

# Utility of Pre-Hematopoietic Cell Transplantation Sinus CT Screening in Children and Adolescents

J.H. Harreld, R.A. Kaufman, G. Kang, G. Maron, W. Mitchell, J.W. Thompson, and A. Srinivasan



## ABSTRACT

**BACKGROUND AND PURPOSE:** The clinical benefit of pre-hematopoietic cell transplantation sinus CT screening remains uncertain, while the risks of CT radiation and anesthesia are increasingly evident. We sought to re-assess the impact of screening sinus CT on pretransplantation patient management and prediction of posttransplantation invasive fungal rhinosinusitis.

**MATERIALS AND METHODS:** Pretransplantation noncontrast screening sinus CTs for 100 consecutive patients (mean age, 11.9 ± 5.5 years) were graded for mucosal thickening (Lund-Mackay score) and for signs of noninvasive or invasive fungal rhinosinusitis (sinus calcification, hyperattenuation, bone destruction, extrasinus inflammation, and nasal mucosal ulceration). Posttransplantation sinus CTs performed for sinus-related symptoms were similarly graded. Associations of Lund-Mackay scores, clinical assessments, changes in pretransplantation clinical management (additional antibiotic or fungal therapy, sinonasal surgery, delayed transplantation), and subsequent development of sinus-related symptoms or invasive fungal rhinosinusitis were tested (exact Wilcoxon rank sums, Fisher exact test, significance  $P < .05$ ).

**RESULTS:** Mean pretransplantation screening Lund-Mackay scores ( $n = 100$ ) were greater in patients with clinical symptoms ( $8.07 \pm 6.00$  versus  $2.48 \pm 3.51$ ,  $P < .001$ ) but were not associated with pretransplantation management changes and did not predict posttransplantation sinus symptoms ( $n = 21$ ,  $P = .47$ ) or invasive fungal rhinosinusitis symptoms ( $n = 2$ ,  $P = .59$ ).

**CONCLUSIONS:** Pre-hematopoietic cell transplantation sinus CT does not meaningfully contribute to pretransplantation patient management or prediction of posttransplantation sinus disease, including invasive fungal rhinosinusitis, in children. The risks associated with CT radiation and possible anesthesia are not warranted in this setting.

**ABBREVIATIONS:** ENT = ear, nose, and throat; GVHD = graft versus host disease; HCT = hematopoietic cell transplantation; IFRS = invasive fungal rhinosinusitis

Due to prolonged immunosuppression, children undergoing hematopoietic cell transplantation (HCT) are at increased risk of opportunistic infections, including potentially lethal invasive fungal rhinosinusitis (IFRS).<sup>1-5</sup> Children at St. Jude Children's Research Hospital, therefore, undergo rigorous pretransplantation evaluation, including ear, nose, and throat

(ENT) examination, infectious disease risk assessment, fungal serologies, and noncontrast sinus CT.

However, the clinical utility of screening sinus CT remains unclear, and the practice is not universal. According to the American Academy of Pediatrics and the American College of Radiology, uncomplicated sinusitis should be a clinical diagnosis,<sup>6,7</sup> and several large studies ( $n \geq 100$ ) have failed to identify pre-HCT imaging features predictive of post-HCT sinusitis.<sup>8-10</sup> Fewer studies have evaluated the contribution of pretransplantation CT to patient management or prediction of posttransplantation IFRS. A small study in adults found that screening sinus CT did not contribute to a pretransplantation diagnosis or management or predict posttransplantation sinusitis or IFRS, but it was limited by a small sample size.<sup>11</sup> A study of 187 children reported an association between pre-HCT sinus CT findings and management changes, but while 119 (64%) had abnormal sinus CT findings, only 29 had symptoms and were treated, suggesting symptoms, not imaging, drove treatment.<sup>12</sup>

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From the Departments of Diagnostic Imaging (J.H.H., R.A.K.), Biostatistics (G.K.), Infectious Diseases (G.M.), Bone Marrow Transplantation and Cellular Therapy (W.M., A.S.), and Surgery (J.W.T.), St. Jude Children's Research Hospital, Memphis, Tennessee; and Department of Otolaryngology (J.W.T.), University of Tennessee Health Sciences Center, Memphis, Tennessee.

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Please address correspondence to Julie H. Harreld, MD, Department of Diagnostic Imaging, St. Jude Children's Research Hospital, 262 Danny Thomas Place, MS 220, Memphis, TN 38105; e-mail: Julie.harreld@stjude.org

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While the benefits of pre-HCT sinus CT remain unclear, the risks associated with sinus CT are well-established and include a low-but-real risk of radiation-induced cancers<sup>13,14</sup> and early cataract formation.<sup>15</sup> Evidence is also emerging that anesthesia, required by some children to complete CT, may negatively impact cognitive development.<sup>16,17</sup> On the other hand, advances in fungal prophylaxis have significantly reduced the incidence of invasive fungal infections in immunocompromised children.<sup>18</sup>

Given these potential shifts in the risk-benefit ratio, we sought to re-evaluate the clinical utility of pre-HCT screening sinus CT for IFRS risk assessment and its role in pre-HCT management of pediatric patients.

## MATERIALS AND METHODS

With institutional review board approval and waiver of consent, imaging, clinical, ENT risk assessment, and laboratory data were prospectively recorded for 100 sequential participants who had pre-HCT screening sinus CT at our institution between June 2015 and April 2017. A sample size of 100 was chosen to detect at least 1 case of IFRS, which has an incidence of approximately 2% in patients with hematologic disorders.<sup>2</sup> The patients' medical records were reviewed for microbiologic diagnosis of IFRS for at least 100 days posttransplantation. With additional institutional review board approval and waiver of consent, medical records were retrospectively reviewed for subsequent clinical, imaging, and laboratory data until the patient's death or November 2017.

### Clinic and Laboratory

Recorded data included primary diagnosis; transplant donor type; absolute neutrophil count at imaging; pretransplantation imaging indication; development of posttransplantation graft versus host disease (GVHD) grades II–IV (moderate-to-life-threatening); pretransplantation galactomannan (*Aspergillus* antigen); sinonasal symptoms (rhinorrhea, congestion, nasal/facial pain, swelling, visible nasal lesion), or fever at pretransplantation evaluation; and changes to pretransplantation management (changes in fungal prophylaxis regimen, addition of antibiotics, sinonasal operation, or delay of HCT) attributable to screening sinus CT.

ENT pretransplantation risk assessment included visualization of the nasal septum, palate, and back of throat under magnification and complete allergy and sinusitis histories. These findings were summarized as “at-risk” or “not at-risk” for IFRS.

For patients requiring post-HCT sinus imaging for symptoms, we recorded symptoms, galactomannan serologies, endoscopy findings, fungal organism (if applicable), and consecutive days of neutropenia (absolute neutrophil count < 500/mm<sup>3</sup>) immediately preceding imaging. The date of acquisition of tissue positive for IFRS by microbiologic/pathologic examination was considered the date of diagnosis.

### Imaging

CTs were axially acquired with a section thickness of ≤2.5 mm on a LightSpeed VCT or Revolution CT scanner (GE Healthcare) with bone and soft-tissue reconstructions. The average effective dose for all ages was ~0.8 mSv; the eye/lens dose was 0.7–1.2 mGy.

Images were reviewed in consensus by a board-certified pediatric radiologist with 40 years' experience (R.A.K.) and a board-certified neuroradiologist with 10 years' experience (J.H.H.) for the presence or absence of bone destruction, extrasinus inflammation, and nasal mucosal ulceration, associated with IFRS.<sup>4,19–22</sup> Because noninvasive fungal disease could theoretically predispose to IFRS with pre-HCT conditioning/immunodepletion, the presence of calcifications and sinus hyperdensity was also noted.<sup>23</sup>

Each anterior and posterior ethmoid, maxillary, frontal, and sphenoid sinus was graded as clear = 0, partially opacified = 1, or completely opacified = 2; each ostiomeatal unit was graded as clear = 0 or occluded = 2; and the numbers were added per Lund and Mackay.<sup>24</sup> To account for age-related differences in sinus development, we calculated an adjusted Lund-Mackay score as<sup>25</sup>

Adjusted Lund Score =

$$\text{Raw score} \times \frac{24}{\text{Maximum Lund for No. Pneumatized Sinuses}}$$

### Statistical Analysis

Sinus CT scores, laboratory values, symptoms, changes in management, and ENT risk were compared using the Fisher exact test or the Pearson  $\chi^2$  test for categorical variables and a 2-sample *t* test or (exact) Wilcoxon rank sum test for continuous variables, based on the normality assumption. The Lund-Mackay scores between pre- and posttransplantation were compared using a 1-sample *t* test or Wilcoxon signed rank test, depending on the normality assumption. All *P* values are 2-sided and were considered statistically significant if <.05. Statistical analyses were performed with R-3.6.1 (R statistical and computing software; <http://www.r-project.org/>).

## RESULTS

One hundred participants (60 males, 40 females; 8 months to 24 years of age; mean, 11.9 ± 5.5 years; males, 11.6 ± 5.7 years; females, 12.5 ± 5.2 years) had screening sinus CT an average of 24.6 ± 9.6 days before transplantation for IFRS risk assessment. Patient characteristics, imaging, and clinical findings are summarized in Table 1.

Follow-up for survivors (*n* = 82) ranged from 189 to 889 days post-HCT. During the follow-up period, 9 patients died of relapsed disease from 28 to 519 days post-HCT. Nine died of complications between 23 and 557 days post-HCT, none related to sinus disease.

### Clinical Symptoms and Provided Imaging Indications

At the time of the screening sinus CT, 18 patients had sinonasal symptoms documented in the medical record: Thirteen had rhinorrhea, 2 had nasal congestion, and 3 had both. No patients had overt signs or symptoms of IFRS or complicated rhinosinusitis—localized facial pain or inflammation, nasal ulcer/eschar, fever, or altered mental status—documented in the medical record at the time of CT.

The provided indication for 98/100 screening sinus CTs was “pretransplantation evaluation.” Symptoms mentioned for 2 patients did not match the medical record, possibly being erroneous or outdated. One request indicated fever without localizing symptoms, though the clinical examination documented congestion and rhinorrhea without fever. The other request indicated possible periorbital edema, which was not present on CT or the physical examination. On examination, the patient had clear rhinorrhea and nasal wash positive for enterovirus/rhinovirus and was determined eligible for transplantation the same day.

### Pretransplantation Screening and Management

Mucosal thickening was present (Lund-Mackay score of  $\geq 1$ ) at screening in 66/100 patients, including 48/82 (58.5%) asymptomatic patients and all 18 symptomatic patients. No asymptomatic patients received antibiotics based on sinus CT.

The Lund-Mackay score was higher for patients with symptoms documented in the medical record ( $P < .0001$ , Table 2). Patients with clinical symptoms were more likely to be treated

with antibiotics (5/18 with symptoms versus 0/82 asymptomatic,  $P = .0001$ ). The Lund-Mackay scores were greater for symptomatic patients who received antibiotics ( $n = 5$ ,  $12.8 \pm 5.72$ ) compared with those who did not ( $n = 13$ ,  $6.25 \pm 5.25$ ), but this finding did not reach statistical significance ( $P = .058$ ) (Table 2).

All 5 patients treated with pretransplantation antibiotics had clinical sinusitis. Nasal wash was positive for enterovirus/rhinovirus in 3/5 (60%). Two received antibiotics primarily for pneumonia and secondary coverage of possible bacterial sinusitis. None developed IFRS before or after transplantation.

One patient had a smooth nasal septal perforation, which was negative for IFRS at screening endoscopy. Two others had sinus calcifications. All 3 were asymptomatic, and none developed IFRS or symptoms posttransplantation. No patients (0/100) had sinus hyperdensity, nasal ulceration, extrasinus inflammation, or bone destruction at screening.

No patients underwent a pretransplantation sinus operation, received new antifungal therapy, or had HCT delayed as a result of screening sinus CT.

**Table 1: Patient characteristics**

| Characteristics                             |                |
|---|----------------|
| No.   | 100            |
| Male  | 60             |
| Female                                      | 40             |
| Age (mean) (yr)                             | $11.9 \pm 5.5$ |
| Primary diagnosis (No.) (%)                 |                |
| Hematologic malignancy                      | 65, 65%        |
| Acute myeloid leukemia                      | 34, 34%        |
| Acute lymphoblastic leukemia                | 17, 17%        |
| Hodgkin lymphoma                            | 8, 8%          |
| Myelodysplastic syndrome                    | 5, 5%          |
| Anaplastic large-cell lymphoma              | 1, 1%          |
| Hematologic disorder                        | 5, 5%          |
| Severe aplastic anemia                      | 3, 3%          |
| Sickle cell disease                         | 2, 2%          |
| Solid tumor                                 | 28, 28%        |
| Neuroblastoma                               | 15, 15%        |
| Ewing sarcoma                               | 9, 9%          |
| Germ cell tumor                             | 3, 3%          |
| Desmoplastic small round cell tumor         | 1, 1%          |
| Immune disorder                             | 2, 2%          |
| Severe combined immunodeficiency            | 1, 1%          |
| Wiskott-Aldrich syndrome                    | 1, 1%          |
| Transplant donor (No.) (%)                  |                |
| Allogenic                                   | 66, 66%        |
| Autologous                                  | 34, 34%        |
| Disease status at transplantation (No.) (%) |                |
| Complete remission                          | 82, 82%        |
| Active disease                              | 18, 18%        |
| T-cell depletion (No.) (%)                  | 2, 2%          |
| GVHD II–IV (No.) (%)                        | 15, 15%        |

**Table 2: Pretransplantation sinus CT Lund-Mackay scores, sinonasal symptoms, and management**

|                                     | No. (Frequency) | Pre-HCT Lund-Mackay Score (Mean) | P Value |
|-------------------------------------|-----------------|----------------------------------|---------|
| All at screening                    | 100 (100%)      | $3.48 \pm 4.58$                  |         |
| No symptoms at screening            | 82 (82%)        | $2.48 \pm 3.51$                  | $<.001$ |
| Symptoms at screening               | 18 (18%)        | $8.07 \pm 6.00$                  |         |
| With symptoms, received antibiotics | 5 (28%)         | $12.80 \pm 5.72$                 | .058    |
| With symptoms, no antibiotics       | 13 (72%)        | $6.25 \pm 5.25$                  |         |

### Posttransplantation Imaging

Symptoms prompted posttransplantation evaluation of 21 patients whose Lund-Mackay scores had increased ( $7.43 \pm 6.36$ ) from baseline screening CT ( $3.87 \pm 4.99$ ;  $P = .007$ ).

Two of the 21 (9.5%) symptomatic patients or 2% (2/100) of the entire cohort developed IFRS, 615 days (*Bipolaris* spp) and 248 days (*Fusarium* spp) posttransplantation. Pretransplantation, neither had symptoms. These 2 patients had lower Lund-Mackay scores ( $4.5 \pm 3.54$ ) than symptomatic patients without IFRS ( $n = 19$ ,  $7.74 \pm 6.57$ ), but this finding was not statistically significant ( $P = .59$ ).

### Prediction of Posttransplantation Sinus Disease

The degree of mucosal thickening (Lund-Mackay score) on pretransplantation CT did not predict posttransplantation symptoms ( $P = .47$ ) or posttransplantation IFRS ( $P = .58$ ) (Table 3).

The pretransplantation test for galactomannan was negative in all patients at screening. The mean absolute neutrophil count at screening was  $2510 \pm 5568$  (range, 0–50,200). There was no association between screening absolute neutrophil count and pre-HCT symptoms, post-HCT symptoms, or post-HCT IFRS. Disease status, transplant donor, T-cell depletion, and posttransplantation GVHD grades II–IV did not predict development of IFRS ( $P = 1$  for all; Table 4).

Of 96 participants evaluated by ENT, 29 were considered at risk for IFRS. ENT risk assessment did not predict development of IFRS ( $P = .61$ ). There was no association between the Lund-Mackay score and the ENT risk stratum ( $P = .99$ ).

The presence of symptoms before transplantation ( $n = 18$ ) did not predict posttransplantation symptoms ( $n = 21$ ); only 3 patients were symptomatic both before and after transplantation ( $P = .62$ ).

## DISCUSSION

In this study, we found no association between pre-HCT screening sinus CT and changes in pretransplantation

**Table 3: Pre-HCT Lund-Mackay scores versus posttransplantation sinus outcomes**

|                            | Pre-HCT Lund-Mackay |              | P Value |
|----------------------------|---------------------|--------------|---------|
|                            | No. (Frequency)     | Score (Mean) |         |
| All at screening           | 100 (100%)          | 3.48 ± 4.58  | .47     |
| No post-HCT symptoms       | 79 (79%)            | 3.38 ± 4.49  |         |
| Post-HCT symptoms          | 21 (21%)            | 3.86 ± 5.00  |         |
| Post-HCT symptoms, IFRS    | 2 (9.5%)            | 4.00 ± 4.24  |         |
| Post-HCT symptoms, no IFRS | 19 (90.5%)          | 3.84 ± 5.17  | .58     |

**Table 4: Clinical findings at screening for patients who did and did not develop IFRS after transplantation**

|   | All at Pre-HCT Screen | No Post-HCT IFRS | Post-HCT IFRS | P Value |
|---|-----------------------|------------------|---------------|---------|
| No.   | 100                   | 98               | 2             |         |
| ENT risk estimate (No.) (frequency)                 |                       |                  |               |         |
| At risk   | 29 (29%)              | 28 (29%)         | 1 (50%)       | .61     |
| Low risk  | 67 (67%)              | 62 (63%)         | 1 (50%)       |         |
| Not evaluated                                       | 4 (4%)                | 8 (8%)           | 0             |         |
| ANC at imaging (mean)                               | 2510 ± 5568           | 2524 ± 5622      | 1800 ± 1697   | .86     |
| Transplant donor (No.) (frequency)                  |                       |                  |               |         |
| Allogenic   | 66 (66%)              | 65 (66%)         | 1 (50%)       | 1       |
| Autologous  | 34 (34%)              | 33 (34%)         | 1 (50%)       |         |
| Disease status at transplantation (No.) (frequency) |                       |                  |               |         |
| Complete remission                                  | 82 (82%)              | 80 (80%)         | 2 (100%)      | 1       |
| Active disease                                      | 18 (18%)              | 18 (18%)         |               |         |
| T-cell depletion (No.) (frequency)                  | 2 (2%)                | 2 (2%)           | 0             | 1       |
| GVHD II–IV (No.) (frequency)                        | 15 (15%)              | 15 (15%)         | 0             | 1       |

**Note:**—ANC indicates absolute neutrophil count.

patient management, including the addition of antibiotics or changes to the antifungal prophylaxis regimen or transplantation schedule. Like other authors,<sup>9,10</sup> we found no association between pretransplantation Lund-Mackay scores and the development of posttransplantation sinus symptoms or IFRS. Unlike Won et al,<sup>9</sup> we did not find pre-HCT symptoms predictive of post-HCT symptoms. In our study, clinical and laboratory features, including pretransplantation ENT evaluation, also failed to predict posttransplantation sinusitis and IFRS. Our findings are in agreement with adult studies by Thompson et al<sup>8</sup> ( $n = 100$ ) and Moeller et al<sup>11</sup> ( $n = 71$ ), which found no benefit at all for pre-HCT sinus screening. A similar study of 1589 adult patients with kidney transplants found no increase in the prevalence of rhinosinusitis posttransplantation, concluding that routine pretransplantation sinonasal evaluation is not warranted.<sup>26</sup>

The origins and evidence supporting pre-HCT screening sinus CT are unclear. In a 1995 study, Shibuya et al<sup>27</sup> recommended screening CT on the basis of 33/107 pretransplantation patients with clinical sinusitis and imaging abnormalities, despite imaging only symptomatic patients. At our institution, the practice may date back to a 1982 article by Bartley et al,<sup>28</sup> prompting routine screening abdominal CT for detection of hepatosplenic fungal abscesses, to which chest and sinus CT were subsequently added. Subsequent work by Kasow et al<sup>12</sup> found no utility in routine chest or abdominal CT in asymptomatic patients but suggested that sinus CT drove changes in management. However, supporting data were sparse, and the number of treated and symptomatic patients precisely matched ( $n = 29/187$ , 15.5%), suggesting a clinical basis for treatment. In a small ( $n = 51$ ) study

in 2000, Billings et al<sup>29</sup> found that children with severe sinus disease on pre-bone marrow transplantation CT were more likely to have sinusitis after bone marrow transplantation and reported a trend toward decreased survival in these children, but these findings were not statistically significant ( $P = .750$ ). In a study of 252 adults, Won et al<sup>9</sup> found that asymptomatic radiographic sinus abnormalities did not increase the risk of post-HCT sinusitis, but they also reported a trend toward reduction of post-HCT sinusitis with the treatment of asymptomatic abnormalities, which did not reach statistical significance ( $P = .057$ ). To our knowledge, no investigators have identified pretransplantation imaging predictors of IFRS.

It has been suggested that CT might be a surrogate for inflammatory symptoms in immunocompromised patients, who may not be able to mount an inflammatory response.<sup>27,30</sup> However, evidence shows that clinical sinusitis and imaging severity go hand in hand, even in immunocompromised children.<sup>10,29,30</sup> This was also true in our study, in which Lund-Mackay scores were greater in the presence of symptoms.

The American Academy of Pediatrics and American College of Radiology guidelines dictate that diagnosis and treatment of acute sinusitis should be clinical, with imaging reserved for suspicion of orbital or CNS complications.<sup>6,7</sup> IFRS typically presents with a combination of fever, facial pain, nasal congestion, headache, eye symptoms, and/or facial swelling, which should also prompt imaging, and likely endoscopy.<sup>3-5,31</sup> On pretransplantation physical examination, none of the 100 patients in our series had findings suggestive of orbital, CNS, or fungal involvement warranting imaging evaluation.

On the other hand, isolated radiographic abnormalities, common in asymptomatic children,<sup>32</sup> may be confusing or lead to overtreatment.<sup>33</sup> In our series, 58.8% of 82 asymptomatic children had mucosal thickening on pre-HCT CT. As suggested by other authors,<sup>9,30</sup> a thorough sinus history and examination are likely to be more meaningful than CT, without the associated risk of radiation-induced cancers and cataracts.<sup>13-15,34</sup>

Our findings suggest that there is insufficient benefit to justify the risks of radiation exposure, and potentially of anesthesia, associated with pre-HCT screening CT.<sup>13,15-17</sup> To reduce the risk of radiation-induced cancers, to which children are particularly susceptible,<sup>34</sup> the As Low As Reasonably Achievable principle dictates the use of the lowest possible radiation dose necessary for diagnosis.<sup>34</sup> Most pediatric imaging centers, like ours, use targeted protocols with dose-reduction techniques like iterative reconstruction and low tube voltage wherever possible.<sup>35</sup>

However, the best way to reduce the pediatric radiation dose is to eliminate imaging that does not meaningfully contribute to diagnosis or management.<sup>14</sup> The preponderance of the evidence, including ours, suggests that pre-HCT screening sinus CT falls into this category and that the practice should be discontinued.

This study had several weaknesses. Clinical evaluation was rarely performed on the same day as screening sinus CT, and symptoms were recorded from the medical record because they were frequently omitted from the imaging requisitions. These features could result in a mismatch between symptoms and imaging manifestations. Although a trend toward greater Lund-Mackay scores in symptomatic patients receiving antibiotics was not statistically significant, the sample size was small. It is possible that the degree of mucosal thickening on sinus CT unduly influenced the decision to treat with antibiotics, which should be based on history and examination.<sup>6,7</sup> Mucosal thickening on CT does not differentiate between bacterial and viral pathogens, and 3 of 5 patients receiving antibiotics in this study had nasal washes positive for viral pathogens. Next, only patients undergoing imaging work-up were considered symptomatic post-HCT. It is possible that some patients were treated on the basis of clinical symptoms with no imaging, though observation of our current clinical practice suggests that this is unlikely. Similar to other studies,<sup>2,4</sup> only 2% (2/100) of this study population ultimately developed IFRS, limiting statistical evaluation. However, neither had clinical or imaging findings suspicious for IFRS pretransplantation. Although a single-institution sample size of 100 children undergoing HCT may be considered large, given the rarity of the condition, it was nonetheless insufficient to identify clinical or imaging features associated with IFRS. A retrospective case-control study would be more practical for such analysis.

## CONCLUSIONS

Pre-HCT sinus CT does not meaningfully contribute to pretransplantation patient management or prediction of posttransplantation sinus disease, including IFRS, in children. The risks associated with CT radiation and possible anesthesia are not warranted in this setting.

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