases, 9 were not diagnosed in the years 2004 to 2006. Thirty-two cases met all the adjudication criteria and were diagnosed in the period 2004 to 2006. Of the 32 cases, informed consent for chart review was obtained for 11 patients (34%) and these patients' charts were reviewed.

*Clinical characteristics and risk factors for ONJ.* All cases with ONJ had been receiving BP within 6 months of the ONJ diagnosis. Table 1 shows the clinical characteristics of the 32 ONJ cases separated into 2 groups according to the indication for BP use. Nineteen patients were receiving IV BP treatment for cancer-related bone disease and 13 patients were receiving oral BP for either osteoporosis or metabolic bone disease. The mean age of the 2 groups was similar. Limited data were available for duration of exposure, concomitant therapies, and recent dental procedures. Duration of exposure was available for only 25% of cases. For these cases the median duration of exposure to BP use was 42 months (range 11–79 mo) for the IV BP group and 36 months (range 24–120 mo) for the oral BP group. Concomitant treatment status was available by treatment as follows: chemotherapy, data available for 75% of cases; radiotherapy, data available for 81% of cases; and corticosteroid use, data available for 88% of cases. For these cases, all IV BP patients (100%) were receiving chemotherapy, 38% were also being treated with radiotherapy, and 66% were also receiving corticosteroids. For oral BP cases, 15% were receiving chemotherapy, 8% radiotherapy, and 15% corticosteroids. Data on recent dental procedures were available for 50% of cases. For these cases, the majority in both groups had received a recent dental procedure (IV BP, 70%; oral BP, 83%). However, twice as many cases in the IV BP group had undergone dental extractions.

*Cumulative incidence.* The cumulative incidence of BP-associated ONJ in Ontario over the 3-year period is presented in Table 2. The cumulative incidence was estimated

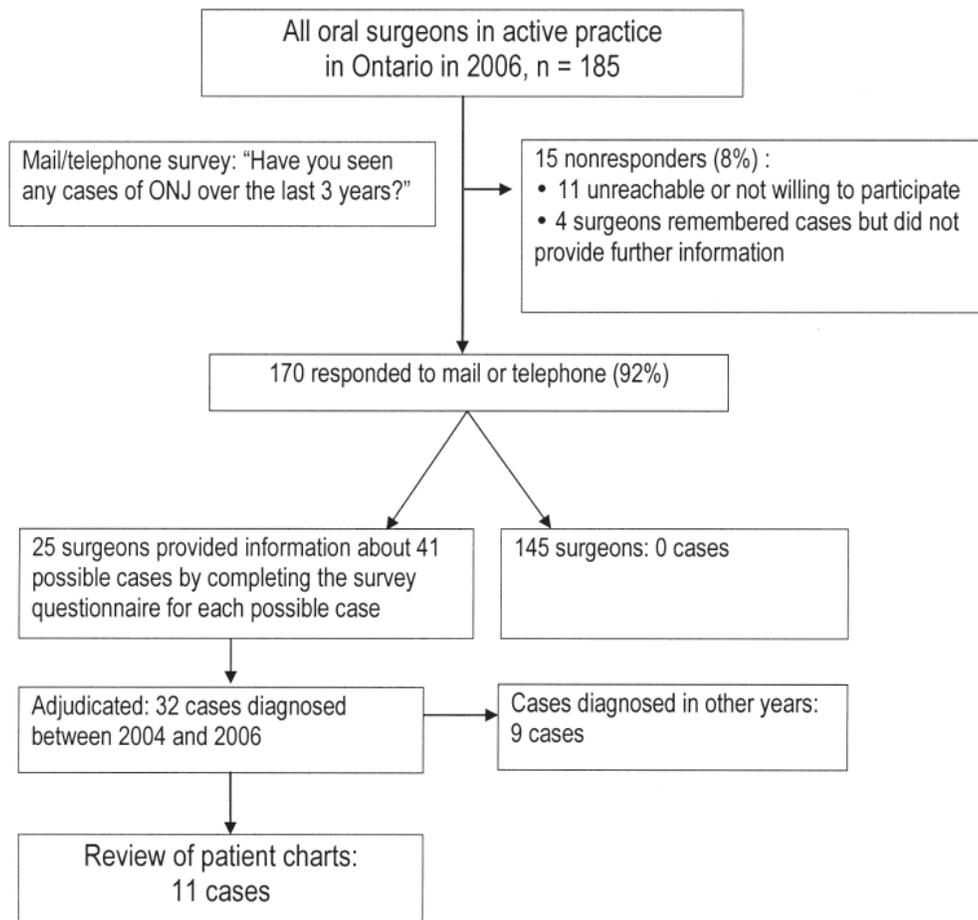


Figure 2. The survey procedure. ONJ: osteonecrosis of the jaw.

Table 2. Clinical characteristics of 32 cases of osteonecrosis of the jaw in Ontario.

Characteristic (number with available data)	Patients on IV Bisphosphonate	Patients on Oral Bisphosphonate
Total (n = 32)	19	13
Indication (n = 32), % of population		
Cancer-related bone disease	100	0
Osteoporosis	0	92
Metabolic bone disease	0	8
Months of bisphosphonate use (n = 8), median; range	42; 11–79	36; 24–120
Female (n = 16), % of population	14	89
Years of age (n = 16), median; range	70; 54–78	69; 6–89
Concomitant therapies, % of population		
Chemotherapy (n = 24)	100	15
Radiotherapy (n = 26)	38	8
Corticosteroid use (n = 28)	66	15
Recent dental procedures, % of population		
Any dental procedure (n = 16)	70	83
Dental extraction (n = 16)	60	33

at 0.442% of cancer patients (442 per 100,000) receiving high-dose IV BP between January 2004 and December 2006. For patients with osteoporosis or other metabolic bone

disease receiving oral or low-dose IV BP, the cumulative incidence was estimated at 0.001% over the same 3-year period (1.04 per 100,000).

**Relative risk.** The relative risk of low-dose IV/oral BP-associated ONJ was 0.002 (95% CI 0.001, 0.005) compared to high-dose IV BP; that is, the true population relative risk value is likely to fall between 0.001 and 0.005 (with a probability of 95%).

**Locations of the ONJ lesions and therapy.** ONJ lesions were more frequently found involving the mandible (23 cases) in comparison to the maxilla (10 cases), and 3 individuals had both mandibular and maxillary lesions. The most common site for ONJ was the lingual surface of the mandible, 18 cases, corresponding to 56% of the 32 ONJ cases. The frequency of each treatment received is given in Table 3. Twenty patients received antibiotics and 17 underwent debridement. Debridement was conservative in most cases, and no surgeon reported the use of hyperbaric oxygen.

## DISCUSSION

Our study shows the cumulative incidence of ONJ in the

Table 3. Cumulative incidence of bisphosphonate-related ONJ in Ontario.

Cumulative Incidence of ONJ related to use of BP for osteoporosis or other metabolic bone disease	
Numerator: number of ONJ cases using BP for osteoporosis or other metabolic bone disease: 13	
Denominator: number of individuals that filled at least 1 prescription for alendronate, risedronate, etidronate, or zoledronic acid	
2004:	385,925
2005:	419,411
2006:	449,575
2004–2006:	1,254,911 total observations
Cumulative incidence: 13 cases / 1,254,911 total observation = 0.001% of observations (1.04 per 100,000 cases) between January 2004 and December 2006	
Cumulative Incidence of ONJ related to use of BP for cancer bone disease: 19	
Numerator: number of ONJ cases using BP for cancer bone disease: 19	
Denominator: number of individuals that filled at least one prescription for pamidronate, intravenous clodronate, or zoledronic acid	
2004:	1528
2005:	1429
2006:	1359
2004–2006:	4316 total observations
Cumulative incidence: 19 cases / 4,316 total observations = 0.442% of observations (442 per 100,000) between January 2004 and December 2006	
ONJ: osteonecrosis of the jaw; BP: bisphosphonate.	

Table 4. Therapy received among the 32 cases of ONJ.

Treatment	n	%
Rinse	10	31
Antibiotics only	5	16
Debridement only	2	6
Antibiotics and debridement	17	53
Total antibiotics	20	62
Total debridement	17	53
Hyperbaric oxygen	0	0

cancer population in Ontario was roughly 0.442% of observations (442 per 100,000) between January 2004 and December 2006. In this 3-year period, in the population with osteoporosis and other metabolic bone disease, the cumulative incidence was 0.001% of observations (1.04 per 100,000).

There are a number of strengths to our survey; we had a high response rate, greater than 90%. Double-counting of cases was avoided by evaluating the demographic data and the clinical characteristics, and also by reviewing the reporting surgeons' names. A working definition of BP-associated ONJ was clearly provided in the survey. All cases were adjudicated by one author (LR) and the oral pathologist (EP), both of whom were blinded to the use of BP. A standardized abstraction form was used for the chart review with assessment of coexisting risk factors for development of BP-associated ONJ. The Brogan database provided us with the num-

bers of patients who filled the prescriptions. This information did not need to be calculated from the number of prescriptions filled. In the Australian survey<sup>23</sup> the number of patients receiving the drug was calculated by dividing the number of prescriptions filled by 9, assuming a compliance of 75% or 9 of 12 months' use. Such assumptions were not necessary for our study as the Brogan database provided the number of patients receiving the drug.

There are a number of limitations to the study. We were able to obtain informed consent from only 33% (N = 11) of patients for chart review. While we chose to report these particular results (duration of use, concomitant therapies, dental procedures), we advise that they be interpreted with caution and as preliminary. In addition, our estimation of incidence may not be accurate, as there were some factors for which we were not able to control that could have caused overestimation or underestimation of the incidence of ONJ. The denominator we used to calculate incidence is probably smaller than the real number of people exposed to BP, since it did not include the patients paying cash, which is estimated to be as large as 7%–10%. Also, off-label use of Zometa<sup>®</sup> or pamidronate for osteoporosis was not included in our denominator. This could have led to approximately 10% overestimation of the incidence of ONJ. On the other hand, a number of limitations led to an underestimation of the incidence. That this was a retrospective survey, leading to a recall bias and an under-reporting of cases, is also a limitation. There were 15 (8%) nonresponder surgeons and some

of them, especially those working at a tertiary referral center, may have seen a significant number of cases. In addition, we did not identify patients with ONJ who were not referred to an oral surgeon and were evaluated only by their dentist. In the study it was assumed that adherence was 100%, and that the patients who filled their prescriptions took their medication. These assumptions may have led to underestimation of the true incidence of BP-associated ONJ. It is difficult to quantify the magnitude of the underestimation of the incidence. If we assumed an extreme situation in which we identified only 10% of the actual cases of ONJ that occurred, the 3-year cumulative incidence of ONJ would have been 0.01% (10/100,000) in patients with osteoporosis and 4% (400/100,000) in patients with cancer.

We were not able to calculate the incidence rate (that is, incidence in relation to the time of exposure to BP) as this information was not available. Therefore, our denominator may have included individuals taking BP for 3 years whereas others may have filled only 1 prescription. This could explain why we observed a cumulative incidence roughly 40 times lower than the cumulative incidence reported in clinical series of patients using BP for cancer. Similarly, our cumulative incidence of ONJ in osteoporosis patients, expressed as the number of individuals receiving BP, may underestimate the risk of ONJ in real practice, where osteoporosis patients usually receive BP therapy for many years. Therefore, incorporating time of exposure to BP is an important consideration for future study.

We found that the risk of ONJ was 500 times lower among low-dose BP users in comparison to high-dose BP users (relative risk = 0.002). This difference in risk may be related to many factors in addition to the difference in the dose of the BP. The low-dose BP group consisted of patients being treated for osteoporosis. Although, 3 patients in this group also had a history of cancer, and 2 of them had received chemotherapy within 2 years of the ONJ diagnosis, they did not have metastatic disease. In contrast, the high-dose BP group consisted of patients with malignancy receiving bisphosphonates for the management of cancer-related skeletal complications, and all patients also received chemotherapy in addition to having other important risk factors for ONJ.

This study provides the first approximation of cumulative incidence of ONJ with BP use for patients with osteoporosis in Ontario, Canada. This information is of value for patients, as a number of individuals have stopped using the BP prescribed for their osteoporosis treatment. It is necessary to adequately educate the patient population to ensure that they are able to appreciate the size of the risk with BP use in comparison to the benefit offered by reducing the risk of fracture by approximately half<sup>5</sup>. These numbers are small and it is necessary to quantify them prospectively with an accurate assessment of coexisting risk factors.

The Canadian Task Force on ONJ has recommended that

a registry be maintained of all cases identified in Canada and this has been supported by the Canadian Association of Oral and Maxillofacial Surgeons (CAOMS Annual General Meeting 2008). Prospective data will enable better understanding of the pathophysiology resulting in ONJ. Risk stratification and effective management strategies can be further refined on the strength of prospective data. Our study estimates the risk of BP-associated ONJ in the population with osteoporosis to be low, supporting the work of other investigators<sup>3,23,24</sup>.

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